



INVITED REVIEW ARTICLE

Blastopathies and microcephaly in a Chernobyl impacted region of Ukraine

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ABSTRACT This population-based descriptive epidemiology study demonstrates that rates of conjoined twins, teratomas, neural tube defects, microcephaly, and microphthalmia in the Rivne province of Ukraine are among the highest in Europe. The province is 200 km distant from the Chernobyl site and its northern half, a region known as Polissia, is significantly polluted by ionizing radiation. The rates of neural tube defects, microcephaly and microphthalmia in Polissia are statistically significantly higher than in the rest of the province. A survey of at-birth head size showed that values were statistically smaller in males and females born in one Polissia county than among neonates born in the capital city. These observations provide clues for confirmatory and cause-effect prospective investigations. The strength of this study stems from a reliance on international standards prevalent in Europe and a decade-long population-based surveillance of congenital malformations in two distinct large populations. The limitations of this study, as those of other descriptive epidemiology investigations, is that identified cause-effect associations require further assessment by specific prospective investigations designed to address specific teratogenic factors.

Key Words: blastopathies, Chernobyl, congenital malformations, ionizing radiation, sex ratio

INTRODUCTION

The 1986 Chernobyl disaster in Ukraine (Chernobyl in Russian) is among the largest man-caused disasters and has impacted and continues to impact human health, ecologic integrity, and the social welfare of multiple generations of culturally and ethnically diverse large populations. Some have called the Chernobyl tragedy a “natural experiment” and as pointed out by Garruto et al. (1999) such events represent unique opportunities for studying biomedical processes, disease etiology, and pathogenesis in populations with diverse ethnic and genetic structures, living under special circumstances. This report summarizes the results of an investigation aimed at determining population-based rates and patterns of con-

genital malformations (CM) in the Rivne province of Ukraine during the 2000–2009 decade. Although two concurrent identical CM population-based surveillance programs are ongoing in Khmelnytsky and Volyn provinces, which adjoin Rivne, this report is focused on observations in the latter province. The term “blastopathies” appears in the title of this report to stress that the CM reported are present prior to the embryonic implantation and organogenesis, a notion elaborated upon later. To our knowledge, there are no other population-based long term investigations of CM rates and patterns relying on international methods, focusing on an area relatively proximal and heavily impacted by ionizing radiation (IR) from the 1986 Chernobyl disaster (Fig. 1). The northern half of the Rivne province is a region of forested wetlands known as Polissia, which is inhabited by a native population known as Polishchuks. Coincidentally, the fallout of Chernobyl IR impacted mostly the Rivne-Polissia zone henceforth referred to as Rivne-P or simply Polissia (note that there are also Polissia regions in Volyn, Zhytomyr and Kyiv provinces). The non-Polissia regions henceforth referred to as Rivne-nP were less impacted by Chernobyl IR. Noteworthy is that reports on the subject rarely point out contrasts between Rivne-P and Rivne-nP regions (Likhtarev et al. 1996, 2000; Zamostian et al. 2002). Polissia may be referred to as the Prypiat Marshlands or in older medical literature as Polisie, Poliesia, Polesky, and Polesie.

In this report, unless indicated otherwise, Polissia solely refers to Rivne-P, which is described in some detail in the Data Supplement. It is sufficient to underscore here that the native people of Rivne-P are known as Polishchuks and that they represent a population isolate surviving mostly by consumption of locally grown products, foods and fuels inherently contaminated by nuclides. Polishchuks continue to inhale and ingest nuclides and among whom, a growing proportion of individuals are exposed since birth. Furthermore, a growing proportion of pregnant Polishchuk women have themselves incorporated nuclides to which all of their conceived children are exposed prenatally. The large size and well defined nature of the Polishchuk population facilitates long term studies of the health and teratogenic impacts of protracted exposures to low levels of IR.

In this report, we confirm and expand previous studies in Rivne that demonstrated elevated population-based rates of CM and include initial results of a series of surveys that may reflect impacts of IR among other causes (Yuskiv et al. 2004; Wertelecki 2010). To sustain in Rivne and two adjoining provinces (Volyn and Khmelnytsky) ongoing population-based CM monitoring systems, which uphold international standards and international partnership, we established OMNI-Net, a not for profit international organization

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Received September 30, 2013; revised and accepted January 5, 2014.

DEDICATORY

This investigation is dedicated to past, present and future children in Ukraine and Japan.

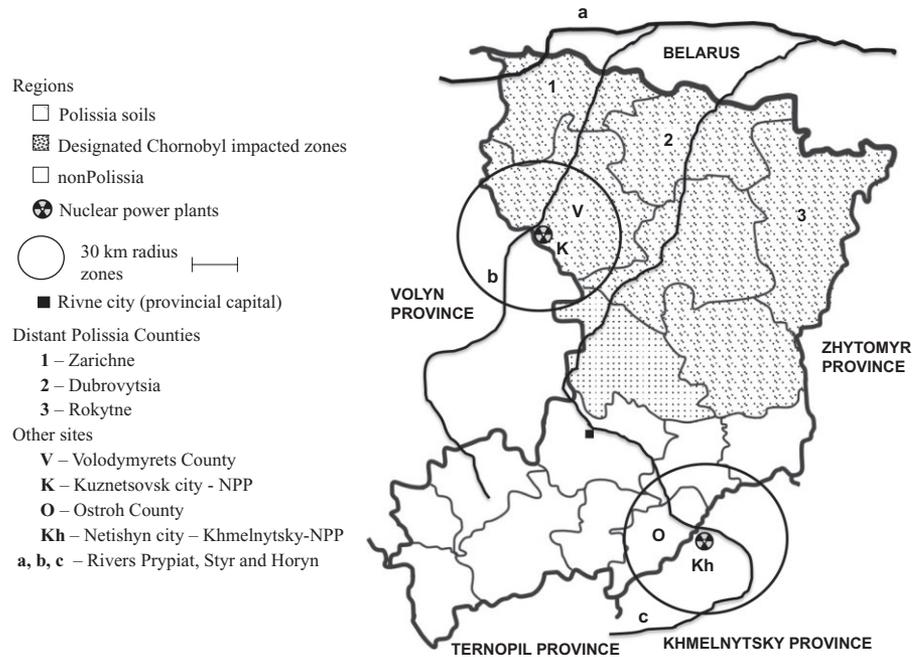


Fig. 1 Schematic representation of Rivne province counties indicating those with soils characteristics of a region called Polissia and those counties designated as impacted by Chernobyl ionizing radiation. Also shown is the area of “distant” Polissia, the location sites of nuclear power plants and the trajectory of major rivers of the region.

registered in Kyiv, Ukraine (Wertelecki 2006). This report primarily concerns observations in Rivne, which are occasionally expanded by observations in the two adjoining provinces. Among the goals of the OMNI-Net is to promote and maintain international research and humanitarian partnerships intended to define causes, and to promote treatments to minimize and prevent CM. In Rivne, the OMNI-Net center is co-located with the Clinical Genetics and Prenatal Fetal Ultrasonography Services of the Provincial Diagnostic Center of the Rivne province, henceforth referred to as OMNI-Net or Diagnostic Center. Our confidence in the significance of the observations we report not only rests in the confirmation of two previous analyses but also on a concurrence of favorable circumstances in Rivne that foster and sustain the ongoing population-based CM surveillance process integrated with clinical services and public health programs.

METHODS AND DATA COLLECTION

In 1999, we designed and tested a birth medical report to concurrently fulfill Ministry of Health, provincial health care, and CM data collection needs. The scope and procedures of CM data collection and analysis are consistent with those upheld by the EUROCAT (European Surveillance of Congenital Anomalies) and ICBDSR (International Clearinghouse for Births Defects Surveillance and Research) consortia of which OMNI-Net became a full partner.

Following approval by Ukrainian health authorities, formal CM population-based data collection started in 2000 and is ongoing. Rivne neonatologists are mandated by health authorities to personally complete a medical birth document that is equivalent to an expanded birth certificate. This investigation is focused on the population-based frequencies of eight CM collectively referred to as core-CM (cCM). Occasionally, five of these eight cCM are referred to as a pentad-cCM composed of conjoined twins (CTW), teratomas (TER), neural tube defects (NTD), microcephalies (MIC), and microphthalmias (mOPH), or as a triad-cCM composed of omphaloceles (OM), gastroschises (GASTR), and urinary bladder exstrophies (BLEXTR), respectively. Two sentinel or index CM, cleft lip with or without concurrent cleft palate (CL/P) and

Down syndrome are presented separately (Table S1d). The frequencies of other CM and malformation complexes mentioned are not population-based. Descriptions and patterns of Fetal Alcohol Spectrum Disorders (FASD) reflect collaborative investigations in partnership with investigators sponsored by the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) promoted by the National Health Institute on Alcohol Abuse and Alcoholism (NIAAA). Occasionally, observations stemming from mirror CM surveillance systems in two provinces that adjoin Rivne (Volyn and Khmelnytsky) are included. A companion Data Supplement includes a list of abbreviations, supplemental tables and figures indicated by a prefix (S), as well as individual summaries of clinical highlights, clues to which are inserted in the text between parentheses.

Definitions of cCM and other CM are those instituted by EUROCAT supplemented as needed by those found in authoritative reviews (Willis 1962; Warkany 1971; Warkany et al. 1981; Stevenson & Hall 2006). Regarding gastroschisis and other abdominal schises, criteria presented by Mastroiacovo et al. (2007) also apply. The computed NTD subcategories are encephaloceles, anencephaly, iniencephaly, cranio-rachis-schisis or anencephaly-spina bifida, and spina bifida. Spina bifida is further subcategorized as cervical, thoracic, and lumbo-sacral-coccygeal on the basis of the highest level and extent of the anomaly. These subcategories are combined into three groups, cephalad-NTD, spina bifida-NTD, and encephaloceles. The cephalad-NTD group includes anencephaly, iniencephaly and cranio-rachis-schisis. Microcephaly implies an occipital-frontal circumference of at least 3 standard deviations (SD) below the mean. When the number of observations permits, cCM are categorized as isolated and the rest as syndromic or not (Tables 1, S1c).

To convey the notion that conjoined twins, teratomas, NTD, OM, and BLEXTR arise prior to embryonal implantation, we may refer to these cCM as “blastopathies”. In the same spirit, those blastopathies associated with body wall defects can be referred to as “celosomias”. Regarding Down syndrome, and CL/P, these may be referred to as “sentinel” CM.

Table 1 Population-based rates of unduplicated individuals and male-female (MF) proportions and ratios (M:F) of selected congenital malformations among live births in Rivne, Ukraine (2000–2009)¹

Categories	<i>n</i>	Rate	Unk ^a	Sex		M : F ^b
				M	F	
Live births	145 437		28	75 292	70 117	1.07
Neural tube defects (NTD)	309	21.2	66	114	129	0.88
Cephalad ²	116	8.0	34	32	50	0.64 ^{**c}
Anencephaly	66	4.5	21	20	25	0.80
Isolated	62	4.3	19	20	23	0.87
Cranio-inien-rachis-schisis ⁴	50	3.4	13	12	25	0.48 ^{**d}
Isolated	35	2.4	8	10	17	0.59
Spina bifida cervico-thoracic	21	1.4	2	13	6	2.17
Isolated	18	1.2	2	11	5	2.20
Spina bifida lumbo-sacral	126	8.7	16	58	52	1.12
Isolated	112	7.7	12	51	49	1.04
Spina bifida site unknown	15	1.0	4	2	9	0.22 ^{**e}
Isolated	15	1.0	4	2	9	0.22 ^{**e}
Spina bifida combined	162	11.1	22	73	67	1.09
Encephalocele	31	2.1	10	9	12	0.75
Isolated	23	1.6	7	5	11	0.45
Microcephaly ⁵	68	4.7	–	32	36	0.89
Isolated	22	1.5	–	6	16	0.38 ^{**f}
Microphthalmos ⁶	24	1.7	–	11	13	0.85
Isolated	12	0.8	–	6	6	1.00
Omphalocele ⁷	38	2.6	12	20	6	3.33 ^{**g}
Isolated	22	1.5	8	11	3	3.67 ^{**h}
Gastroschisis	40	2.8	5	16	19	0.84
Isolated	38	2.6	5	15	18	0.83
Urinary bladder exstrophy ⁸	13	0.9	–	7	6	1.17
Isolated	12	0.8	–	7	5	1.40
Conjoined twins ⁹	7	0.5	2	1	4	0.25
Isolated	5	0.3	2	–	3	n/c
Teratomas	10	0.8	3	1	6	0.17
Isolated	10	0.7	3	1	6	0.17
Sacro-coccygeal	9	0.6	3	1	5	0.20
Isolated	9	0.6	3	1	5	0.20
All	509	35.0	88	202	219	0.92
Isolated	386	26.5	70	145	171	0.85 ^{**i}

*, **, ***, indicate *P*-values of ≤ 0.05 , 0.01, 0.001.

^{1–9}See footnotes in Table 2.

^aUnknown sex.

^bM : F ratios are not counted for categories with less than five individuals of either sex.

	OR	P	CL
c	0.60	0.014	0.37, 0.95
d	0.45	0.014	0.20, 0.92
e	0.21	0.025	0.02, 1.00
f	0.35	0.018	0.11, 0.94
g	3.11	0.008	1.20, 9.45
h	3.42	0.039	0.90, 19.1
i	0.79	0.021	0.63, 0.99

Data collection

Routine data collection is initiated by trained neonatologists who examine every liveborn and complete Part A of the birth document and Part B in the event that CM or dysmorphic signs are noted. Regarding stillbirths, obstetricians complete the birth document. Legal interruptions of pregnancies between 12th and 22nd weeks of gestation are registered separately. Part A of the birth document provides information about parents, conception, pregnancies, current gestation, birth measurements, and health status of every newborn. In Part B are recorded descriptions of anomalies in sufficient detail to fulfill reporting requirements by the Ministry of Health of Ukraine and parameters reported to EUROCAT. Training and formal interactions with neonatologists are at least twice yearly and with obstetricians quarterly in the context of reviews of prenatal fetal examinations. Reported CM or dysmorphic features are reviewed by OMNI-Net clinical geneticists and for the most part trigger tele-consultations and clinical referral of patients for further examinations. Parts A and B of the birth document are incorporated into individual clinical records. Clinical records integrate all other medical information concerning the patient, the parents, and relatives with disregard of the patient's age. Summaries of clinical records of patients with cCM are included in the Data Supplement. The monitoring of CM in Rivne is an active surveillance system. Twice yearly, children under state care in children's homes (former orphanages) are examined by OMNI-Net clinicians. Active search of CM also includes review of admissions to pediatric services, autopsies, and requests for social assistance programs related to childhood disabilities. Family histories are collected routinely from all individuals seeking clinical services from OMNI-Net clinicians. Currently, nearly 70% of pregnant women in Rivne seek prenatal clinical services at the Diagnostic Center generally between 18th–20th weeks of gestation. Virtually all assessed pregnant women agree to undergo fetal ultrasonographic examinations. Also, pregnant women are routinely screened concerning nutrition patterns and alcohol consumption and a substantial proportion agree to participate in clinical investigations sponsored by CIFASD alluded to earlier (Arenson et al. 2010; Mattson et al. 2010). Since 2008, pregnant women are urged and most agree to undergo whole body counts of Bq reflecting levels of incorporated ^{137}Cs . The procedures adhered to are approved by the provincial health authorities and the Ethics Committee of the Lviv National Medical University.

Surveys of teratogenic risk factors

We include in this report initial results of ongoing surveys focused on three known teratogenic risk factors in Rivne: isonomy as an index of elevated rates of consanguinity among the rural isolated Polishchuk native population in Rivne-P, the patterns of alcohol consumption by pregnant women, and the incorporated levels of IR by pregnant women and ambulatory patients. Regarding consanguinity, a survey of isonomy rates of family names (surnames) assigned to all neonates was computed in every county in Rivne. Isonomy rates are computed as the aggregate frequency (percentage) of the five most common family names in each county in Rivne. Other methods are either described in this section or in footnotes of the corresponding figures and tables presenting results. Information regarding nutrition and alcohol consumption is routinely requested from pregnant women seeking medical services from the Rivne Diagnostic Center. In addition, all patients are routinely asked to voluntarily participate in an expanded survey of nutritional habits, sources of inhalation of wood smoke or dust, and consumption of alcohol as well as to voluntarily undergo whole body counts of their incorporated ^{137}Cs levels. These recordings are obtained by use of a single officially-calibrated device operated by

the Rivne Diagnostic Center staff. An additional survey determined incorporated ^{137}Cs and ^{90}Sr by potato plants grown in P.

Case-by-case review, categorization and computation of rates

After a review by at least two clinical geneticists, an individual with a CM is included in the analyses. Singletons and non-singletons, live born or stillborn (fetal death after the 22nd week of gestation) and instances of interruption of pregnancy are included in the analyses, both by OMNI-Net and EUROCAT. Rivne cCM population-based rates are computed in dual terms; as unduplicated individuals or u-rates or as overall rates or t-rates. Implicitly and as shown in Tables 1,2, and S1a,b, u-rates may be lower than corresponding t-rates in function of individuals with multiple cCM (Tables 5,10,11, S2). EUROCAT and most of the literature on the subject report t-rates. Comparisons of Rivne with EUROCAT t-rates are calculated on the basis of 10 000 births. Frequencies within Rivne are in u-rates and t-rates computed on the basis of 10 000 live births. To compute u-rates, an individual with multiple core-CM is represented in the first applicable cCM category in a priority or hierarchical sequence (NTD, MIC, mOPH, OM, GSTR, BLEXTR, CTW and TER). All individuals with NTD are represented only in this category regardless of any other associated CM. The group of individuals with MIC excludes those with NTD and the group of those with mOPH excludes individuals who have either NTD or microcephaly, and so on. Male-Female proportions (M-F) or ratios (M : F) are presented when there are at least five known individuals of either sex.

Statistical comparisons are included in various tables particularly for their descriptive values. We rely on the one-tailed Fisher's exact test, Cochran-Mantel-Haenszel and Breslow-Day tests and for head circumference data analysis on methods as described by Wang and Wertelecki (2013). We chose a significance level of 0.05 and test an alternative hypothesis that the risk is higher in Rivne-P than in Rivne-nP. The *P*-values and 95% confidence intervals are computed using SAS 9.2 software (<http://www.sas.com/>). Generally, the CM rates observed in Rivne are compared with rates from elsewhere reported to EUROCAT, ICBDSR and rates based on analyses of MACDP data (Metropolitan Atlanta Congenital Defects Programs of the Centers for Disease Control and Prevention) or population-based studies. Regarding health effects of exposure to low levels of IR, the core reference source is the BEIR V report (1990).

RESULTS

Among 145 437 live births in Rivne between 2000 and 2009 are included 2348 (1.61%) infants with anomalies noted before one year of age. This analysis concerns eight congenital malformations henceforth referred to as a group of cCM that includes conjoined twins, teratoma, NTD, microcephaly, mOPH, OM, gastroschisis, and extrophy of the bladder. In the Tables 1,2 are shown population-based rates of unduplicated individuals (u-rates) of cCM and male-female proportions (M-F) as well as ratios (M : F) and the actual numbers of observed individuals are shown in Tables S1b and S2 and other companion tables.

The overall M : F ratio in Rivne is 1.07 and in Rivne-P and Rivne-nP is 1.08 and 1.07 respectively (Tables 1 and S2). The relative frequencies of mothers in Rivne-P and Rivne-nP who are under 20 years of age are 8.98% to 9.92%, respectively, and of mothers who are at least 35 years old are 8.87% to 6.75%, respectively. It is beyond the scope of this report to address other demographic characteristics in Rivne-P or Rivne-nP.

Table 2 Population-based unduplicated rates per 10 000 live births of individuals with selected congenital malformations in Rivne, Ukraine¹

Categories	Polissia			Non-Polissia			Polissia vs. non-Polissia		
	2000–2004	2005–2009	2000–2009	2000–2004	2005–2009	2000–2009	OR	P-value	CL
Neural tube defects (NTD)	29.1	23.5	18.4	14.8	26.1	16.4	1.59	***	1.26, 2.02
Cephalad ²	9.5	10.1	7.8	4.8	9.8	6.2	1.59	**	1.08, 2.37
Anencephaly	6.2	4.1	5.1	3.0	5.1	4.0	–	n/s	–
Isolated	5.6	3.9	4.8	3.0	4.7	3.8	–	n/s	–
Non-NTD malformations ³	n/c	n/c	n/c	–	n/c	n/c	–	n/c	–
Cranio-inien-rachis-schisis ⁴	3.3	5.9	2.7	1.8	4.7	2.2	2.15	**	1.15, 4.16
Isolated	2.1	4.1	1.8	1.5	3.2	1.6	1.94	*	0.92, 4.27
Other malformations	n/c	1.8	n/c	n/c	1.5	n/c	–	n/s	–
Spina bifida cervico-thoracic	3.3	1.6	–	n/c	2.3	n/c	4.29	**	1.40, 17.5
Isolated	2.4	1.6	–	n/c	1.9	n/c	3.53	*	1.11, 14.7
Other malformations	n/c	–	–	–	n/c	–	–	n/c	–
Spina bifida lumbo-sacral	10.1	10.3	7.2	7.0	10.2	7.1	1.44	*	0.99, 2.09
Isolated	8.9	9.3	6.0	6.5	9.1	6.3	1.45	*	0.98, 2.16
Syndromes	n/c	–	–	–	n/c	–	–	n/c	–
Other malformations	n/c	n/c	n/c	n/c	0.97	0.8	–	n/s	–
Spina bifida site unknown	3.3	–	n/c	–	1.5	n/c	–	n/s	–
Isolated	3.3	–	n/c	–	1.5	n/c	–	n/s	–
Spina bifida combined	16.6	11.9	8.4	8.0	14.1	8.2	1.71	***	1.24, 2.40
Encephalocele	3.0	1.6	2.1	2.0	2.2	2.1	–	n/s	–
Isolated	2.1	1.3	1.5	1.5	1.7	1.5	–	n/s	–
Syndromes	n/c	n/c	–	–	n/c	n/c	–	n/c	–
Other malformations	n/c	–	n/c	n/c	n/c	n/c	–	n/c	–
Microcephaly ⁵	5.3	6.7	3.3	3.3	6.1	3.3	1.85	**	1.10, 3.18
Isolated	2.7	1.3	n/c	1.3	1.9	1.1	–	n/s	–
Syndromes	n/c	2.8	2.1	1.8	2.1	1.9	–	n/s	–
Other malformations	1.5	2.6	n/c	n/c	2.1	n/c	–	n/s	–
Microphthalmos ⁶	1.8	3.1	n/c	n/c	2.5	0.8	7.57	***	1.76, 68.2
Isolated	n/c	1.6	–	n/c	1.1	n/c	–	n/s	–
Syndromes	–	n/c	n/c	–	n/c	n/c	–	n/c	–
Other malformations	n/c	n/c	n/c	–	1.0	n/c	7.07	*	0.91, 318

Table 2 (Continued)

Categories	Polissia		Non-Polissia		Polissia		Non-Polissia		Polissia vs. non-Polissia	
	2000–2004	2005–2009	2000–2004	2005–2009	2000–2009	2000–2009	2000–2009	2000–2009	OR	P-value
Omphalocele ⁷	1.8	1.8	2.4	4.3	1.8	1.8	3.4	0.52	(*)	0.25, 1.07
Isolated	n/c	n/c	1.8	2.8	0.7	0.7	2.3	0.30	(**)	0.09, 0.84
Syndromes	n/c	n/c	n/c	–	n/c	n/c	n/c	–	n/c	–
Other malformations	n/c	n/c	n/c	1.5	0.8	0.8	1.0	–	n/s	–
Gastrochisis	n/c	3.4	3.3	3.0	2.3	2.3	3.1	–	n/s	–
Isolated	n/c	3.4	3.0	3.0	2.2	2.2	3.0	–	n/s	–
Other malformations	n/c	–	n/c	–	n/c	n/c	n/c	–	n/c	–
Urinary bladder exstrophy ⁸	n/c	n/c	n/c	n/c	1.1	1.1	0.7	–	n/s	–
Isolated	n/c	n/c	n/c	n/c	1.1	1.1	n/c	–	n/s	–
Other malformations	–	–	n/c	–	–	–	n/c	–	n/c	–
Conjoined twins ⁹	n/c	–	n/c	n/c	n/c	n/c	0.7	–	n/s	–
Isolated	n/c	–	n/c	n/c	n/c	n/c	n/c	–	n/c	–
Other malformations	–	–	n/c	n/c	–	–	n/c	–	n/c	–
Teratomas	1.5	n/c	n/c	n/c	0.8	0.8	n/c	–	n/s	–
Isolated	1.5	n/c	n/c	n/c	0.8	0.8	n/c	–	n/s	–
Sacro-coccygeal	1.5	n/c	n/c	n/c	0.8	0.8	n/c	–	n/s	–
Isolated	1.5	n/c	n/c	n/c	0.8	0.8	n/c	–	n/s	–
All	42.4	39.8	29.8	28.4	41.0	41.0	29.0	1.42	***	1.18, 1.70
Isolated	32.6	28.2	22.3	23.3	30.3	30.3	22.9	1.33	**	1.08, 1.63
Syndromes	2.4	4.1	2.7	1.8	3.3	3.3	2.2	–	n/s	–
Other malformations	7.4	7.5	4.8	3.3	7.5	7.5	4.0	1.88	**	1.18, 3.06

¹Actual counts of unduplicated individuals are found in Table S1b. All births in Rivne are 145 437, in Polissia, 72 379, and in non-Polissia, 73 058 (observations in non-Polissia are in italics). Individuals with congenital malformations (CM) are represented only in one category and include those liveborn or not and singletons or not; individuals with holoprosencephaly are excluded from the Tables 1, 2, and S1a,b,c series; population rates of CM detected up to one year of age are calculated per 10 000 live births. One-tailed *P*-values are calculated with 95% confidence limits for categories with at least five individuals represented or alternatively are shown as not computed (n/c). *P*-values are denoted by

***, ≤0.001; **, ≤0.01; *, ≤0.05, or n/s for non-significant. *P*-values in parentheses indicate a negative association. Odds ratio (OR) and confidence limits (CL) are also shown.

²Cephalad includes iniencephaly, anencephaly (or acrania) associated or not with rachis-schisis or spina bifida. Encephaloceles are computed separately.

³Microphthalmia (c-1); cleft lip (c-2); omphalocele (c-3); esophageal atresia (d-1).

⁴Includes iniencephaly and anencephaly-rachis-schisis.

⁵Excluded are two singletons and one twin with holoprosencephaly (hol-6, 20; tw-1); also excluded is an individual incompletely described (z-2) diagnosed at 20 weeks of gestation with a holoprosencephaly spectrum and a single orbit, who is represented among conjoined twins. Included in this category as isolated microcephaly are two individuals who had microcephaly and microphthalmia not associated with extra-ocular anomalies (ri-8, 12).

⁶Excluded is one individual represented among anencephalics (c-1); four individuals with microcephaly (ri-8, 12; t-8; s-2); and one individual (z-2), who is represented among conjoined twins and further described in footnote (5).

⁷Excluded is one individual represented among anencephalics (c-3); seven individuals with cranio-rachis-schisis (f-2, 4–8; g-4); six individuals with spina bifida (h-1, 3; l-5, m-2, 5, 6); two individuals with microcephaly (t-9, u-2); and two individuals with microphthalmia (v-1; w-1).

⁸Excluded is one individual with spina bifida (h-3).

⁹Excluded is one member of a set of conjoined twins (h-1) with spina bifida and represented among other individuals with spina bifida.

Table 3 Highest population rates^a in Europe (2005–2009)^b of four congenital malformations (including percent of NTD-impacted terminated pregnancies)^c compared to rates in Polissia and non-Polissia regions of Rivne Province, Ukraine (2000–2009)

Neural tube defects	Microcephaly	Microphthalmia	Conjoined twins
25.96 (51) ^c Polissia	6.35 Polissia	3.57 Polissia	0.55 Rivne
16.33 (68) non-Polissia	5.35 Wales	1.63 Wales	0.49 North England
14.47 (81) N. England	5.03 South-West England	1.51 Dublin	0.35 Wales and Wessex
13.60 (84) Wales	4.52 Valencia	1.22 N Netherlands and non-Polissia	0.31 E. Midlands and South Yorkshire
12.77 (87) Paris	3.88 Basque C. (Spain)	1.21 South-West England	0.26 Wiekopolska

^aRate per 10 000 births of congenital malformations (not individuals) inclusive of live births, fetal deaths of 20 or more weeks of gestation and termination of pregnancies.

^bRates reported by full member registries located in Europe who reported at least 30 000 births during the 2006–2008 and at least 30 instances of neural tube defects (NTD). These criteria were met by the 19 registries shown. Excluded were registries from Zagreb (Croatia), Odense (Denmark), Strasbourg (France), Mainz (Germany), Cork and Kerry (Ireland), SE Ireland, Malta, Barcelona (Spain), Vaud (Switzerland); South Portugal. Excluded are registries from Saxony-Anhalt (Germany) and Styria (Austria) whose data are under review. Ukraine is excluded and instead, rates from Rivne province in Ukraine subdivided as Polissia and non-Polissia regions are presented. The rates are calculated adhering to EUROCAT methods. Eurocat data are accessible on the web-site. Note: EUROCAT occasionally introduces data updates. The data shown above was accessed on 29 November 2013.

^cPercent of pregnancy terminations.

In Rivne, large proportions of pregnancies associated with cCM are detected prenatally and are medically interrupted. In Polissia, during the first and second 5-year study periods, 69% and 88% of NTD were detected prenatally, respectively. In nP the percent was 82–97%. Many of these NTD related pregnancies were medically interrupted; in Polissia, during the first and second 5-year periods, 47% and 55% respectively and in Rivne-nP the percent was 59–75%, respectively (Data Supplement). The above described temporal and Rivne-P-nP contrasts reflect, in our view, a gradual introduction of upgrades of technical resources combined with cognitive enhancements, particularly in the sphere of fetal ultrasonography. These trends spread from the capital city where OMNI-Net is located toward the peripheries such as the most distant northern counties in the Polissia region. The frequency of NTD-related pregnancy terminations across Europe compared with Polissia and Rivne-nP are summarized in Table 3 and in Table S5, which also include observations concerning OM and data from most partners of EUROCAT. The frequency of terminations of OM-related pregnancies is consistently lower than terminations of NTD-related pregnancies. The terminations of NTD-related pregnancies in Rivne-P are the lowest reported to EUROCAT. These comparisons sustain our view that higher rates of prenatal detection are not a basis for the pentad-cCM rates in Polissia to be among the highest in Europe.

Concerning other temporal contrasts of CM frequencies in Rivne-P and Rivne-nP, while the overall frequencies of cCM, NTD, and spina bifida are statistically significantly higher in P during both 5-year study periods, the frequencies of cranio-inien-rachis-schisis, MIC, and mOPH are statistically significantly higher only during the second 5-year study period. However, it is also evident that the frequencies of all of these cCM are higher in P during the first and second study periods. This fact, in our view, is biologically significant although in some instances such contrasts do not reach statistical significance, which is at least in part due to a limited number of observations (Table S1a,b).

NTD

In Rivne, there are 309 individuals with NTD, of whom 31 (10%) have an encephalocele (Table 1 and S1b). The prevalence of

encephaloceles is similar in Polissia and Rivne-nP. The overall M-F proportion in Rivne among non-syndromic encephaloceles is 7–12 (Table S9). To provide sufficient data to compute sub-categories of encephaloceles, an analysis expanded to include encephaloceles observed in Rivne and two adjoining provinces where the t-rates are 2.13 and 1.54, respectively. Among 63 non-syndromic encephaloceles, 41 (65%) were occipital and the M-F proportion was 10–18 (Table S9).

In Rivne, and in contrast to encephaloceles, NTD subcategories are statistically significantly more frequent in Polissia. The overall M:F ratio in Rivne is 1.07 compared to 0.64 among those with cephalad-NTD and 1.09 among those with spina bifida, respectively. Another NTD preferential association is with OM noted in 4.5% of individuals or conversely in 25% of individuals with OM. An analysis of this association noted in Rivne and the two adjoining provinces demonstrates that it is the strongest among instances of cephalad-NTD (Table S7). The association was noted in 1.8%, 29%, 9%, 3.2% and 2.3% among 223, 17, 85, 62 and 280 instances of anencephaly, iniencephaly, cranio-rachis-schisis, “high” spina bifida (above the first lumbar vertebra), and lumbo-sacral spina bifida, respectively. In Rivne, a female prevalence was evident among the cephalad-NTD-OM and absent among those with spina bifida-OM associations where the M-F proportions were 2-9 and 3-2 respectively.

The 14 instances of NTD-OM preferential associations or dyads is indicative of a significantly higher risk for individuals to have this association ($P < 0.001$, odds ratio in Rivne-P is 93.12 and the 95% confidence limits are from 23.28 to 273.05; in Rivne-nP, the odds ratio is 268.81 and the 95% confidence limits are from 106.24 to 648.18). The Cochran-Mantel-Haenzel and Breslow-Day tests show that the strength of the NTD-OM association is similar in Polissia and Rivne-nP (P -value = 0.1157), and that the overall risks are still very significant (P -value < 0.0001; OR = 174.95; 95% CL, 95.59 to 325.79). Another NTD preferential association is with twinning, which was noted in eight individuals or 2.6% of NTD instances (Table S4). A tendency to engender twinning events is also evident among relatives of NTD patients, in particular if maternal (Fig. 3).

Table 4 Individuals^a with prevalent malformation syndromes associated with microcephaly in Rivne Province (2000–2009)

Category ^a	Rate ^a	Polissia			Non-Polissia				Rivne Province			
		Sex			Sex				Sex			
		All	M	F	Rate	All	M	F	Rate	All	M	F
FASD ^b	5.1	37	19	18	5.7	42	25	17	5.4	79	44	35
Included in alternative categories	1.4	10	7	3	1.5	11	6	5	1.4	21	13	8
among Microcephaly	1.2	9	7	2	1.5	11	6	5	1.4	20	13	7
PATAU SYNDROME/TRISOMY 13	n/c	9	5	4	n/c	11	8	2	n/c	20	13	6
Included in alternative categories	n/c	8	5	3	n/c	9	6	2	n/c	17	11	5
Holoprosencephaly	n/c	5	3	2	n/c	6	4	1	n/c	11	7	3
Microphthalmia	n/c	2	1	1	n/c	1	1		n/c	3	2	1
Omphalocele	n/c	1	1		n/c	1		1	n/c	2	1	1
Microcephaly					n/c	1	1		n/c	1	1	
HOLOPROSENCEPHALY ^c	n/c	13	8	5	n/c	23	12	7	n/c	36	20	12
Associations												
and Microcephaly ^d	n/c	2	2		n/c	1	1		n/c	3	3	
and Microphthalmia ^e	n/c	3	2	1	n/c	2	1	1	n/c	5	3	2
and Teratoma ^f	n/c	1		1					n/c	1		1

^aIn contrast to Table 2 and its derivatives where individuals are only represented once, in this table the rate is calculated as total impacted individuals who may be represented in several malformation categories (shown in capital letters). Individuals represented in sub-categories are mutually exclusive. Also note an alternative presentation of similar data in Table 4,5 and clinical summaries of all individuals contained in the Data Supplement. M indicates males and F indicates females.

^bFASD, Fetal Alcohol Spectrum Disorders.

^cIncludes Patau syndrome (see above).

^dIncludes one individual (hol-6) with holoprosencephaly-microcephaly-microphthalmos association.

^eExcludes above individual (hol-6).

^fIncluded one individual with cervico-faringeal teratoblastoma (neo-1).

n/c, not computed.

Microcephaly u-rates and t-rates are summarized in Tables 1,2,4,5 and S1b,2. The Rivne u-rate of 4.7 reflects the ascertainment of 68 unique individuals with microcephaly inclusive of instances of concurrent mOPH and exclusive of instances associated with holoprosencephaly or NTD. The u-rates in Polissia and Rivne-nP are 6.1 and 3.3, respectively, which represents a statistically significant contrast (Table 2 above). Among individuals with microcephaly, female prevalence is most evident in instances of isolated microcephaly where the M-F proportion is 6–16 (Table 1). In contrast, there is no female prevalence among those with syndromic microcephaly including instances of FASD or Patau or trisomy 13 syndromes. There are 30 individuals with mOPH who are not concurrently microcephalic, 12 of whom have no associated CM. Among these 30 individuals, 22 and eight are from Polissia and Rivne-nP, respectively, which represents a statistically significant contrast. Concerning sex prevalence, the observed M-F proportions are equivocal. In Table 4, syndromes and CM complexes often associated with microcephaly and/or mOPH are shown.

In Table 5, we present the instances and t-rates of microcephaly and/or mOPH associated with holoprosencephaly, FASD and Patau-trisomy 13 complexes.

Among 71 individuals with microcephaly, 28% represent instances of FASD and 1.4% represent Patau syndrome. From a perspective of FASD, 75% of individuals did not meet the strict definition of microcephaly adopted for this investigation (3 SD below norm). However, these individuals may have lesser degrees

of microcephaly or reductions of head circumferences. Among 36 individuals with holoprosencephaly, 22% had concurrent microcephaly, mOPH or both and furthermore, nearly 50% of individuals with Patau syndrome had concurrent holoprosencephaly. These observations are among the reasons for the exclusion of holoprosencephaly from computations of microcephaly u-rates reported in Tables 1,2. In summary, instances of isolated microcephaly represent 32% and instances associated with non-syndromic CM represent another 25% (Table S1b and Data Supplement).

Regarding alcohol teratogenesis, a survey of alcohol consumption by pregnant women demonstrated, as summarized in Table 6, that alcohol consumption during pregnancy was least prevalent in Polissia and most prevalent in the eponymous capital cities of Rivne and Khmelnytsky. Furthermore, as shown in Table S3 the frequency of instances of FASD is higher in Rivne-nP than in Polissia.

Microcephaly may be caused by autosomal recessive and other genetic mutations as well as by teratogenic impacts such as from IR or alcohol, among other environmental insults. In anticipation of prospective investigations oriented to determine the pathogenesis and etiology of microcephaly and other cCM, there are several ongoing surveys in Rivne. Concerning genetic mutations, initial results of a survey of isonomy rates of family surnames assigned to all neonates in every county in Rivne are summarized in Figure S1 where the highest rates are evident in the most northern counties of Polissia.

Table 5 All individuals with microcephaly and associated anomalies in Rivne Province, Ukraine (2000–2009)^a

Category ^a	Polissia				Non-Polissia				Rivne Province		
	All	Rate*	Sex		All	Rate	Sex		All	Rate	M : F
			M	F			M	F			
MIC (all individuals) ^b	46	6.4	22	24	25	3.4	13	12	71	4.9	0.97
MIC (no HOLOP, no mOPH) ^c	26	3.6	10	16	10	1.4	4	6	36	2.5	0.64
Isolated	12	1.7	3	9	8	1.1	3	5	20	1.4	0.43
MIC and HOLOP (no mOPH) ^c	1	n/c	1		1	n/c	1		2	n/c	n/c
Isolated					1	n/c	1		1	n/c	n/c
MIC and mOPH (no HOLOP) ^c	3	n/c		3					3	n/c	n/c
Isolated	2	n/c		2					2	n/c	n/c
MIC and mOPH and HOLOP ^c	1	n/c	1						1	n/c	n/c
Syndromic MIC	15	2.1	10	5	14	1.9	8	6	29	2.0	1.64
Patau Syndrome					1	n/c	1		1	n/c	n/c
FASD ^d	9	1.2	7	2	11	1.5	6	5	20	1.4	1.86
mOPH (no MIC) (all individuals)	22	3.0	10	12	8	1.1	4	4	30	2.1	0.88
mOPH (no HOLOP) ^c	16	2.2	7	9	5	0.7	2	3	21	1.4	0.75
Isolated	8	1.1	5	3	4	n/c	1	3	12	0.8	1.00
mOPH and HOLOP ^c					2	n/c	1	1	2	n/c	n/c
Isolated					1	n/c	1		1	n/c	n/c
Syndromic mOPH	6	0.8	3	3	1	n/c	1		7	0.5	n/c
mOPH and Patau Syndrome ^e	5	0.7	3	2	1	n/c	1		6	0.4	n/c

*Statistically significantly higher t-rates in Polissia are noted among all MIC individuals (P -value 0.008; OR 1.86; CL 1.12, 3.16); among MIC excluding HOLOP and mOPH (P -value 0.005; OR 2.63; CL 1.23, 6.10); among mOPH excluding MIC (P -value 0.008; OR 2.78; CL 1.19, 7.21); among mOPH excluding HOLOP (P -value 0.01; OR 3.23; CL 1.13, 11.3); and nearly significantly higher rates among syndromic mOPH (P -value 0.06; OR 6.06; CL 0.73, 278.6).

^aIndividuals may be represented in various categories. Unduplicated individuals are presented in Table 2 and further information is given in the Data Supplement.

^bIncludes 4 individuals with mOPH.

^cExcludes associated syndromic malformations.

^dIncludes one individual (s -2) with concurrent MIC-FASD-mOPH.

^eIncludes two individuals with mOPH-Patau-HOLOP combination (hol-22, 23).

F, female; FASD, fetal alcohol spectrum disorder; HOLOP, holoprosencephaly; M, male; M : F, male : female ratio; MIC, microcephaly; mOPH, microphthalmia; n/c, not computed.

Concerning IR, an analysis of whole body counts of incorporated ¹³⁷Cs obtained from 6026 pregnant women shows that the highest levels are found among those who reside in the same three northernmost counties of Rivne-P with the highest isonomy rates. The actual IR levels incorporated by pregnant women, by site of residence, are illustrated in Table 7 and in Figure S2 of the Data Supplement. In terms of official IR protection standards, 48% of pregnant women residing in northern counties of Polissia incorporated ¹³⁷Cs above the maximum permissible level. The analysis of 12 327 and 6706 recordings obtained from ambulatory pediatric and adult male patients demonstrates that 12% and 6%, respectively, incorporated ¹³⁷Cs above official norms.

Taking into consideration the high consumption by the Polissia population of locally grown potatoes, the results of a survey of incorporated IR by these plants shown in Table 8 are of interest. An analysis of dry stems of potato plants shows ¹³⁷Cs and ⁹⁰Sr incorporated levels by these plants in approximately 2:1 proportions.

Table 9 illustrates major sources of incorporation of nuclides by pregnant women in Polissia. Main sources of inhalation are from

smoke and dust and sources of ingestion are from the use of water from shallow water-wells and consumption of locally produced nutrients. The calculated levels of ¹³⁷Cs ingested daily are 268 Bq or above the declared daily upper limit of 210 Bq by the Ministry of Health (Decree 106, 1991).

The current analysis of microcephaly defined as an occipito-frontal circumference (OFC) at least 3 SD below norms excludes lesser degrees of head size reductions. To assess this omission, we analyzed birth weights and at-birth OFC measurements obtained from all infants born in a Polissia county (Zarichne) and Rivne city located in Rivne-nP. The analysis compared 2476 male and 2305 female infants born in Zarichne county with 13 086 male and 12 155 female infants born in Rivne city. The physiologic slightly larger birth weights of male infants were evident among infants from the Rivne-P and Rivne-nP sites. As shown in Figure S3, sex-specific birth weights in Rivne-nP and Rivne-P were similar. On the other hand, the occipito-frontal head circumferences (OFC) of the same infants were smaller among those from Polissia (Fig. 2). Analyses limited to infants born after at least 38 weeks of gestation

Table 6 Alcohol consumption by pregnant women (%)

Area of Residence	Women	AE ¹	OR	P	CL
Polissia	852	13 (1.53)	–	–	–
Non-Polissia	1417	67 (4.73)	0.31	<0.001	0.16, 0.58
Rivne City	566	36 (6.36)	0.23	<0.001	0.11, 0.45
Khmelnysky City	1062	47 (4.43)	0.33	<0.001	0.17, 0.63

Data from Rivne (2009–2010) and Khmelnytsky (2010–2011).

¹“Alcohol Exposed” implies occasional consumption prior or during pregnancy of at least ≥ 5 standard drinks (sd), three times, or 3–4 sd, four times, or 1–2 sd, ≥ 10 times or alternatively almost daily consumption of small amounts or alternatively, a positive answer to at least two questions that follow: “in the past year”.

“Has a friend or family member ever told you about things you said or did while drinking that you could not remember?”.

“Have close friends or relatives worried or complained about your drinking?”.

“Have you had a drink first thing in the morning to steady your nerves or to get rid of a hangover?”.

“Have you felt you ought to cut down on your drinking?”.

“Have people annoyed you by criticizing your drinking?”.

“Have you felt bad or guilty about your drinking?” (adapted from *Kfir M, Yevtushok L, Onishchenko S et al. in Ultrasound ObstetGynecol 2009;33:683–689; Bakhireva L, Wilsnack S, Kristjanson A et al. in J Stud Alcohol Drugs 2011;72(4):536–544*).

Table 7 Whole body counts of incorporated ionizing radiation in Rivne diagnostic center’s ambulatory outpatients

	Distant Polissia ^a	Non-Distant Polissia ^b	Non-Polissia ^c
Pregnant Women ^d	1156	2534	2336
Above Bq norm ^e (%)	557 (48.2)	155 (6.1)	3 (0.1)
Children ^f	1338	3671	1697
Above Bq norm (%)	162 (12.1)	50 (1.4)	1 (0.1)
Adult Males ^f	2117	5885	4325
Above Bq norm (%)	136 (6.4)	22 (0.4)	–

^aIncludes Zarichne, Dubrovytsia, and Rokytne counties.

^bIncludes Volodymyrets, Sarny, Berezne, and Kostopil counties.

^cIncludes remaining Rivne counties not mentioned in (a) or (b).

^dPregnant women seeking prenatal ultrasound examinations at the Rivne Regional Diagnostic Center (2008–2011) who volunteered to undergo the procedure.

^eOfficial limits (norms) are 3700 and 14 800 Bq of ¹³⁷Cs for subjects under 15 years of age and adults respectively.

^f2000–2011 data.

Table 8 Radiometry of dried stems of potato plants from Rivne Polissia region

Sample	Measurements		¹³⁷ Cs, Bq/kg
	⁹⁰ Sr, Bq/kg		
	Initial	Repeat	
A	43.4 ± 17.2	46.8 ± 21.4	88.3 ± 36.4
B	49.9 ± 17.9	32.1 ± 24.1	63.6 ± 39.3
C	41.3 ± 19.9	46.4 ± 19.2	24.0 ± 22.0
D	82.3 ± 21.3	72.2 ± 20.0	
E	88.3 ± 23.1	84.4 ± 28.1	46.1 ± 34.6
F	95.6 ± 23.1	143.2 ± 29.6	
G	327.2 ± 86.6	87.3 ± 25.1	54.8 ± 31.4

Table 9 Water, fuel and food sources consumed in Polissia^{a,b}

	Well	Spring	Bottled	Piped
Water (%) ^b	85.4	9.4	50.0	5.3
Fuel (%)	Wood	Gas	Central	Peat
Heating	76.7	17.5	9.0	1.8
Cooking	52.3	48.9	–	–
Food (%)	Own	Local	Imported	
Pork	91.3	9.9	0	
Chicken	77.3	16.2	2.0	
Milk	71.8	15.1	0	
Vegetables	98.0	6.4	1.2	
Apples	91.6	17.2	3.2	
Estimated daily ¹³⁷ Cs intake				Bq
Polissia				268.25
Upper permissible limit ^c				210.00

^aExtract from Dancause et al. (2010).

^bMixed use, not additive percents.

^cMinistry of Health 1997 guidelines.

or limited to the same infants and free from anomalies detected at birth showed the same contrast. The average OFC values, from largest to smallest, were 34.57 (males from Rivne-nP), 34.31 (males from Polissia), 34.11 (females from Rivne-nP), and 33.84 cm (females from Polissia), respectively. The average OFC values of the same infants born after ≥ 38 weeks of gestation were 34.74, 34.45, 34.27, 33.96 cm, respectively. Statistically, the differences of OFC between infants of the same sex from Polissia and Rivne-nP are significant (P -value < 0.0001). Clinically, the significance of these observations remains to be determined.

In contrast to pentad-cCM, the triad-cCM (OM, GASTR and BLEXTTR) are neither more frequent in Rivne-P nor more prevalent among females (Tables 1,2 and Table 10). Aside from 18 instances of OM associated with NTD (14 instances), MIC (two instances) or with mOPH (two instances), there are 38 other instances of OM (Table 10). The M-F proportion among those of known sex is 20-6.

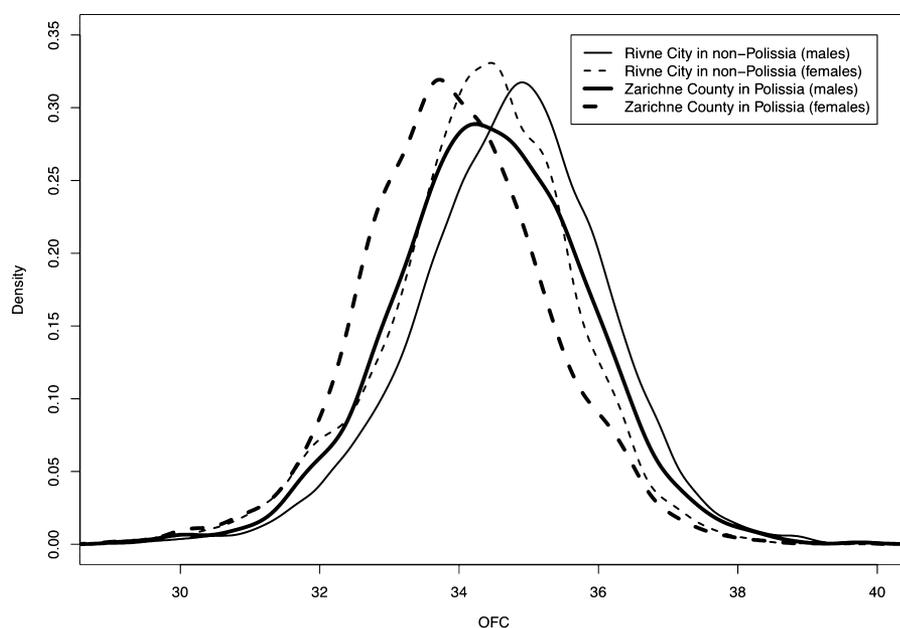


Fig. 2 Occipito-frontal circumferences (OFC in cm) of infants born after at least 38 weeks of gestation. Measurements were obtained from 2398 males and 2240 females from Zarichne county in the Polissia region compared to those of 12 542 males and 11 649 females from Rivne city located in the non-Polissia region of the Rivne province. The OFC values of males and females are smaller in Zarichne county. The contrast is statistically significant (P -value <0.0001 using permutation test and other) (Wang and Wertelecki 2013).

Table 10 All individuals with omphaloceles or gastroschisis (2000–2009)

Category ^a	Rate	Polissia			Non-Polissia			Rivne Province			
		All	Sex		Rate	All	Sex	Rate	All	M : F	
OMPHALOCELE	3.5	25	M	F	4.2	31	M	F	3.9	56	2.80
Isolated	0.7	5	4		2.3 ^b	17	7	3	1.5	22	3.67
Not isolated	2.8	20	10	5	1.9	14	7	2	2.3	34	2.43
Syndromic ^c	n/c	3	3		n/c	2	1	1	0.3	5	n/c
Non-Syndromic	2.3	17	7	5	1.6	12	6	1	2.0	29	2.17
Neural tube defects	1.4	10	2	4	n/c	4	2		1.0	14	n/c
Microcephaly	n/c	1	1		n/c	1	1		n/c	2	n/c
Other Anomalies	0.8	6	4	1	1.0	7	3	1	0.9	13	3.50
GASTROSCHISIS	2.3	17	5	12	3.1	23	11	7	2.8	40	0.84
Isolated	2.2	16	5	11	3.0	22	10	7	2.6	38	0.83

^aIndividuals represented in sub-categories are mutually exclusive.

^bA statistically significantly higher rate (P -value 0.009; OR 0.30; CL 0.09, 0.84).

^cIncludes four individuals ($v-1$; $aa-2$; $w-1$; $bb-1$) with Patau syndrome; includes two individuals ($v-1$; $w-1$) with omphalocele-Patau syndrome-microphthalmos.

F, females; M, males; M : F, male : female ratio; n/c, not computed.

Among these 38 instances, 12 (32%) were detected before the 15th week of gestation. Such early detections often limit the depth of clinical descriptions necessary to fully categorize OM as representing particular patterns of CM such as syndromes or complexes such as the OEIS (omphalocele-exstrophy of the cloaca-imperforate anus-low lumbo-sacral spina bifida). Among these 38 individuals with OM, 16 (42%) had associated CM including two instances of Patau or trisomy 13-like syndrome ($aa-2$, $bb-1$) and one instance of Wiedemann Beckwith syndrome ($aa-1$). One individual had a concurrent skeletal dysplasia ($dd-6$). The remaining 12 individuals we dichotomized into those with cephalad or caudad associated CM, 10 had cephalad and two had caudad CM.

The OM-cephalad CM associations included a twin ($dd-1$) with ectopia cordis (suspected as an instance of a pentalogy of Cantrell complex), CL/P ($cc-2$); cleft lip-hypoplastic heart ($dd-3$); truncus arteriosus ($cc-1$); A-V septal defect ($dd-4$), a-v canal-upper limbs reductions ($cc-5$); stenotic pulmonary artery ($dd-5$); dextrocardia ($dd-7$), and diaphragmatic hernia ($cc-4$, $dd-2$); the caudad array of OM-CM associations included one individual with cloacal exstrophy ($cc-6$) and another with male genital anomalies and an accessory spleen ($cc-3$). We found this schematic cephalad-caudad dichotomization of OM-CM associations to be simpler and easier to implement and to be more acceptable to fetal ultrasonographers than alternative categorizations of celosomias calling for

categorizations such as OEIS or other complexes referred to by other acronyms. The comparison of OM rates in Polissia vs. Rivne-nP is based upon u-rates which are 1.8 and 3.4, respectively, and are indicative of a statistically significantly higher frequency in Rivne-nP. In terms of isolated OM, u-rates in Polissia vs. Rivne-nP are 0.7 and 2.3, respectively, which demonstrates a higher prevalence in Rivne-nP. The overall M-F proportion among OM individuals is 20-6, a clear demonstration of a statistically significant male prevalence, which is likewise evident among subcategories of OM.

Regarding gastroschisis, among 40 individuals, 38 (95%) did not have associated CM, one had associated duodenal atresia (ff-1) and another (ff-2) had renal anomalies. The u-rates in Polissia and Rivne-nP are 2.3 and 3.1, respectively, and the M : F are 0.42 and 1.57, respectively. If confirmed by follow-up monitoring, the female prevalence in Polissia and male prevalence in Rivne-nP will be surprising. We also note that in 23 (58%) of individuals had birth weights under 2500 g. The association of gastroschisis with younger maternal ages is evident in Rivne as well as in the adjoining two provinces. In Rivne, 40% of mothers of gastroschisis infants were under the age of 20 years compared to an overall frequency of 9.45% (Table S8).

Concerning a group of 12 individuals with urinary bladder exstrophy, which excludes one individual (h-3) included in the NTD category and suspected to represent an OEIS complex – the noted CM include spina bifida, OM, anomalous male genitals and anal atresia. Another excluded individual (arj-2) has abdomino-caudal complex anomalies described later. Nearly half of the 12 individuals with urinary bladder exstrophy have a concurrent epispadias, while no instances of epispadias occurred in Rivne that were not associated with an exstrophy of the bladder. Four of the five individuals with epispadias were males. Among this group of 12 individuals, the M-F proportion was 3-5 among individuals from Polissia and 4-0 among those from Rivne-nP. None of the 12 individuals had other concurrent CM, except for one who had undescended testicles. Noteworthy is that all 12 individuals were liveborn and that their birth weights were above 3000 g with the exception of two instances whose birth weight was nearly 3000 g (Data Supplement). It may be of interest to note that in contrast to individuals with urinary bladder exstrophies, the birth weights of infants born near term with isolated microcephaly or recto-anal anomalies are frequently reduced. Among 22 individuals with isolated microcephaly and 20 individuals with isolated recto-anal anomalies delivered at ≥ 38 weeks of gestation, 12 (55%) and five (25%) had birth weights ≤ 3000 g, respectively, (Data Supplement).

The t-rates of CM in Rivne can be compared with the t-rates observed elsewhere in Europe and reported by EUROCAT. As summarized in Table 3 and reported in more detail in Table S5 in the Data Supplement, the pentad-cCM rates in Rivne are among the highest in Europe. On the other hand, the triad-cCM t-rates in Rivne fall within the range of those reported to EUROCAT.

Salient cCM inter-associations and associations with other CM are illustrated in Table 11. The most salient dyads are: cephalad NTD-OM, recto-anal-renal anomalies, renal-limb anomalies, CL/P-OM, spina bifida-OM, spina bifida-limb anomalies, microcephaly-mOPH; CL/P-renal anomalies; and CL/P-limb anomalies.

To complete a perspective of body wall schises or celosomias, we describe seven additional individuals with ectopia cordis, two of which are included among individuals with other cCM. These two individuals with ectopia cordis associated with cCM include one (q-3) who had an encephalocele and was included in the NTD category and another (dd-1) who had complex associated CM suggestive of a pentalogy of Cantrell and was included among other

instances of OM. The remaining five individuals with ectopia cordis (ect-1–5) include individual ect-3 who had severe spinal deformities and reduction anomalies of the left arm and individual ect-4 who had a retroflexed spine and eviscerated organs adjoining the placenta, anomalies that probably represent an instance of a body stalk anomaly complex. Regarding four other individuals with thoraco-abdomino-schises not associated with ectopia cordis, the patterns of associated CM were similar to those associated with ectopia cordis. One of these four individuals was an anencephalic (g-2) with severe “s-like” spine deformity; a second individual (thab-1) was detected by ultrasonographic fetal examination during the 16th week of gestation that failed to visualize the body stalk and demonstrated a fetal spine adjacent to the uterine wall and severe reduction of a lower limb. A third individual (thab-2) had body stalk anomalies detected during the 12th week of gestation and a fourth individual (thab-3) was detected by prenatal ultrasound during the 19th week of gestation and had evisceration without a membranous envelope and amniotic bands not connected to the fetal body. These four individuals with thoraco-abdomino-schisis associated with other CM and fetoplacental anomalies illustrate the difficulties inherent in the categorization of early celosomias. On the basis of a total of 11 instances of thoraco-abdomino-schisis, associated or not with ectopia cordis, the t-rate in Rivne, at a minimum is 0.76 or the t-rate of ectopia cordis at a minimum is 0.48. The computation of M-F proportions was unfeasible due to limitations inherent in early gestational prenatal ultrasonographic examinations.

Among other caudal malformation complexes is included a sole individual (cc-6) with an exstrophy of the cloaca, a large male infant (3900 g) whose mother was not diabetic. One stillborn of ambiguous sex (arj-1) had body stalk anomalies, a caudal regression sequence, absent kidneys, adrenals, spleen, urinary bladder, rectum, and one foot. A liveborn female (arj-2) had urinary bladder exstrophy and absent left kidney, hemipelvis, lower limb, and recto-anal agenesis. She survived and demonstrated normal intellectual and social skills by finishing standard high school and being bi-lingual. Two individuals, both stillborns, had sirenomelia and inherently recto-anal agenesis. The first individual (sir-1) had a nephroblastoma, renal hypoplasia and the second individual (sir-2) was a di-amniotic, di-chorionic twin who had bilateral renal agenesis, absence of the left arm and ambiguous sexual development. His co-twin was a stillborn male whose legs were not visualized by ultrasound.

Regarding recto-anal anomalies, among 45 individuals, six had associated cCM, the first (h-3) had an OM-spina bifida-urinary bladder exstrophy and is included in the NTD group; a second individual (cc-6) had OM-exstrophy of the cloaca; a third individual (m-4) had a spina bifida-diaphragmatic hernia; a fourth (s-5) had Down syndrome-microcephaly; a fifth individual (clr-4) had a CL/P-ectopic kidney dyad; and a sixth individual (hol-29) had holoprosencephaly-mOPH association. Excluding the above-mentioned six individuals and two other individuals with sirenomelia (implicitly associated with recto-anal anomalies), there are 37 instances of recto-anal anomalies in Rivne, 14 of which are from Polissia and 23 are from Rivne-nP, which translates in corresponding u-rates, at a minimum, of 1.93 and 3.15, respectively (Table S2). Among these 37 individuals, 20 had isolated recto-anal urinary bladder exstrophy except that 14 had concurrent fistulas. The u-rates of isolated recto-anal CM in Rivne, Polissia and Rivne-nP are, at a minimum, 1.38, 0.97 and 1.78 respectively (Data Supplement). It is also evident that the birth weight of infants born near term with non-syndromic recto-anal anomalies is often diminished – 25% of such infants had birth weights under 3000 g. Another contrast concerns M-F among infants with and without

Table 11 Non-syndromic associations of congenital malformations^a, Rivne Province, Ukraine (2000–2009)

Category	CTW	CEPH	SB	MIC	mOPH	CL/P	OM	GSTR	ESOPH	DIAPH	RENAL ^b	BLEXTR	RECTAN	LIMB
P	3	71	102	46	26	78	25	17	26	24	62	9	16	31
nP	5	45	60	25	9	79	31	23	17	26	63	5	29	49
LB	1	0	72	69	30	129	20	17	32	27	85	14	39	58
S	1	19	10	2	3	3	7	2	3	9	14	0	6	4
ToP	5	87	70	0	2	21	24	19	7	13	23	0	0	15
SA	1	10	10	0	0	4	5	2	1	1	3	0	0	3
U	2	34	22	0	0	2	18	5	3	6	11	0	3	9
M	1	32	73	35	16	100	28	16	22	26	69	8	22	37
F	5	50	67	36	19	55	10	19	18	18	45	6	20	34
Twin	0	5	3	1	0	0	1	1	1	0	2	0	1	4
CTW	8	0	1	0	0	0	1	0	0	0	0	0	0	0
CEPH	0	116												
SB	1	0	162											
MIC	0	0	0	71										
mOPH	0	1	0	5	35									
CL/P	0	2	2	4	4	157								
OM	1	8	6	2	2	6	56							
GSTR	0	0	0	0	0	0	0	40						
ESOPH	0	4	0	2	2	3	0	0	43					
DIAPH	0	3	1	1	2	3	3	0	2	50				
RENAL ^b	0	2	3	4	2	5	3	1	4	3	125			
BLEXTR	0	0	1	0	0	0	1	0	0	0	1	14		
RECTAN	0	0	2	1	1	1	2	0	5	2	8	2	45	
LIMB	0	1	5	4	2	5	2	0	1	1	7	1	4	80

^aThe regional and perinatal observations are presented above the diagonal of grey cells. In the grey cells are given the total numbers of individuals with the particular malformation (including those with holoprosencephaly). The numbers below the diagonal of grey cells reflect the associations with other malformations. Individuals with multiple malformations may be represented in multiple cells.

^bIncluded are individuals with renal agenesis, hypoplasia, cystic kidneys and excluded are hydronephroses and ureteral obstructions.
 ANOR, anorectal anomalies; BLEXTR, urinary bladder exstrophy; CEPH, cephalic neural tube defects; CL/P, cleft lip/palate; CTW, conjoined twins; DIAPH, diaphragmatic defects; ESOPH, esophageal anomalies; F, female; GSTR, gastroschisis; LB, live birth; LIMB, limb reduction defects; M, male; MIC, microcephaly; mOPH, microphthalmia; nP, non-Polissia region; OM, omphalocele; P, Polissia region; RENAL, renal anomalies; S, stillbirth; SA, spontaneous abortion; SB, spina bifida; ToP, termination of pregnancy; U, unknown sex.

concurrent fistulas – among those with fistulas, males were prevalent 5-1 and among those without fistulas, the M-F was 6–8. Among 15 individuals with recto-anal anomalies associated with other CM, the M : F was 1.03 and the most salient associations were with esophago-gastro-intestinal anomalies (ari-24, 26, 27, 28, 30, 33, 34) in particular esophageal (ari-24, 27, 33, 34). Other individuals with recto-anal anomalies include one individual with body stalk anomalies (arj-1), and another individual with caudal dysplasia and lower limb reduction anomalies (arj-2).

Conjoined twins, teratomas

Among 145 437 births, there were 347 MF, 423 MM and 419 FF twin pairs (Table S4). The MM : FF pairs ratio is 1.01 and is virtually the same in Polissia and Rivne-nP as is the overall frequency of twin pairs. There were five instances of acardia among the 842 same-sex pairs (0.59%). Four of the five acardics were noted among 415 same-sex twin pairs in Polissia (0.96%). Eight conjoined twin pairs were born in Rivne during the 2000–2009 period, a ninth set was born during 2010 and five other pairs of conjoined twins were born in the two adjoining provinces of Rivne. The u-rate in Rivne is 0.55 and in the two adjoining provinces combined is 0.19 (Table S6). Family histories of conjoined twins show a considerable frequency of twinning events (Fig. S4).

An analysis of teratomas also included observations in the two provinces adjoining Rivne. The u-rate in Rivne is 0.76, which is similar to the 0.77 u-rate in the two adjoining provinces combined (Table S6). Among a total of 29 teratomas in the three provinces, 25 (86%) were sacro-coccygeal and the M-F proportions in Rivne and adjoining provinces were similar, 7–19 and 7–15 respectively. Among the 29 teratomas, two (7%) included tissues characteristic of teratoblastomas, one was a sacro-coccygeal (vter-11) and the other a cervico-pharyngeal teratoma (neo-1).

Concerning CM-neoplasia associations, in addition to a pharyngeal congenital teratoblastoma (neo-1) mentioned above, there were two other instances: an ependymoma (clr-5) associated with cataracts and a nephroblastoma (sir-1) associated with renal hypoplasia and sirenomelia.

DISCUSSION

This investigation seeks to document population-based rates of congenital malformations (CM) computed with adherence to EUROCAT and international standards in the Rivne province of Ukraine, which was impacted by the IR following the 1986 Chernobyl disaster. The investigation concerns eight CM visually evident at birth and collectively referred to as core-CM (cCM) as well as surveys concerned with three prominent teratogenic risk factors in Rivne; consanguinity rates, alcohol, and ionizing radiation (IR). The object of this discussion is to emphasize contrasts of the frequencies and patterns of cCM in Rivne compared with those in the rest of Europe as well as to compare observations in Polissia with those in the rest of the province. The nature of each of the cCM noted is consonant with reports by recognized experts (Willis 1962; Warkany 1971; Stevenson & Hall 2006). Concerning the health effects of exposure to low levels of IR, this subject is expertly summarized by the Committee on Biological Effects of Ionizing radiation, which was established by the National Research Council (BEIR V Report 1990). The object of this discussion is focused on rates and patterns of cCM in Rivne in the context of related observations elsewhere.

Blastopathies

“Blastopathy” and “celosomia” are notions we find useful to convey an overview of the cCM observed in Rivne. Blastopathies are

anomalies that arise prior to embryonal implantation and organogenesis and the term “celosomia” refers to blastopathies characterized by a failure of closure of the anterior body wall reflecting abnormalities of the embryonal folding process (Schinzel et al. 1979; Czeizel and Opitz 1981; Martinez-Frias et al. 1997; Opitz et al. 2002). The array of blastopathies includes monozygotic twinning, conjoined twinning, acardia, teratomas, NTD, OM and urinary bladder exstrophy, which are emphasized in this report as well as thoraco-abdomino-schisis-ectopia-cordis, body stalk defects, diaphragmatic anomalies, renal agenesis, esophageal-gastric-intestinal-colonic-recto-anal anomalies, cloacal dysgenesis-exstrophy, recto-anal-sacral and other caudal anomalies including sirenomelia and lower limb dysgenesis, among other complexes. The unifying notion implicit in blastopathies, in particular celosomias, is that these CM are the result of an altered process of embryonic folding (Duhamel 1963; Stevenson & Hall 2006). In brief, prior to the onset of embryonic folding process, during gastrulation, the embryonic disc develops in a cephalad-caudad and dorsal-ventral axes followed by the emergence of embryonic ecto-endo-meso-blast layers. The mesoblast becomes interposed between the expanding ecto and endoblast layers of the embryonic disc with the exception of two didermic sites, the oral and cloacal membranes. Dorsally, the ectoblast forms a medial notochord. Somites and nephrotomes develop laterally and extend peripherally to give rise to lateral laminae, which divide to form dorsally the amniotic and ventrally the celomic cavities. The embryonal folding process results from a more vigorous dorso-cephalic growth of the tri-laminar germ disc, which induces the transformation of a flat embryonal plate into a cylindrical ventrally bent embryo. The faster growth of the cephalad-dorso-cephalic area induces a cephalic folding from which the ventral zone will give rise to the heart, foregut and anterior diaphragm. Normally, the concurrent cephalad, lateral, and caudad embryonic folding converge to form an apex or omphalon preceded by a body stalk that evolves into an umbilical stalk to become the base of the umbilical cord. Altered growth and closure of the dorsal neural tube may impede normal embryonal ventral folding and result in celosomias, as is probably reflected in the preferential cephalad-NTD-omphalocele associations observed in Rivne. Symmetric anterior body wall growth failures give rise to a “middle celosomia” or omphaloceles (OM). Less symmetric folding failures may result in “upper” (cephalad) or “low” (caudad) celosomias. The “upper” celosomia group, for example, includes the pentalogy of Cantrell complex and the “low” group includes complexes like the OEIS defined earlier. Generally, celosomias are detected in early gestation and impacted infants are non-viable, which enhances a tendency for prenatal diagnosis detection to be promptly followed by terminations of pregnancy and descriptions of the anomalies noted to be limited. Often, descriptions allude to “suspected” instances of OEIS or other CM complexes without substantiation of such conclusions. One alternative is to rely on schematic descriptions such as outlined above, which prompt the actual description of anomalies noted during fetal ultrasound or post-mortem examinations. “Tail end” embryonal anomalies arise after the formation of the embryonal axis and closure of the posterior neuropore during the 4th week. The tail-bud during the 5–6th week, the Hensen’s node and the caudal end of the cord are in continuity with the notochord and the post-anal dimple marks the site of the final closure of the posterior neuropore and site of post-anal sinuses. As the retrogression of the tail occurs during the 7–8th weeks, duplications and secondary posterior neuropores and other anomalies are relatively common in human embryos. These malformations of the hind end of the embryo show little constancy of patterns and include absence of one or both lower limbs and

sirenomelia. Our observations in Rivne demonstrate an excess of “cephalad” cCM and no evidence of an excess of “caudad” or “tail end” malformations.

Rates

A perspective highlighting frequencies of cCM demonstrates that those of pentad-cCM in Rivne are among the highest reported to EUROCAT. Also, the rates in Polissia are statistically higher than in the rest of Rivne (Tables 3 and S5). After Polissia, the next highest rates of conjoined twins, NTD, microcephaly and mOPH noted in Europe are reported from Northern England, South West England and Wales. Two other independent investigations determined that in Finland the rates of conjoined twins and sacro-coccygeal teratomas also are among the highest in Europe although they are not higher than in Polissia (Mutchinick et al. 2011; Pauniahio et al. 2013). The mentioned regions in the UK and the central regions of Norway and Sweden are, like Polissia, particularly impacted by Chornobyl IR (Gillett et al. 2001). Although teratoma rates are not reported to EUROCAT, other investigations in Northern England demonstrated a prevalence of sacro-coccygeal teratomas of 0.37 compared to that in Rivne of 0.62 (Table S6). The frequency of triad-cCM in Polissia or Rivne is not distinct from elsewhere in Europe.

The frequency of NTD and NTD-OM preferential associations in Rivne and in Polissia in particular, is among the highest in Europe. On the other hand, an extensive review of OM in Europe by Calzolari et al. (1995, 1997) determined that the total OM prevalence is 2.52 or nearly the same as that in Rivne. The NTD-OM preferential association, as presented later, is more frequent in regions with high NTD rates, particularly in Polissia and the British Isles. Regarding individuals with “para-omphaloceles” or gastroschisis, this cCM represents a localized aplasia or dysplasia of the abdominal wall lateral and generally to the right of the umbilicus and is unrelated to the formation of the umbilicus or amniotic sac. In Rivne, 43% of instances of gastroschisis were liveborn and as noted in the Data Supplement another 48% of instances were associated with induced pregnancy terminations. A worldwide survey of 3322 instances of gastroschisis showed that 86% had no associated CM compared to 95% in Rivne. The 2.34 and 3.13 t-rates of gastroschisis in Polissia and Rivne-nP are within the range of 0.89–6.22 t-rates reported to EUROCAT from across Europe (Table S5). Another celosomia in the cCM triad is urinary bladder exstrophy, which is discussed later jointly with other caudad or “tail end” blastopathies.

Among “high” celosomias are included instances of thoraco-schisis, which often is associated with ectopia cordis, and both of these anomalies are included in the spectrum of the pentalogy of Cantrell complex. In Rivne, thoraco-abdomino-schisis-ectopia-cordis complexes are nearly as frequent as urinary bladder exstrophies. Recto-anal anomalies are the most frequent category of caudal or “low” celosomias, followed in frequency by urinary bladder exstrophies. Urinary bladder exstrophy rates in Rivne fall within the range of rates in Europe reported to EUROCAT. In contrast to individuals who are liveborn near term with isolated urinary bladder exstrophies and birth weights near the norm, those with isolated recto-anal anomalies who are born near term have reduced birth weights (Data Supplement).

Twinning and female prevalence

Many investigations demonstrated that children from multiple births, in particular monozygotic twins, are at a higher risk to have CM. A population-based cohort study by Li et al. (2003) demonstrated a relative risk ratio increase for CM of 1.9 for twins, 2.7 for triplets and 4.6 for quadruplets and higher. The rate of anencephaly

among singletons and multiple births was 1.1 and 2.9, respectively, and equivalent to a statistically significant risk ratio of 2.64 in contrast to spina bifida without anencephaly, which had a similar frequency among singletons and twins. The proposition forwarded by Schinzel et al. (1979) and grounded in solid clinical observations holds that blastopathies reflect mechanisms in common with those of the monozygotic twinning process. Experts assert that twinning impacts approximately 1 in 40 (2.5%) individuals and therefore, in Rivne, an estimated 3636 twin infants were expected to have been born, in contrast to the 2378 (1.94%) observed (Phelan and Hall 2006). This contrast suggests that the frequency of twinning in Rivne is unlikely to be elevated. Experts also assert that population rates of dizygotic twinning are higher in proportion to the number of pregnancies reflecting advanced maternal age or reliance on IVF-ART (in vitro fertilization – assisted reproductive technology) procedures. IVF-ART procedures are rarely performed in Rivne and although maternal ages at delivery tend to be higher in Polissia than in Rivne-nP, we conclude that these factors are unlikely to significantly impact the observed twinning patterns in the province. Regarding conjoined twinning, the association with an altered monozygotic twinning process is self-evident, a process that may also be associated with the pathogenesis of sacro-coccygeal teratomas. The NTD-twinning association is also well established (Table S4) (Windham and Sever 1982; Garabedian and Fraser 1994; Kallen et al. 1994). The degrees of twinning associations with various subcategories of NTD and among relatives of conjoined twins, teratoma and NTD individuals are discussed below along with other aspects of the nosology of cCM.

In humans, the proportion of males at birth is generally slightly above 0.51 and is remarkably consistent among different populations over time. The sex proportion is slightly lower among twins and higher-order multiple births than among single births. Among monozygotic twins the M : F is lower than among dizygotic twins. Among monozygotic twins, the frequency of male pairs and even more so among conjoined twins is lower. A prevalent interpretation is that dichorionic, monoamniotic and conjoined twins reflect increasingly late embryonic duplications resulting in conjoined or twins pairs (Derom et al. 1988; James 1988; Phelan and Hall 2006). The question arises whether females are more prone to embryonic splitting since during early embryonic formation their development is slower, a point elaborated upon later.

Among the leading investigations of sex differences in the prevalence of CM are those by Lary and Paulozzi (2001) and Shaw et al. (2003). Both studies demonstrated, as observed in Rivne, a female prevalence among instances of NTD as well as among instances of microcephaly. Female prevalence among microcephalic individuals was also demonstrated by two independent investigations in Hungary (Abdel-Salam and Czeizel 2000; Szabo et al. 2010). It is provocative that several reviews of reports of microcephalia vera demonstrating female prevalence fail to stress this phenomenon (Warkany et al. 1981, chapter 1). The study by Shaw et al. (2003) included an analysis of individuals with mOPH among whom females were likewise prevalent in contrast to Kallen et al. (1996) who found no evidence of sex preference. Female prevalence among conjoined twins and teratomas, as noted in Rivne, is also well known (Table S2) (Warkany 1971; Phelan and Hall 2006). A repeatedly demonstrated phenomenon, also evident in Rivne, is a provocative shift away from the female prevalence among cephalad-NTD compared to spina bifida. An analysis of 226 fetuses with NTD demonstrated clear contrasts of M : F ratios among NTD reflecting their location. Among anencephalics (exclusive of mero-acrania), spina bifida above the lumbar spine and spina bifida below the thoracic spine the M : F ratio was <0.6, 0.4 and >1.4. Among

individuals with mero-acrania (intact posterior skull and foramen magnum) the M : F ratio was 1.08 (Tapper and Lack 1983; Seller 1987, 1995). Another shift of M-F proportions is noted among encephaloceles when subdivided as occipital and non-occipital. In Rivne and two adjoining provinces there were 31 and 36 instances of encephaloceles among which 20 and 21, respectively, were non-syndromic occipital encephaloceles. The M-F proportions in Rivne and the two adjoining provinces were 9–12 and 12–12, respectively, compared to non-syndromic occipital encephaloceles which were 5–9 and 5–9, respectively. The total encephalocele population-based rates in Rivne and two adjoining provinces combined were 2.13 and 1.54, respectively; and the respective non-syndromic occipital encephaloceles were 1.38 and 0.90 (Table S9). Another shift away from a female prevalence evident among sacro-coccygeal teratomas is noted among individuals with teratomas in other locations (Tapper and Lack 1983; Stevenson & Hall 2006). An analysis of death certificates of children with teratomas by Fraumeni et al. (1973) determined that among 198 instances, 56 were malignant and that the M-F proportions reflected their location. The M-F proportions were 24–60, 5–17, 15–14 and 4–5 among instances of sacro-coccygeal, retroperitoneal, cranial and cervico-pharyngeal teratomas, respectively. These investigators also noted a high frequency of anomalies associated with sacro-coccygeal teratomas, in particular of the lower vertebrae and pelvic anomalies attributable to twinning or duplications of the hind gut. Among the 198 teratoma patients investigated by Fraumeni et al. (1973), five individuals were twins and one was a triplet.

Both in Rivne and Denmark, investigations did not produce evidence of an OM-twinning association (Bugge 2010). However, OM as a component of the OEIS complex is associated with twinning and likewise with body stalk anomalies (Bugge 2012). Furthermore, two investigations led by Mastroiacovo et al. (1992, 2007) and by Lee et al. (1999) summarized autopsy and clinical findings of the OEIS complex with an emphasis on its association with monozygotic twinning. The cited studies by Mastroiacovo noted that large body wall defects may be reported as body stalk anomalies or as a large gastroschisis. Perhaps this possibility may be reflected in observations by Hwang and Kousseff (2004) of an elevated frequency of twins among patients with OM and gastroschisis. Reid et al. (1986) also noted elevated twinning rates among patients with gastroschisis when associated with amyoplasia-related anomalies. Also, Moore and Nur (1986) noted an OM-twinning association and not with gastroschisis. These complexities probably reflect the heterogeneity of OM and inadequacies of the current classifications.

Of note is that among recto-anal anomalies, instances with and without fistulas have different M-F proportions, which in Rivne are 5–1 and 6–8, respectively. In Rivne and among 1846 cases of anal atresia surveyed by Cushieri (2001), 44% and 36% of instances were isolated anomalies, respectively (Table S2). Among recto-anal anomalies, 10% are above the level of the levator ani muscle and are prevalent among males. In Rivne, the M : F ratio among those with supralevator and infralevator anal atresias was 6.2 and 2.3, respectively.

Preferential associations of CM

Non-syndromic CM associations are illustrated in Table 11. The most frequent CM dyads are: cephalad-NTD-OM, renal-recto-anal; renal-limbs; spina bifida-OM; and CL/P-OM. An expanded analysis of NTD-OM dyads in Rivne and in two adjoining provinces showed 27 instances – two were encephaloceles (ov-2, 5). This group of 27 individuals included 17 (63%) instances of cephalad-NTD, among which eight (47%) had cranio-rachis-schisis, and the overall M-F

proportion was 2-9 (Table S7). These preferential OM associations with cephalad-NTD and the prevalence among females are similar to observations by McKeown et al. (1953), Smithells et al. (1964), Windham and Sever (1982), and Doyle et al. (1990). An extensive analysis by Calzolari et al. (1995, 1997) showed that in the British Isles (UK and Ireland) among 70 OM-NTD dyads, 48 were associated with cephalad-NTD, 21 with spina bifida and six with encephaloceles. In Continental Europe, only 18 individuals had an OM-NTD dyad and among these, 12 had spina bifida and five had cephalad-NTD, a reversed proportion from that observed among instances in the British Isles. In this context, the number of NTD-OM dyads observed in Rivne and two adjoining provinces is probably greater than in the rest of Continental Europe combined. The studies by Calzolari et al. (1995, 1997) demonstrate that the high frequency of NTD-OM dyads in the British Isles reflects high frequency of NTD and are not correlated with the frequency of OM.

In Rivne there were 38 other instances of OM, not associated with NTD, 13 of which represent non-syndromic OM-CM associations. Schematically, most of these associated CM were cephalad with respect to the OM (Data Supplement). Regarding celosomias, these are increasingly detected by prenatal ultrasonography during early stages of pregnancy and often are incompatible with postnatal survival, thus terminations of pregnancies frequently follow. These circumstances foster relatively limited clinical descriptions. There also is a tendency to categorize early complex celosomias as suspected instances of complexes such as OEIS rather than description of actual visualized anomalies. An example of an alternative approach was used by Mastroiacovo et al. (1992) who studied a large number of “Gross Body Wall Defects” and categorized these as OM or gastroschisis inclusive of all degrees of limb reductions or the presence of sirenomelia. Among the 215 infants, 19% had NTD and 5.6% had a twin. Other investigators point out that an OM-twinning association is a landmark of OEIS (Martinez-Frias et al. 2000; Keppler-Noreuil et al. 2007). In our analysis, we tested a schematic categorization of OM-CM associations and found that the proportion of OM-cephalad CM and OM-caudad CM was 9-2. To what extent such topologic categorization of OM associations with other CM is nosologically informative remains to be seen. Of interest is that Russo et al. (1993) proposed that the Limb-Body-Wall complex consists of at least two distinguishable phenotypes. The first phenotype, which we refer to as cephalad-LBW includes encephalocele or anencephaly associated with facial cleft and a second phenotype, we refer to as caudad-LBW, which excludes cranio-facial defects and includes urogenital, recto-anal, lumbosacral meningocele, fetoplacental attachments, short cord, and lower limb anomalies. Representative clinical observations in Rivne of the caudad-LBW complex are two infants (arj-1, arj-2) the second of which survived and is the high-school graduate described earlier.

In Rivne and elsewhere, gastroschisis is for the most part an isolated anomaly. However, Reid et al. (1986) demonstrated an association with twinning and amyoplasia. These investigators noted that in a series of 216 patients with amyoplasia, 5% had gastroschisis and another 6% had other defects, mainly bowel atresia and/or trunk wall musculature anomalies. In Rivne, the above associations have not been documented thus far. On the other hand, the well-known association of gastroschisis with younger maternal age at delivery is evident in Polissia, Rivne-nP as well as in the provinces adjoining Rivne (Table S8) (Curry et al. 2006). Also, gastroschisis is reported to be prevalent among males (Boyadjiev et al. 2004; Gambhir et al. 2007), although in Rivne, the M-F proportion is 16-19 and in Polissia and Rivne-nP is 5-12 and 11-7, respectively.

The array of cCM investigated, based on the number of observations, should be expanded to include instances of thoraco-abdomino-schises and ectopia cordis. The estimated rate of ectopia cordis in Rivne is, at a minimum 0.48 or several-folds higher than those reported by other studies (Carmi and Boughman 1992; Botto et al. 2011). Regarding caudal blastopathies, the perspective is complex. In addition to exstrophy of the urinary bladder, recto-anal anomalies and sacro-coccygeal teratomas, also noted are instances of combinations of exstrophy of the cloaca, sacral dysgenesis, sirenomelia, and lower limb dysgenesis. Furthermore, an analysis by Kallen et al. (1991) underscores that sirenomelia and cyclopia are prevalent among females and twins, which is conducive to considerations concerning holoprosencephaly, which was excluded from this analysis.

A salient characteristic, probably of most blastopathies, is that survivors, including individuals with the most severe CM complexes, can develop their full intellectual potential (Opitz et al. 2002). This fact is illustrated by a girl with severe caudal dysplasia (arj-2) and by an individual with sirenomelia studied by Pinette et al. (2005).

Teratogenic risks

This descriptive epidemiology study is not designed to investigate cause-effect relationships although it does provide some clues to orient prospective cause-effect investigations and prevention interventions. Three categories of teratogenic risk factors were addressed by surveys included in this analysis: gene mutations, alcohol, and IR. Regarding gene mutations, our concern is that Polishchuks represent a population isolate, a condition that would result in higher rates of consanguinity and homozygosity. This view is sustained by the survey of isonomy rates of county-specific family surnames of newborns. Isonomy rates are an indirect index of endogamy and consanguinity and the analysis summarized in Figure S1 shows that isonomy rates are highest in three northern counties of Polissia (Colantonio et al. 2003). The implications of this observation are described further in the context of nosology considerations.

Regarding alcohol teratogenesis, a survey of alcohol consumption by pregnant women and an analysis of Fetal Alcohol Spectrum Disorders frequencies demonstrated that neither is prevalent in Polissia. The results indicate that alcohol is unlikely to be a main teratogenic cause of the higher rates of microcephaly and mOPH noted in Polissia (Tables 4,5,S2 and S3).

Regarding IR, it is undeniable that since 1986, pregnant women and children in Polissia continue to be exposed to IR. Official estimates of levels of IR are based on measurements reflecting ^{137}Cs , and reports rarely emphasize contrasts between Polissia and the rest of Rivne. Estimates of ingestion of ^{137}Cs are, with few exceptions, not based on diets consumed in Polissia. With these considerations in mind, our past surveys demonstrated that in addition to ingestion, inhalation is an additional mode of incorporation of IR. In Polissia, smoke from frequent forest fires, incineration of biomass after harvests, and burning wood for cooking and heating are prevalent. Another prominent source of exposure to IR in Polissia is consumption of water from shallow wells, local fish, wild mushrooms and berries, and locally produced potatoes and dairy products (Dancause et al. 2010). We calculated the daily intake of ^{137}Cs by pregnant women to be 268 Bq. Other investigators calculated a daily intake in Rivne at 571 Bq, the highest among 25 regions investigated in Ukraine, including Kyiv and Zhytomyr, which are most proximal to the Chernobyl site (Shiraishi et al. 2008). Such estimates are above the recommended 210 Bq daily upper limit for adults advocated by the Ukrainian Ministry of

Health (Tables 7,9) (Decree 106, 1991). In Ukraine, the highest index of soil-to-food chain transfer of ^{137}Cs is in Polissia (Likharev et al. 1996, 2000). Our surveys also show that in fact, nearly 50% of pregnant women residing in northern (distant) Polissia have incorporated levels of ^{137}Cs above the upper limits considered as safe by the Ukrainian Ministry of Health (Table 7 and Fig. S2). Furthermore, these measurements of incorporated ^{137}Cs do not account for additional incorporated nuclides such as ^{90}Sr found in Polissia plants as demonstrated by our survey of potato plants, which represent a major dietary staple.

Skepticism and denials of teratogenic impacts of Chernobyl IR are centered on matters of dosimetry. The official view of many agencies is summarized in a 2006 Joint News Release by WHO/IAEA/UNDP (World Health Organization, International Atomic Energy Agency and the United Nations Development Programs) which asserts “. . . Because of the relatively low doses to residents of contaminated territories, no evidence or likelihood of . . . effect on the number of stillbirths, adverse pregnancy outcomes, delivery complications or overall health of children . . . A modest but steady increase in reported congenital malformations . . . appears related to better reporting, not radiation” (Hoffman and Fleming 2005; IAEA 2006). Until the present, such assertions remained untested by independent population-based investigations of well-defined populations living in relative proximity to the Chernobyl site and using established international methods. This report takes into account the manifest pervasive skepticism and presents the observations in Rivne in detail, which is further expanded in a Data Supplement.

Official assertions generally rest upon interpretation of investigations sponsored by ABCC (Atomic Bomb Casualty Commission) in Hiroshima and Nagasaki. Among the most influential ABCC sponsored investigations are the classic reports by Professor J. Neel and associates. Virtually all such investigations were focused on genetic rather than teratogenic impacts of the atomic blasts. The studies were initiated nearly 5 years after the blasts and concerned children unexposed to radiation whose parents survived the post-war circumstances. The investigation showed that the radiation impacts on parents were not statistically significantly associated with higher rates of congenital malformations in their offspring (Neel 1958, 1994; Neel and Schull 1991). We know of two sets of ABCC sponsored investigations focused on teratogenic impacts of the atomic bombs. The first investigation concerned 205 nearly 5-year-old children exposed *in utero* to the bomb blasts. Clinical examinations without a concurrent control group showed that 24 (12%) had anomalies including two instances of Down syndrome, six (3%) instances of microcephaly associated with mental subnormality, four instances of dislocations of the hip, three children were suspected of having congenital heart alterations; and nine others who had a variety of anomalies, some of which would currently not be categorized as CM (Plummer 1952). Another set of investigations was focused on mental retardation. The corresponding reports include information on microcephaly but do not focus on concurrent CM (Wood et al. 1967a, 1967b, 1967c; Otake and Schull 1984, 1998; Schull and Otake 1999). The study group consisted of 1613 children who were exposed to the atomic blasts during various states of gestation. The study group was subdivided according to the distance of the parent from the hypocenter of the blasts. The subjects were grouped as proximal to the blast (within 2000 m) and distal (beyond 3000 m). Children exposed in the 2001–2999 m category were excluded from the study “to create a distinct distance between the proximal and distal groups”. Significant effects were evident among those who survived infancy and were exposed at 8–15 and 16–25 weeks after ovulation, namely, reduction of cognitive function, severe mental retardation, and reduction of head

size or frank microcephaly defined as head circumferences less than two SD from the mean. In 1987, it became possible to assign updated DS86 dose estimates to individual cases. Such an analysis estimated a decrease in IQ score at 25–29 IQ points per GY estimated uterine absorbed dose. The authors noted that doses as low as 10 cGY can impact migration of neocortical neurons. These investigations also established the widely accepted notion that the period of maximum sensitivity to radiation induced human cerebral anomalies is between 8 and 15 weeks of gestation. However, the investigators also point out that with respect to microcephaly, such a generalization did not hold.

Following the 1986 Chernobyl disaster, a series of clinical observations indicated a rise of the frequency of CM, in particular anencephaly. The impact of these reports was reviewed and eclipsed by an analysis of CM rates among populations residing in regions of Western Europe remote from Chernobyl. No evidence of a generalized detectable increase of the prevalence on CM within 2 years following the Chernobyl disaster was evident (Dolk and Nichols 1999). Regarding IR exposures from nuclear power plants, three investigations are of particular interest. Two independent and nearly concurrent investigations sponsored by the CDC (US Centers for Disease Control and Prevention) sought to determine teratogenic impacts of IR stemming from the Hanford Nuclear complex in Washington State. One investigation detected higher NTD rates in two counties proximal to the nuclear complex and the second investigation demonstrated higher rates of NTD associated with parental occupational exposures to low-level IR. The investigators considered the research results to be sound but rejected them as “falsely positive conclusions”. The results of the first study were rejected mainly because they could not be explained by reported patterns of IR emissions from the plant. The results of the second investigations were rejected because they were contradictory to conclusions drawn from the cited ABCC investigations (Sever et al. 1988a, 1988b). A third investigation concerned fathers employed at the Sellafield Nuclear Complex in the Cumbria region of Northern England. The results showed a positive association between total exposure to external IR before conception and a higher risk for stillbirths with congenital anomaly and highest for stillbirths with NTD (Parker et al. 1999). To our knowledge, this investigation has not been repeated. However, we note that the rates of NTD, microcephaly, mOPH, and conjoined twin rates in Northern England and Wales reported to EUROCAT are concurrently among the highest in the UK and Europe and approach the rates noted in Rivne (Table S5). It is relevant to note that the impact of the Chernobyl fallout on the UK was particularly significant on regions in Cumbria in Northern England, Wales, and Southwest England (Gillett et al. 2001). In the context of slightly reduced head circumferences among neonates born in Polissia compared to those born in Rivne city, two independent studies in Scandinavia, another region of Europe significantly impacted by Chernobyl IR, drew our attention. Both investigations, one in Norway and the other in Sweden, note that individuals most exposed *in utero* to Chernobyl IR show significant negative impacts on their cerebral functions (Almond et al. 2009; Heiervang et al. 2010). The observations in Scandinavia combined with those in Polissia indicate that further investigation of OFC measurements among Rivne neonates and children need to be expanded.

Pathogenesis

The nature of the cCM observed in Rivne is expertly reviewed and summarized by Warkany (1971) and Stevenson and Hall (2006). Likewise, a review concerning the impact of twinning is elegantly presented by Phelan and Hall (2006). A large study by Windham

and Sever (1982) explored in detail the NTD-female and NTD-twinning preferential associations. The notion that blastopathies reflect an altered process of twinning was advanced by Schinzel et al. (1979), and this has been sustained by other investigators (Czeizel and Opitz 1981; Carmi and Boughman 1992; Martinez-Frias et al. 1997). This notion is rooted in embryologic observations summarized by Newman (1917, 1923). Newman and other students of embryogenesis established that in vertebrates, early cleavage cells appear to be totipotent and essentially are germinal in character and able to become a new apical point to establish new axes of polarity and symmetry. Newman highlighted experiments by Spemann and Falkenberg (1919) demonstrating that twins may be produced experimentally by various means that lower the embryonic developmental rate. Clinical observations combined with the notion of “arrested or delayed development” led to propositions of impacts of anomalous X chromosome inactivation patterns proposed by James (1988) and more recently reviewed by Curry et al. (2006, chapter 23).

In the context of failures of neural tube closure being more prevalent among females, Seller (1987, 1995) points out that the neural tube is formed before gonadal differentiation and that although both sexes start to cleave concurrently, males reach the blastocysts stage before females which may result in a greater propensity for NTD among females. There is evidence that in the mouse, males reach the blastocysts stage before females and that in bovine embryos, females develop slightly slower than males, observations that led to the notion of “epigenetic lag” or “developmental drag” which impact the process of neural folding and may be attributed to the inactivation of an X chromosome in females. Further investigations suggest that the female excess among human instances of anencephaly or cranial-NTD probably are not due to gonadal hormones or slower overall female developmental rate or an excess of male deaths, but instead, probably reflect the presence of two X chromosomes, a cause of what is referred to as an “inactive X sink”. This proposition points out that females methylate most of the DNA in the inactive X chromosome after every cell division (“inactive X sink”), which reduces methylation elsewhere (Juriloff and Harris 2012). Some investigators speculate that the “inactive X sink” relates to the female “development drag”. Currently, such issues are in the research domain of molecular embryology and planar cellular polarity (PCP) concerned with epithelial cellular signaling mechanisms controlling early developmental stages. Disturbances of the PCP process are conducive to neoplasia and prenatally, to alterations of the gastrulation process, twinning, somite and cilia development, duplications, anomalies of usual symmetry or asymmetry patterns, failures of NTD or body wall closures, and CM syndromes such as Meckel-Gruber and *situs inversus*, among others (Ueno and Greene 2003; Wallingford 2006; Wu et al. 2011; Vandenberg and Levin 2012; Yang 2012). Investigations show that impacts on PCP may alter patterning and polarity of neurons, perhaps a point relevant to the observed elevated rates of microcephaly in Polissia. In any case, the Polissia high rates of pentad-cCM are not associated with an increased frequency of monozygotic twinning, while higher rates of conjoined twins are associated with high rates of pentad-cCM. It appears that the causes of monozygotic twinning per se and alterations of the process giving rise to conjoined twins and blastopathies may reflect distinct risk factors.

Female prevalence among instances of sacro-coccygeal teratomas and conjoined twins is well established. There are occasional observations of individuals with an incorporated conjoined-twin or fetus-in-fetu and a concurrent teratoma. It is unlikely that such concurrent anomalies represent independent

events particularly in instances where DNA markers were identical (Du Plessis et al. 1974; Spencer 2001; Gilbert-Barness et al. 2003; Higgins and Coley 2005). The notion of “fetus-fetus” as a destructive process was elaborated upon by Knox (1974) who proposed that it is a cause of NTD reflecting the destruction of one fetus with the surviving fetus having NTD anomalies. A linkage of anencephaly, spina bifida, twins and teratoma was proposed by Rogers (1976) who, in brief, notes that twins may develop epithelial defects that may be conducive to embryonic adhesions and destruction of the interamniotic partition resulting in a secondary mono-amniotic pregnancy. Thus monozygotic or dizygotic pregnancies are liable to undergo fetus-fetus destructive interactions. Under such circumstances, one embryo may be reabsorbed or “vanish” and the remaining twin become malformed or a teratoma. Such hypotheses are consistent with observations that NTD affected twins are usually discordant for the anomaly and generally sex-concordant. This assertion is sustained by observations in Rivne where among eight twin-NTD discordant pairs, six were concordant for sex (Table S4). Edmonds and Hawkins (1941) noted that the incidence of twinning whether measured by the percentage of families with twins or by the ratio of twin births to total births is similar and consistently high in families with childhood teratomas – a suggestion that the pathogenesis of teratomas and twinning includes shared elements. This observation is also consistent with observations in Rivne of high frequency of twinning events among relatives of NTD and conjoined twins individuals (Figs 3 and S4). These hypotheses were framed with awareness that the frequency of NTD and dizygotic twins among populations are highly variable and that the rates of both are correlated. Most provocatively, a significant and unexplained correlation in frequencies of NTD and dizygous twinning was detected by one of the earliest investigations of these anomalies implemented by the World Health Organization in 24 centers in 16 countries (Stevenson et al. 1966). Another large investigation by Windham and Sever (1982) demonstrated that: NTD were more frequent among twins than among singletons among whom the M : F ratios were 0.55 and 0.77, respectively; that among female twins, NTD were more frequent than among singleton females; that the lowest M : F ratio was 0.36 observed among anencephalic twins; and that a reversal toward male prevalence was evident among twins with spina bifida among whom the M : F ratio was 5.0 compared to 0.93 among singletons with spina bifida. The female sex bias does not apply to all sites of the NTD axis, which led Seller (1987) and later Hall et al. (1988) to underscore that among putative pathogenic mechanisms of cephalad-NTD (defects above the first lumbar vertebra and including encephaloceles) reflect defects of neurulation in contrast to lumbo-sacral spina bifidas, which are anomalies of canalization of the neural caudal cord. Garabedian and Fraser (1994) proposed a maternal factor as a cause of a higher frequency of NTD among maternal than paternal relatives of patients with “high” (above the first lumbar vertebra) NTD. According to these investigators, NTD among relatives may reflect a maternal factor since such instances are more common among maternal relatives. A similar pattern is evident in Rivne (Fig. 3) and was also noted by Marriman and Hamel (1992). Familial twinning is also evident among relatives of conjoined twins (Fig. S4).

An analysis of 16 instances of sirenomelia by Thottungal et al. (2010) led to their conclusion that caudal dysplasia and sirenomelia have a single pathogenesis. A review by Orioli et al. (2011) confirmed such a view and noted a sirenomelia-twinning association in 9% of patients. A review by Siebert et al. (2005) correlated caudal duplications with the vanishing twin phenomenon, conjoined twinning, caudal dysplasia, sirenomelia, and OEIS. A clinical illustration of this concept was reported by Fowler (1998) who studied

an individual with a large OM, duplicated lower spine, and an intra-abdominal sack containing a skin covered “leg”. An analysis of monozygotic twins discordant for body stalk anomalies led Daskalakis et al. (1997) and Daskalakis and Nicolaides (2002) to postulate an early amnion rupture before obliteration of the celomic cavity. The rupture allows parts of the fetal body to pass through the membranes out of the amniotic cavity into the celomic cavity leading to structural defects and amniotic bands associated with body wall defects, encephalocele, CL/P and limb amputations as well as a short umbilical cord and a fetus almost attached to the placenta. Among alternative hypotheses, an abnormal embryonic folding and persistence of the celomic cavity may render the amniotic cavity prone for rupturing. Such twins, if incorporated, may have characteristics of conjoined twins, fetus-in-fetu, fetiform tumor or teratoma (Phelan and Hall 2006; Dhingra et al. 2008; Fuentes et al. 2010). A demised twin may result in the “vanishing twin” phenomenon or be incompletely resorbed by the host and disrupt the development of the surviving twin. Daskalakis and Nicolaides (2002) suggest that incorporated blighted conjoined twins may be a cause of cloacal exstrophy, which are strongly associated with OM and twinning (Martinez-Frias et al. 2001; Casale et al. 2004; Siebert et al. 2005). A female prevalence among patients with exstrophy of the cloaca was also observed by Caton et al. (2007). A concordant view was formulated by Feldkamp et al. (2011), who noted that cloacal exstrophy is etiologically heterogeneous, more frequent among monozygotic twins, and recurrent in families.

In summary, the observations in Rivne sustain the view that conjoined twins, sacro-coccygeal teratomas, cephalad-NTD, isolated microcephaly and their association with female prevalence and among twins probably are outcomes of shared mechanisms.

Etiology

The teratogenic risk factors manifesting in the reported rates and patterns of cCM remain unknown. Among three principal teratogenic risk factors and the higher rates of cCM in Polissia, our surveys indicate that alcohol is an unlikely candidate. Concerning genomic mutations associated with higher sensitivity to teratogens, in particular IR, their frequency in Polissia may be higher but have not been directly investigated (Ziolkowska et al. 2006). The impact of folate deficiencies on DNA repair and rates of NTD remain to be investigated in Polissia and Ukraine in general. Recent observations of radiation induced transgenerational inheritance of genomic instability have focused attention on the role of hypomethylation of DNA. Such discoveries, as summarized below, provide an increasingly complete framework linking modest IR exposures and other environmental factors with twinning and blastopathies as well as associations with preferential sex. Studies show that the NTS1 Slavic or NBN (c.657_651del5) mutation is more prevalent in regions proximal to Polissia. Carriers of this mutation associated with the Nijmegen chromosome breakage syndrome (NBS) are more sensitive to IR DNA damage and suffer the consequences of impeded double-stranded DNA repair manifested as a large array of CM and higher cancer risks. The frequency of this mutation in the eastern part of Wielkopolska province in Poland and in adjoining Ukraine is estimated at 1.3% (Ziolkowska et al. 2006; Chrazanowska et al. 2012). Also, among a plethora of reports and reviews, of direct interest are those of Dubrova et al. (1996) and Pils et al. (1999) who noted that exposure to low dose radiation resulted in minisatellite DNA mutations and could be followed by teratogenic effects in the subsequent generation; Morgan et al. (2002) proposed that radiation induces factors that stimulate production of reactive oxygen species that induce genomic and chromosomal

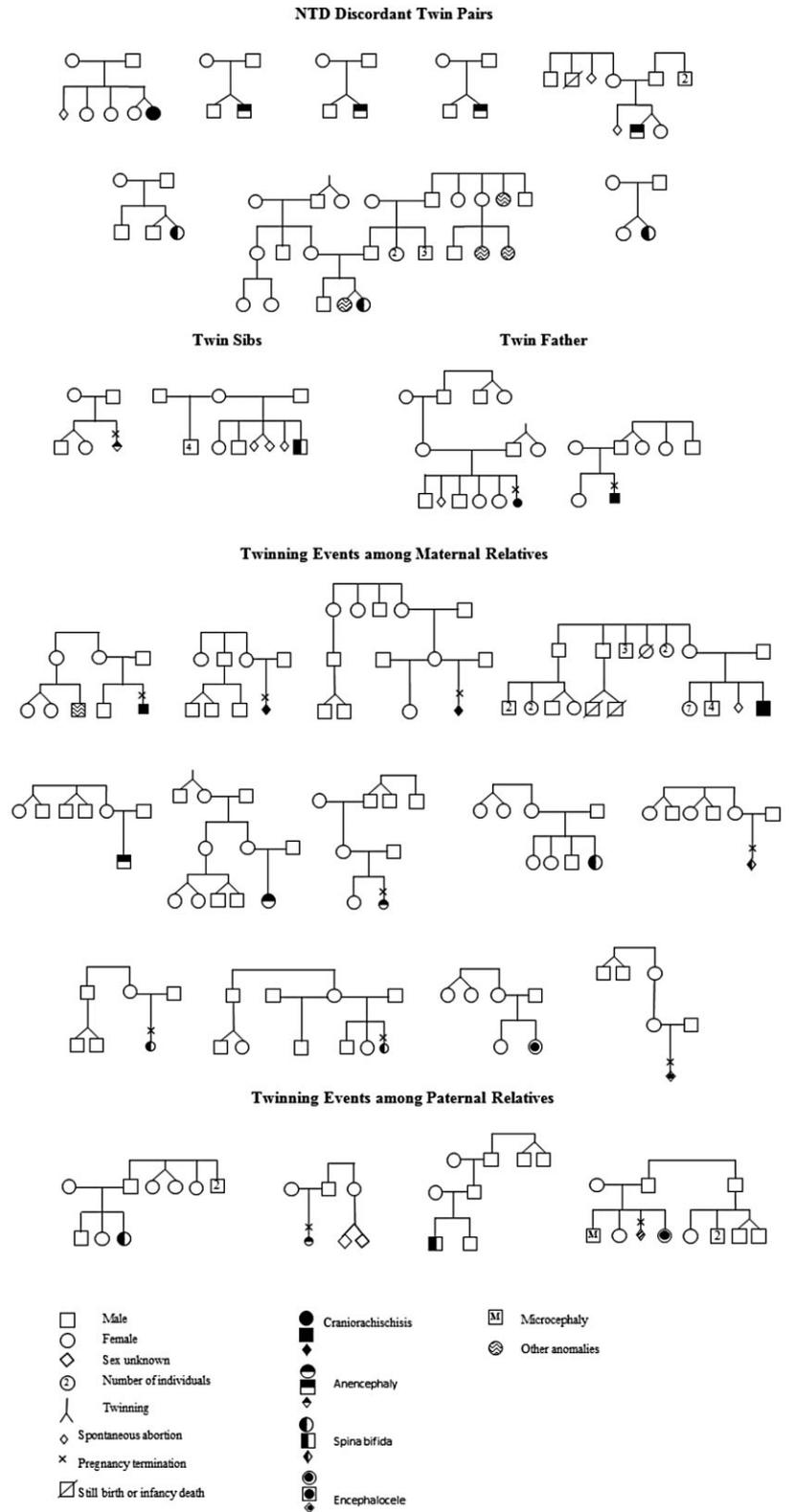


Fig. 3 Twin individuals with neural tube defects (NTD) and twinning events among their relatives (2000–2009).

instability over multiple cell cycles; Kovalchuk and Baulch (2008) noted that bystander IR effects can span several generations and influence the progeny of exposed parents associated with altered DNA methylation patterns; Filkowski et al. (2010) noted

hypomethylation and genome instability in the germ line of exposed parents (paternal germ lines are more sensitive) associated with altered miRNA expression; the integration in Developmental Biology of epigenetic transgenerational inheritance with genetics is

reviewed by Skinner (2011) in particular, regulatory DNA methylation such as X chromosome inactivation as well as impacts of environmental disruptors of erasure of DNA methylation during gonadal sex determination; Hales et al. (2011) reviewed the epigenetic marks, DNA methylation, histone modifications and noncoding RNAs critical role in cell memory during the development of gametes to blastocysts; excess risk for monozygotic twinning after IVF (*in vitro* fertilization) was noted by Ericson and Kallen (2001); increased risk of blastogenesis related malformations after ART (assisted reproductive technologies) procedures was demonstrated by Ben-Ami et al. (2011). These hypotheses and those alluded to earlier are generally consistent with the view that blastopathies result from embryonal developmental “delays”. This notion was proposed as early as 1651 by William Harvey in his “De Generatione Animalium” which followed his teacher’s Fabricius ab Aquapentende (1537–1610) report on “De Formato Foetu”. During the second half of the eighteenth century, von Haller and C. F. Wolff applied the principle of arrested development to explain ectopia cordis and exomphalos along with experimental studies of “duplicity” and twinning, which strengthened the notion of arrested development as epigenetic in nature. One landmark is the 1921 voluminous monograph “Developmental rate and Structural Expression” by Stockard and given a wider perspective by Newman (1923). It was Ballentyne (1904, chapter XI, page 158) who described human blastopathies and asserted that embryologic theories dealt with pathogenesis and not etiology. The incorporation and expansion of the notion of arrested development in Medical Teratology and Pathology is reviewed by Willis (1962, chapter 4, page 132) and in Clinical and Experimental Teratology by Warkany (1971, chapter 2, page 17). A review of current molecular hypotheses of epigenetic mechanisms impacting neural fold development conducive to elevated rates and female excess of NTD as observed in Polissia, is presented, among others, by Juriloff and Harris (2012).

The persistent learned debate of *in utero* exposures to low-levels of IR impacts on human health became invigorated by the investigations of Alice Stewart (2000). Her studies led her to conclude that the ABCC sponsored investigations of the acute injuries of atomic bomb survivors “are biased in favor of exceptionally low levels of radiosensitivity”. Such a conclusion poses a challenge to official assertions concerning health impacts related to Chernobyl IR exposures. This view is underscored by an early classic investigation by MacMahon (1962) who noted that *in utero* exposure to diagnostic doses of X-ray increased subsequent mortality from neoplastic disease during childhood. A cluster of childhood leukemia noted in the vicinity of the Krummel nuclear plant near Hamburg, Germany, led the government to sponsor an investigation that in 1992 found a statistically significant threefold increase of leukemia risk for children below age 5 residing in the 5 km zone of 20 German nuclear facilities. In 1997, a second official study reported a 50% increased leukemia risk for this target group, which was only marginally significant ($P = 0.060$). In 1999, Korblein and Hoffmann (1999) re-analyzed the same data but only for the 15 sites of operating German nuclear power plants, omitting five small research facilities and decommissioned plants. They discovered a significant 76% increased risk at the $P < 0.01$ level. These controversial results prompted the German government to sponsor the “Epidemiologische Studie zu Kinderkrebs in der Umgebung von Kernkraftwerken” known by the acronym KiKK. The results of this case-control study, a 120% increase relative leukemia risk for children under five in the 5 km zone, were published by Kaatasch et al. in 2008 (Kaatasch et al. 2008). But they also state that “based on the available information about radiation emissions from German

nuclear power plants, a direct relation to radiation seems implausible. Many factors may conceivably cause leukemia . . .”. Fairlie (2009) suggests that leukemia in children under five is induced *in utero* and that the effect could be teratogenic in nature rather than stochastic. In Polissia, until proven otherwise, it is prudent to view the persistent incorporation of nuclides by pregnant women, both as teratogenic and oncogenic.

In the field of radiobiology, dilemmas such as those mentioned above are relatively common and call for adherence to the “precautionary principle” endorsed by the majority of the scientific community. Under this principle, those who dictate or advocate policies in the absence of scientific evidence or consensus have the responsibility to demonstrate that their proposed, imposed, or advocated policies, including those by silence or unresponsiveness, are not harmful to the public or the environment. Arguably, official assertions that Chernobyl IR is not teratogenic contradict this precautionary principle. In any case, the repeated unsubstantiated official denials of teratogenic impacts or even the possibility of such impacts posed by Chernobyl had a chilling effect on initiatives to investigate their validity. In terms of the Fukushima disaster, it is self-evident that the circumstances, ecology and populations are distinct from those in Rivne. On the other hand, it is also evident that IR is a measurable teratogen that impacts in a similar manner human embryos anywhere. It is prudent to assume that whatever is learned concerning the teratogenic impacts in Polissia may be relevant in the context of Fukushima and elsewhere.

Prevention

In Rivne, specific prevention interventions are needed to reduce the high rates of NTD and other CM, to reduce the high levels of incorporated IR by pregnant women and others, and to reduce exposures to alcohol teratogenesis. The existing population-based CM monitoring program can facilitate concurrent investigations of synergistic impacts of risk factors and effectiveness of their interruption by prevention-interventions. Likewise, such initiatives can expand conclusions of prior investigations including those that have shown that maternal alcohol consumption impedes absorption of folates and has no impact on NTD rates (Halsted et al. 2002; Makelarski et al. 2013). Assessment of the proven reduction of NTD rates by folic acid supplementation programs, in the context of IR exposures in Polissia, are likewise of considerable interest (Berry et al. 2010).

CONCLUSIONS

The results of this descriptive epidemiological study provide a starting point for prospective investigations of cause-effect associations. The strengths and weaknesses of this investigation can be described with consideration of the well-known principles set by Sir Austin Bradford Hill (1965) as criteria defining causal relationships from observed associations, in this instance, the association in Polissia of high rates of pentad-cCM with Chernobyl IR. Among the strengths of this study are: (i) adherence to prevalent international methods; (ii) concurrent study of two distinct large populations of similar size, only one of which is chronically exposed to IR; (iii) concurrent statistically significantly elevated population-based rates of cCM; (iv) the array of elevated cCM in Polissia includes those known to result from experimental and human exposures to IR; and (v) elevated incorporated IR levels in pregnant women are detected solely among those living in Polissia. Concerning plausibility, three teratogenic risks are of concern in Rivne: alcohol, genomic mutations, and IR. As noted earlier, alcohol teratogenesis

is not prevalent in Polissia and genomic mutations are unlikely to cause the blastopathies observed. The concurrence of elevated rates of cCM with elevated IR levels in Polissia lends coherence to a hypothetical cause-effect association. Advances in molecular biology and embryology suggest that the cCM-IR association may reflect altered methylation processes associated with sex, greater sensitivity of paternal germ lines to some teratogens, and potential causes of genomic instability. Among the weaknesses of this investigation are: (i) lack of CM data prior to the onset of this investigation; (ii) lack of data of actual levels of parental incorporated IR of infants with cCM compared to matched controls; (iii) limited data concerning prenatal loss of conceptions; and (iv) limited data concerning cCM, microcephaly and reduced head size beyond 12 months of age.

In summary, the present descriptive investigation documents higher population-based rates of some CM in a population isolate impacted by Chernobyl IR. In our view, prospective cause-effect investigations by national and international scientists are warranted.

ACKNOWLEDGMENTS

The authors thank Drs Ralf M. Garruto (Biomedical Anthropology program, Binghamton University, SUNY, Binghamton, NY) and Yuri S. Korzhynskyy (Department of Pediatrics, Lviv School of Medicine) for their helpful discussion. These studies were supported by the OMNI-Net for Children International Charitable Fund.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1 County Isonomy Rates of Neonates (Aggregate Frequency of Five Most Common Family Names).

Fig. S2 Whole Body Counts of incorporated ionizing radiation (Bq ¹³⁷Cs) among 6026 pregnant women residing in Rivne Province (2008–2011). The (*) indicates the official upper norm for children under the age of 15 years (3700 Bq). (Decree #106 of Cabinet of Ministers of Ukrainian Soviet Socialist Republic of July 23, 1991. – See references).

Fig. S3 Birth weight of liveborns of all gestational ages (2000–2009) in Polissia and non-Polissia regions of Rivne province of Ukraine.

Fig. S4 Twinning Events among Relatives of Conjoined Twins (2000–2010).

Table S1a Temporal Contrasts between Polissia (POL) and non-Polissia (nPOL)⁽¹⁾ of Population-Based Rates of Core Congenital Malformations.

Table S1b Temporal Contrasts within Polissia and non-Polissia⁽¹⁾ of the Number of Observed Individuals with Core Congenital Malformations.

Table S1c Unduplicated Individuals with Core Congenital Malformations after Exclusion of Those with Clinically Recognizable Malformation Syndromes, Genomic Mutations, Cytogenetic Anomalies and Recognizable Teratogenic Effects⁽¹⁾.

Table S1d Overview of Unduplicated Individuals in Polissia and non-Polissia with Non-Syndromic Congenital Malformations⁽¹⁾ or Sentinel Anomalies (2000–2009).

Table S2 Total Number of Malformations and Rates per se (not Unique Individuals) and Male-Female (MF) Proportions and Ratios (M : F) in Polissia and non-Polissia^(a).

Table S3 All Individuals with Fetal Alcohol Spectrum Disorder (FASD). Non-Population-Based Observations.

Table S4 All Non-Singletons Including Those with Congenital Malformations (2000–2009)⁽¹⁾.

Table S5 Population Rates of Neural and Other Malformations (not Individuals) in the Polissia and non-Polissia Regions of Ukraine and other regions of Europe.

Table S6 Teratomas – Rivne, Volyn (2000–2009) and Khmelnytsky (Kh) Provinces (2002–2009)^(a).

Table S7 Non-Syndromic NTD Associated with Omphaloceles (OM), Body Wall and Other Anomalies in Rivne, Khmelnytsky and Volyn Provinces (2000–2009)^(a).

Table S8 Gastroschisis and Maternal Age at Delivery: Rivne and Volyn Provinces (2000–2009) and Khmelnytsky Province (2002–2009).

Table S9 Encephaloceles and Male-Female (M-F) Proportions.

DATA SUPPLEMENT

BLASTOPATHIES AND MICROCEPHALY IN A CHORNOBYL IMPACTED REGION OF UKRAINE

NOTICE: The following was edited by the authors and differs from the version posted on the internet by the “Congenital Anomalies” journal. The changes introduced seek to facilitate a review by readers. The contents of tables and figures are identical to the electronic version posted on the internet.

THE POLISSIA REGION IN RIVNE, UKRAINE

Polissia is the largest forested wet-land region in Europe, roughly the size of Bavaria. The region is also known as Prypiat Marshlands which extend across northern Ukraine and southern Belarus from its start in eastern Poland to its end in western Russia. The “Polishchuks” or “forest dwellers” live in isolated scattered villages. The environment, in particular poor soils, result in subsistence patterns emphasizing consumption of water from shallow wells, locally produced potatoes, eggs, lactic products and pork meat as well as local fish, wild mushrooms, berries, and wood for heating and cooking. The Polishchuks are viewed in Ukraine as representing a distinct ethnic group with characteristics of a population isolate (Kovalchuk et al. 2009; Dancause et al. 2010).

The Rivne province is located in northern Ukraine, some 250 km to the west from the Chernobyl disaster site (see report, Figure 1). The northern half of the province is Rivne-Polissia, henceforth referred to as Rivne-P. The Rivne-P is divided into seven counties, six of which are officially recognized as being impacted by Chernobyl IR. No other counties in Rivne are officially considered as Chernobyl IR polluted. Impacted areas are defined as those with average deposition density of ^{137}Cs in excess of 37 kBq/m^2 . The USSR and international agencies initially failed to include Rivne-P among regions officially designated as Chernobyl IR impacted. In 1991, among actions that culminated in the Ukrainian declaration of independence from the USSR, the omission of Rivne-P was corrected (Decree 106, 1991). The Chernobyl IR pollution in Rivne-P is not uniform due to “hot spots” of high levels of IR scattered across the territory. Another source of variability relates to soils. In Polissia, most soils are rich in peat which translates into a high index of transfer of ^{137}Cs from soil to the food chain. This index is among the highest in Ukraine (Zamostian et al. 2002). This is an important factor resulting in higher levels of incorporation of IR in Rivne-P than in other areas more proximal to Chernobyl. Official estimates and scientific reports concerning Rivne that do not distinguish Rivne P from the rest of the province may implicitly under-estimate the incorporation levels of ionizing radiation by the Polishchuk population. Most exposure risks to IR are calculated solely in terms of estimates of dietary ingestion of ^{137}Cs . Not reflected in such estimates are inhalation and the presence of ^{90}Sr and other nuclides. In Rivne-P, infants, children, and pregnant women are regularly exposed to IR polluted smoke from forest fires and burning of biomass following harvests. In addition, chronic exposure to wood smoke in dwellings is another source of inhalation of IR. About 50% of dwellings burn wood for heating and cooking. In such a context it is preferable to rely on individual whole body counts of incorporated ^{137}Cs expressed in Bq than on extrapolations based on averaged estimated ^{137}Cs contents in soil and diets. An analysis of individual whole body Bq counts of incorporated ^{137}Cs are found in the companion report. A prior survey of 344 women from each Rivne-P county estimated the dietary average daily intake of ^{137}Cs at 268 Bq which is above the upper limit advocated by the authorities (Dancause et al. 2010).

In addition to the Chernobyl disaster, other sources of IR in Rivne are two nuclear power plants complexes (NPP). Both NPP complexes were built concurrently with the Vladimir Lenin NPP complex now known as the Chernobyl-Prypiat complex. Each NPP complex is adjacent to urban areas and the Rivne-NPP is adjacent to Kuznetsovsk city in Polissia. The Khmelnytsky-NPP is located in Khmelnytsky province just across the southern limit of the Ostroh county in Rivne (see report, Figure 1). This NPP-complex adjoins the sister-cities Ostroh-Netishyn in Rivne and Khmelnytsky provinces respectively.

The isolation and small settlements inhabited by Polishchuks are associated with localized predominance of characteristic family names. High frequencies of family names or isonymy rates typical of particular counties suggest higher endogamy rates as well as higher levels of genomic homozygosity (Colantonio et al. 2003). The isonymy and life-style surveys are consistent with general notions in Ukrainian that Polishchuks represent a large, stable, culturally distinct population isolate who have been exposed to protracted IR exposures since 1986. The circumstances in Polissia

represent a “natural experiment” offering an opportunity for long term investigations of health effects of an anthropogenic environmental insult on the health of a defined large human population (Garruto et al. 1999).

SUPPLEMENTAL TABLES

Table S-1a. Temporal Contrasts between Polissia (POL) and non-Polissia (nPOL)⁽¹⁾ of Population-Based Rates of Core Congenital Malformations

	2000-2004					2005-2009				
	POL	nPOL	OR	P	CL	POL	nPOL	OR	P	CL
Live Births	33703	33205				38676	39853			
Neural Tube Defects (NTD)	98	61	1.59	**	1.14, 2.22	91	59	1.59	**	1.13, 2.25
Cephalad ⁽²⁾	32	26	-	n/s	-	39	19	2.12	**	1.19, 3.88
Anencephaly	21	17	-	n/s	-	16	12	-	n/s	-
Isolated	19	16	-	n/s	-	15	12	-	n/s	-
Non-NTD Malformations ⁽³⁾	2	1	-	n/c	-	1	0	-	n/c	-
Cranio-inien-rachis-schisis ⁽⁴⁾	11	9	-	n/s	-	23	7	3.39	**	1.41, 9.35
Isolated	7	6	-	n/s	-	16	6	2.75	*	1.02, 8.58
Other Malformations	4	3	-	n/c	-	7	1	7.21	*	0.93, 325
Spina Bifida Cervico-Thoracic	11	0	-	***	-	6	4	-	n/s	-
Isolated	8	0	-	**	-	6	4	-	n/s	-
Other Malformations	3	0	-	n/c	-	0	0	-	n/c	-
Spina Bifida Lumbo-Sacral	34	24	-	n/s	-	40	28	-	n/s	-
Isolated	30	20	-	n/s	-	36	26	-	n/s	-
Syndromes	1	0	-	n/c	-	0	0	-	n/c	-
Other Malformations	3	4	-	n/c	-	4	2	-	n/s	-
Spina Bifida site not reported	11	4	-	n/s	-	0	0	-	n/c	-
Isolated	11	4	-	n/s	-	0	0	-	n/c	-
Spina Bifida combined	56	28	1.97	**	1.23, 3.23	46	32	1.48	*	0.92, 2.41
Encephalocele	10	7	-	n/s	-	6	8	-	n/s	-
Isolated	7	5	-	n/s	-	5	6	-	n/s	-
Syndromes	2	0	-	n/c	-	1	0	-	n/c	-
Other Malformations	1	2	-	n/c	-	0	2	-	n/c	-
Microcephaly ⁽⁵⁾	18	11	-	n/s	-	26	13	2.06	*	1.02, 4.37
Isolated	9	3	-	n/s	-	5	5	-	n/s	-
Syndromes	4	7	-	n/s	-	11	7	-	n/s	-
Other Malformations	5	1	-	n/s	-	10	1	10.3	**	1.47, 447
Microphthalmos ⁽⁶⁾	6	2	-	n/s	-	12	4	3.09	*	0.94, 13.2
Isolated	2	0	-	n/c	-	6	4	-	n/s	-
Syndromes	0	1	-	n/c	-	3	0	-	n/c	-
Other Malformations	4	1	-	n/c	-	3	0	-	n/c	-
Omphalocele ⁽⁷⁾	6	8	-	n/s	-	7	17	0.42	(*)	0.15, 1.08
Isolated	3	6	-	n/s	-	2	11	0.19	(**)	0.02, 0.86
Syndromes	1	1	-	n/c	-	1	0	-	n/c	-
Other Malformations	2	1	-	n/c	-	4	6	-	n/s	-
Gastroschisis	4	11	-	n/s	-	13	12	-	n/s	-
Isolated	3	10	0.30	(*)	0.05, 1.15	13	12	-	n/s	-
Other Malformations	1	1	-	n/c	-	0	0	-	n/c	-
Urinary Bladder Exstrophy ⁽⁸⁾	4	3	-	n/c	-	4	2	-	n/c	-
Isolated	4	2	-	n/c	-	4	2	-	n/c	-
Other Malformations	0	1	-	n/c	-	0	0	-	n/c	-
Conjoined Twins ⁽⁹⁾	2	2	-	n/c	-	0	3	-	n/c	-
Isolated	2	1	-	n/c	-	0	2	-	n/c	-
Other Malformations	0	1	-	n/c	-	0	1	-	n/c	-

Teratomas	5	1	-	n/s	-	1	3	-	n/c	-
Isolated	5	1	-	n/s	-	1	3	-	n/c	-
Sacro-coccygeal	5	1	-	n/s	-	1	2	-	n/c	-
Isolated	5	1	-	n/s	-	1	2	-	n/c	-
All	143	99	1.43	**	1.10, 1.86	154	113	1.41	**	1.10, 1.81
Isolated	110	74	1.47	**	1.08, 2.00	109	93	-	n/s	-
Syndromes	8	9	-	n/s	-	16	7	2.36	*	0.92, 6.77
Other Malformations	25	16	-	n/s	-	29	13	2.30	**	1.16, 4.82

For footnotes see Table 2.

Table S-1b. Temporal Contrasts within Polissia and non-Polissia⁽¹⁾ of the Number of Observed Individuals with Core Congenital Malformations

	Polissia			Non-Polissia			Overall Rivne		
	2000-2004	2005-2009	Total	2000-2004	2005-2009	Total	2000-2004	2005-2009	Total
Live Births	33703	38676	72379	33205	39853	73058	66908	78529	145437
Neural Tube Defects (NTD)	98	91	189	61	59	120	159	150 ^(a)	309
Cephalad ⁽²⁾	32	39	71	26	19	45	58	58	116
Anencephaly	21	16	37	17	12	29	38	28 ^(b)	66
Isolated	19	15	34	16	12	28	35	27 ^(c)	62
Non-NTD Malformations ⁽³⁾	2	1	3	1	0	1	3	1	4
Cranio-inien-rachis-schisis ⁽⁴⁾	11	23	34	9	7	16	20	30	50
Isolated	7	16	23	6	6	12	13	22	35
Other Malformations	4	7	11	3	1	4	7	8	15
Spina Bifida Cervico-Thoracic	11	6	17	0	4	4	11	10	21
Isolated	8	6	14	0	4	4	8	10	18
Other Malformations	3	0	3	0	0	0	3	0	3
Spina Bifida Lumbo-Sacral	34	40	74	24	28	52	58	68	126
Isolated	30	36	66	20	26	46	50	62	112
Syndromes	1	0	1	0	0	0	1	0	1
Other Malformations	3	4	7	4	2	6	7	6	13
Spina Bifida site unknown	11	0 ^(d)	11	4	0 ^(e)	4	15	0 ^(f)	15
Isolated	11	0	11	4	0	4	15	0	15
Spina Bifida combined	56	46	102	28	32	60	84	78	162
Encephalocele	10	6	16	7	8	15	17	14	31
Isolated	7	5	12	5	6	11	12	11	23
Syndromes	2	1	3	0	0	0	2	1	3
Other Malformations	1	0	1	2	2	4	3	2	5
Microcephaly ⁽⁵⁾	18	26	44	11	13	24	29	39	68
Isolated	9	5	14	3	5	8	12	10	22
Syndromes	4	11	15	7	7	14	11	18	29
Other Malformations	5	10	15	1	1	2	6	11	17
Microphthalmos ⁽⁶⁾	6	12	18	2	4	6	8	16	24
Isolated	2	6	8	0	4	4	2	10 ^(g)	12
Syndromes	0	3	3	1	0	1	1	3	4
Other Malformations	4	3	7	1	0	1	5	3	8
Omphalocele ⁽⁷⁾	6	7	13	8	17	25	14	24	38
Isolated	3	2	5	6	11	17	9	13	22
Syndromes	1	1	2	1	0	1	2	1	3
Other Malformations	2	4	6	1	6	7	3	10	13
Gastroschisis	4	13 ^(h)	17	11	12	23	15	25	40
Isolated	3	13 ^(h)	16	10	12	22	13	25	38
Other Malformations	1	0	1	1	0	1	2	0	2

Urinary Bladder Exstrophy ⁽⁸⁾	4	4	8	3	2	5	7	6	13
Isolated	4	4	8	2	2	4	6	6	12
Other Malformations	0	0	0	1	0	1	1	0	1
Conjoined Twins ⁽⁹⁾	2	0	2	2	3	5	4	3	7
Isolated	2	0	2	1	2	3	3	2	5
Other Malformations	0	0	0	1	1	2	1	1	2
Teratomas	5	1	6	1	3	4	6	4	10
Isolated	5	1	6	1	3	4	6	4	10
Sacro-coccygeal	5	1	6	1	2	3	6	3	9
Isolated	5	1	6	1	2	3	6	3	9
All	143	154	297	99	113	212	242	267	509
Isolated	110	109	219	74	93	167	184	202	386
Syndromes	8	16	24	9	7	16	17	23	40
Other Malformations	25	29	54	16	13	29	41	42	83

(1-8) Please, see the same footnotes (1-9) in Table 2.

(a-h) Statistical analysis results:

	OR	P	CL
a	1.25	≤0.03	0.99, 1.57
b	1.59	≤0.04	0.95, 2.70
c	2.42	0.003	1.32, 4.60
d	Infinity	0.0002	3.67, Infinity
e	Infinity	0.04	1.08, Infinity
f	Infinity	0.0001	5.31, Infinity
g	0.24	0.046	0.03, 1.10
h	0.26	0.02	0.05, 0.96

*, **, ***, indicate P-values of ≤0.05, 0.01, 0.001 (two-tail test***).

(d, e, h) Within Polissia and within non-Polissia, during the first and second study periods, there are no statistically significant contrasts except: (d) odds ratio (OR) = Infinity, P-value (P) = 0.0002, 95% confidence limits (CL): 3.67 to Infinity; (e) OR = Infinity, P-value = 0.04, CL: 1.08 to Infinity; (h), OR 0.26, P-value = 0.02, CL 0.05, 0.96. For further comments see text.

(a-c, f, g) In terms of the overall Rivne province, the statistically significant contrasts of the number of individuals observed during the first and second study periods are: (a), OR 1.25, P-value ≤0.03, CL 0.99, 1.57; (b), OR 1.59, P-value ≤0.04, CL 0.95, 2.70; (c) OR 2.42, P-value 0.003, CL 1.32-4.60; (f) OR = Infinity, P-value > 0.0001, CL: 5.31 to Infinity; (g) OR = 0.235, P-value = 0.046, CL 0.03-1.10. For further comments see text.

Table S-1c. Unduplicated Individuals with Core Congenital Malformations after Exclusion of Those with Clinically Recognizable Malformation Syndromes, Genomic Mutations, Cytogenetic Anomalies and Recognizable Teratogenic Effects⁽¹⁾

Categories	Polissia	Non-Polissia	Polissia vs. non-Polissia		
	2000-2009	2000-2009	OR	P-value	CL
Live Births	72379	73058			
Neural Tube Defects (NTD)	185	120	1.56	***	1.23, 1.98
Cephalad ⁽²⁾	71	45	1.59	**	1.08, 2.37
Anencephaly	37	29	-	n/s	-
Isolated	34	28	-	n/s	-

Cranio-inien-rachis-schisis ⁽⁴⁾	34	16	2.15	**	1.15, 4.16
Isolated	23	12	1.94	*	0.92, 4.27
Spina Bifida Cervico-Thoracic	17	4	4.29	**	1.40, 17.5
Isolated	14	4	3.53	*	1.11, 14.8
Spina Bifida Lumbo-Sacral	73	52	1.42	*	0.98, 2.06
Isolated	66	46	1.45	*	0.98, 2.16
Spina Bifida site unknown	11	4	2.78	0.057	0.82, 12.0
Isolated	11	4	2.78	0.057	0.82, 12.0
Spina Bifida combined	101	60	1.70	***	1.22, 2.38
Encephalocele	13	15	-	n/s	-
Isolated	12	11	-	n/s	-
Microcephaly ⁽⁵⁾	29	10	2.93	**	1.39, 6.74
Isolated	14	8	-	n/s	-
Microphthalmos ⁽⁶⁾	15	5	3.03	*	1.05, 10.65
Isolated	8	4	-	n/s	-
Omphalocele ⁽⁷⁾	11	24	0.46	*	0.20, 0.98
Isolated	5	17	0.30	**	0.09, 0.84
Gastroschisis	17	23	-	n/s	-
Isolated	16	22	-	n/s	-
Urinary Bladder Exstrophy ⁽⁸⁾	8	5	-	n/s	-
Isolated	8	4	-	n/s	-
Conjoined Twins ⁽⁹⁾	2	5	-	n/s	-
Isolated	2	3	-	n/c	-
Teratomas	6	4	-	n/s	-
Isolated	6	4	-	n/s	-
Sacro-coccygeal	6	3	-	n/s	-
Isolated	6	3	-	n/s	-

For footnotes see Table 2.

Table S-1d. Overview of Unduplicated Individuals in Polissia and non-Polissia with Non-Syndromic Congenital Malformations⁽¹⁾ or Sentinel Anomalies (2000-2009).

Categories	Polissia	Rate	Non-Polissia	Rate	Polissia vs. Non-Polissia		
					OR	P-value	CL
Core-Malformations							
Neural Tube Defects	185	25.6	120	16.4	1.56	<0.001	1.23, 1.98
Cephalad ⁽²⁾	71	9.8	45	6.2	1.59	<0.01	1.08, 2.37
Microcephaly ⁽⁵⁾	29	4.0	10	1.4	2.93	<0.01	1.39, 6.74
Microphthalmia ⁽⁶⁾	15	2.1	5	0.7	3.03	<0.05	1.05, 10.65
Sentinel Anomalies							
Cleft Lip and/or Palate ^(a)	67	9.3	69	9.4	-	n/s	-
Down Syndrome ^(b)	101	14.0	97	13.3	-	n/s	-

For footnotes (1, 2, 5-6) see Table 2.

(2) Includes anencephaly and iniencephaly.

(a) Non-syndromic.

(b) Includes one individual with microcephaly and recto-anal atresia (s-5).

Table S-2. Total Number of Malformations and Rates per se (not Unique Individuals) and Male-Female (MF) Proportions and Ratios (M:F) in Polissia and non-Polissia^(a).

Categories ^(a)	Polissia					non-Polissia				
	Rate	Unk	M	F	M:F ^(b)	Rate	Unk	M	F	M:F
Rivne Live Births ^(c)		12	37576	34791	1.08		16	37716	35326	1.07
NEURAL TUBE DEFECTS (NTD)	26.1	30	71	88	0.81*	16.4	36	43	41	1.05
CEPHALAD ^(d)	9.8	15	21	35	0.60*	6.2	19	11	15	0.73
NTD – TWIN INDIVIDUALS	n/c	-	1	2	n/c	0.7	-	3	2	n/c
NTD – OMPHALOCELE	1.4	4	2	4	n/c	n/c	2	2	-	n/c
ANENCEPHALY	5.1	9	12	16	0.75	4.0	12	8	9	0.89
Isolated	4.7	7	12	15	0.80	3.8	12	8	8	1.00
INIENEPHALY	0.8	2	1	3	n/c	n/c	1	1	-	n/c
Isolated	n/c	1	1	2	n/c	n/c	-	1	-	n/c
CRANIO-RACHIS-SCHISIS	3.9	4	8	16	0.50*	1.9	6	2	6	0.33
Isolated	2.6	2	6	11	0.55	1.5	5	2	4	n/c
SPINA BIFIDA ^(e)	14.1	12	46	44	1.05	8.2	10	27	23	1.17
Cervical	0.8	2	3	1	n/c	n/c	-	-	-	n/c
Isolated	0.7	2	2	1	n/c	n/c	-	-	-	n/c
Thoracic	1.5	-	7	4	1.75	n/c	-	3	1	n/c
Isolated	1.2	-	5	4	1.25	n/c	-	3	1	n/c
Lumbo-sacral	10.2	9	34	31	1.10	7.1	7	24	21	1.14
Isolated	9.1	6	31	29	1.07	6.3	6	20	20	1.00
Site unknown	1.5	1	2	8	0.25*	n/c	3	-	1	n/c
Isolated	1.5	1	2	8	0.25*	n/c	3	-	1	n/c
ENCEPHALOCELE	2.2	3	4	9	0.44	2.1	7	5	3	1.67
Isolated	1.7	2	1	9	0.11**	1.5	5	4	2	n/c
MICROCEPHALY-MICROPHTHALMIA	9.4	-	32	36	0.89	4.7	-	18	16	1.13
Isolated	3.0	-	8	14	0.57	1.6	-	4	8	0.50
both Microcephaly-Microphthalmia	n/c	-	-	2	n/c	n/c	-	-	-	n/c
only Microcephaly	1.7	-	3	9	0.33	1.1	-	3	5	0.60
only Microphthalmia	1.1	-	5	3	1.67	n/c	-	1	3	n/c
and Anencephaly ^(f)	n/c	-	-	1	n/c	n/c	-	-	-	n/c
and Conjoined Twin with a single orbit ^(g)	n/c	-	-	-	n/c	n/c	-	1	-	n/c
and Holoprosencephaly ^(h)	0.7	-	4	1	n/c	n/c	-	2	1	n/c
Fetal Alcohol Syndrome ⁽ⁱ⁾	1.2	-	7	2	3.50	1.5	-	6	5	1.20
Other syndromes ⁽ⁱ⁾	1.2	-	4	5	0.80	n/c	-	3	1	n/c
Other non syndromic ^(k)	3.0	-	9	13	0.69	n/c	-	2	1	n/c
OMPHALOCELE	3.5	6	14	5	2.80*	4.2	12	14	5	2.80*
Isolated	0.7	1	4	-	n/c	2.3	7	7	3	2.33
and NTD ^(l)	1.4	4	2	4	n/c	n/c	2	2	-	n/c
and Microcephaly-mOPH ^(m)	n/c	-	2	-	n/c	n/c	-	2	-	n/c
and other malformations ⁽ⁿ⁾	1.1	1	6	1	6.00	1.1	3	3	2	n/c
GASTROSCHISIS	2.3	-	5	12	0.42*	3.1	5	11	7	1.57
Isolated	2.2	-	5	11	0.45	3.0	5	10	7	1.43
URINARY BLADDER EXSTROPHY ^(o)	1.2	-	4	5	0.80	0.7	-	4	1	n/c
CONJOINED TWINS (CTW) ^(p)	n/c	1	-	2	n/c	0.8	1	2	3	n/c
CTW – Spina Bifida – Omphalocele	n/c	-	-	1	n/c	n/c	-	-	-	-
CTW, single orbit, no oral opening	n/c	-	-	-	-	n/c	-	1	-	n/c
TERATOMA ^(q)	1.0	3	1	3	n/c	n/c	-	-	4	n/c
Sacro-coccygeal	0.8	3	1	2	n/c	n/c	-	-	3	n/c
HOLOPROSENCEPHALY ^(r)	^(r)	-	8	5	1.60	^(r)	4	12	7	1.71
and Patau syndrome	^(r)	-	3	2	n/c	^(r)	1	4	1	n/c
FETAL ALCOHOL SPECTRUM DISORD.	5.1	-	19	18	1.06	5.7	-	25	17	1.47
PATAU SYNDROME / TRISOMY 13 ^(t)	^(t)	-	5	4	1.25	^(t)	1	8	2	4.00
DOWN SYNDROME	14.0	-	54	47	1.15	13.3	2	54	41	1.32

CLEFT LIP/PALATE	10.8	2	45	31	1.45	10.8	-	55	24	2.29***
Isolated	7.6	-	38	17	2.24**	7.9	-	42	16	2.63***
Not Isolated	3.2	2	7	14	0.50	2.9	-	13	8	1.63
Syndromes	n/c	-	1	3	n/c	1.2	-	7	2	3.50
Non-Syndromic	2.6	2	6	11	0.55	1.6	-	6	6	1.00
ECTOPIA CORDIS	n/c	2	-	-	n/c	0.7	4	1	-	n/c
THORACO-ABDOMINAL WALL DEFEC.	n/c	3	-	-	n/c	n/c	6	1	1	n/c
RECTO-ANAL ANOMALIES	2.2	1	9	6	1.50	4.0	1	13	15	0.87
Isolated ^(s)	1.0	-	4	3	n/c	1.8	-	7	6	1.17
Not Isolated	1.2	1	5	3	1.67	2.2	1	6	9	0.67
SIRENOMELIA	n/c	-	-	-	-	n/c	2	-	-	n/c

- (a) In contrast to other tables where individuals are only represented once, in this table an individual may be represented in several malformation categories (shown in capital letters). However, within a malformation category (in capital letters) an individual is represented only once.
- (b) M:F is shown only if five individuals of either sex are represented. P-value is denoted by ***, **, *, which are equivalent to P-values ≤ 0.001 , ≤ 0.01 , ≤ 0.05 .
- (c) Excludes 28 individuals of unknown or undetermined (unk) sex.
- (d) Cephalad-NTD includes anencephaly (or acrania), cranio-rachis-schisis, iniencephaly with or without associated spina bifida.
- (e) Excludes cephalic NTDs. Spina bifida locations indicate the highest impacted level of the vertebral column with disregard of the caudal extent.
- (f) One individual is represented among anencephalies (c-1).
- (g) One individual is a conjoined twin with a single orbit (z-2).
- (h) Includes one individual with Holoprosencephaly-Microcephaly-Microphthalmia (hol-6); three individuals with Patau syndrome (hol-22, 23, 25).
- (i) Includes one individual with Fetal Alcohol Spectrum Disorder-Microcephaly-microphthalmia (s-2).
- (j) Includes four individuals with Patau syndrome (v-1, 3; s-11; w-1).
- (k) Includes one individual with Microcephaly-microphthalmia (t-8).
- (l) Includes fourteen individuals also shown separately as a NTD-Ompalocele category (c-3; f-2, 4-8; h-1; h-3, 1-5; g-4; m-2; m-5, 6).
- (m) Includes four individuals also represented in the Microcephaly and/or Microphthalmia category (t-9; u-2; v-1; w-1); two of them have Patau syndrome (v-1; w-1).
- (n) Includes sixteen individuals (aa-1, 2; cc-1-6; bb-1; dd-1-7), two of whom have Patau syndrome (aa-2; bb-1) and one of whom had pentalogy of Cantrel (dd-1).
- (o) Includes one individual with Spina Bifida-Ompalocele (h-3).
- (p) Includes 2000-2010 data.
- (q) Includes one individual with cervical teratoblastoma and Holoprosencephaly (neo-1).
- (r) Non-population-based observations.
- (s) Includes fistulas.

Table S-3. All Individuals with Fetal Alcohol Spectrum Disorder (FASD). Non-Population-Based Observations.

Category	Polissia	non-Polissia	Combined
FASD ^(a)	37 ^(a)	42	79 ^(b)
and Microcephaly ^(c)	9	11	20
Males	7 ^(e)	6 ^(g)	13
Females	2 ^(f)	5 ^(h)	7
No microcephaly	27	31	58

Males	12	19	31
Females	15	12	27
Gestational age (weeks) ^(d)			
<35	8	10	18
35-37	9	14	23
≥38	9	6	15
Birth weight (grams)			
<2500	21	25	46
≥2500	6	6	12
Prenatal diagnosis	6	6	12

- (a) Includes one female from Polissia with NTD (k-1).
(b) Includes 31 instances detected during 2000-2004 and 48 during 2005-2009.
(c) Occipital-frontal circumference ≤3 SD for sex and age.
(d) Excludes two individuals due to lack of information.
(e) Individuals (r-1-5, 8, 15).
(f) Individuals (r-11, 12).
(g) Individuals (s-1, 2, 7, 8, 12, 13).
(h) Individuals (s-3, 4, 6, 9, 10).

Table S-4. All Non-Singletons Including Those with Congenital Malformations (2000-2009)⁽¹⁾

Category	Polissia ^(a)				Non-Polissia ^(b)					Rivne Province				
	M-M	F-F	M-F	U-U	M-M	F-F	M-F	U-U	U-M	M-M	F-F	M-F	U-U	U-M
Quadruplets	-				M-M-F-F					M-M-F-F				
Triplets	M-M-M; F-F-F				M-M-M; five F-F-F ^(c)					Two M-M-M; six F-F-F				
Conjoined twin sets ^(d)	Two F-F ^(e) ; U-U				M-M; three F-F ^(e) ; U-U					M-M; five F-F; two U-U				
All Twin Pairs (per 10,000 live births)	216 (59.7)	199 (55.0)	164 (45.3)	1 (-)	207 (56.7)	220 (60.2)	183 (50.4)	2 (-)	1 (-)	423 (58.2)	419 (57.6)	347 (47.9)	3 (-)	1 (-)
Malformed twin ^(f)	18	9	6	-	13	7	6	2	1	31	16	12	2	1
Holoprosencephaly	1 ^(g)	-	-	-	-	-	-	-	-	1	-	-	-	-
Neural tube defects	1 ^(h)	2 ⁽ⁱ⁾	-	-	2 ^(j)	1 ^(k)	2 ^(l)	-	-	3	3	2	-	-
Ectopia cordis	-	-	-	-	-	-	-	1 ^(m)	-	-	-	-	1	-
Acardia	3 ⁽ⁿ⁾	1 ^(o)	-	-	1 ^(p)	-	-	-	-	4	1	-	-	-
Cardiac malformations	8 ^(q)	3 ^(r)	1 ^(s)	-	4 ^(t)	3 ^(u)	2 ^(v)	-	-	12	6	3	-	-
Gastroschisis	-	-	1 ^(w)	-	-	-	-	-	-	-	-	1	-	-
Other malformations	5 ^(x)	3 ^(y)	4 ^(z)	-	6 ^(aa)	3 ^(bb)	2 ^(cc)	1 ^(dd)	1 ^(ee)	11	6	6	1	1

- (1) Includes individuals with holoprosencephaly or thoraco-abdomino-schises.
(a, b) Excluded subjects whose co-twin was not found, is a vanishing co-twin or deceased without further information provided (21 and 16 instances in Polissia and non-Polissia respectively).
(c) Excluded is one triplet set (*trpl-9*): first co-twin has bilateral cataract and hydrocephaly; second co-twin died at 1 day of age; and third co-twin vanished after 9 weeks of gestation.
(d) All sets are conjoined at some point of the anterior body wall.
(e) Cranio-thoraco-pagus with thoraco-lumbar spina bifida and omphalocele (h-1); thoraco-omphalo-pagus with bilocular heart (z-1).

- (f) Excludes instances of first-degree hypospadias, clubfoot, hip dislocation and dysplasia, and torticollis. Note that all co-twins are malformation-free except for two pairs described in the footnotes (t) and (cc).
- (g-dd) Descriptions of congenital malformations are followed by a clue to clinical summaries shown in square brackets: (g) lobar holoprosencephaly, microcephaly, atresia of ileum, internal hydrocephaly identified among clinical summaries as [individual tw-1]; (h) anencephaly [a-1]; (i) craniorachischisis [e-1]; lumbo-sacral spina bifida with internal hydrocephaly [i-1]; (j) two anencephalics [b-1, 2]; (k) lumbo-sacral spina bifida [j-1]; (l) male with anencephaly [b-3]; female with lumbo-sacral spina bifida and congenital hydrocephaly [j-2]; (m) ambiguous gender, pentalogy of Cantrel, omphalocele, ectopia cordis, deformed spine, unaffected male co-twin [dd-1]; (n) acardia, acephaly [tw-2]; acardia, absent upper limbs [tw-4]; acardia, amorphia [tw-5]; (o) acardia, acephaly [tw-3]; (p) acardia [tw-6]; (q) ventricular septal defect [tw-7, 13, 14]; tetralogy of Fallot [tw-18]; unspecified cardiac malformation [tw-10]; pulmonary artery atresia and aneurism of atrial septum [tw-15]; esophageal atresia, polycystic kidney, tetralogy of Fallot, pectus excavatum, [tw-12]; trilocular heart [tw-8]; (r) ventricular septal defect [tw-17]; unspecified cardiac malformation [tw-9, 16]; (s) male with ventricular septal defect [tw-11]; (t) ventricular septal defect [tw-21, 25, 26-27 (co-twins)]; (u) ventricular septal defect [tw-22]; hypoplastic right heart, atrial septal defect [tw-19]; pulmonary artery stenosis and patent foramen ovale [tw-24]; (v) male, unspecified cardiac malformation [tw-20]; female, pulmonary valve stenosis [tw-23]; (w) female, gastroschisis, intestinal eventration [ee-38]; (x) hydranencephaly [tw-37]; microtia, atretic ear canal [tw-28]; atretic ileum [tw-36]; Down syndrome [tw-29]; balanic hypospadias [tw-32]; (y) polycystic kidney [tw-31]; right cataract [tw-38]; large intestine stenosis [tw-39]; (z) male, amniotic bands, club feet [tw-30]; female, post in vitro fertilization, absent shoulder-forearm-femur, cystic hygroma [tw-34]; male, left uretherohydronephrosis [tw-35]; male, congenital hydrocephaly [tw-33]; (aa) penoscrotal hypospadias [tw-43]; balanic hypospadias [tw-40, 41, 42]; right upper limb reduction anomalies [tw-44]; jejunal atresia [tw-45]; (bb) Dandy-Walker malformation [tw-46]; abdominal wall defect [tw-50]; arthrogyrosis multiple congenital [tw-51]; (cc) male, Down syndrome, secondary atrial septal defect, female co-twin hydrocephalic [tw-47, 48]; (dd) ambiguous gender, bifid scrotum, urogenital sinus, perineal hypospadias [tw-49]; (ee) ambiguous, sirenomelia, absent upper limb [sir-2].

Table S-5. Population Rates of Neural and Other Malformations (not Individuals) in the Polissia and non-Polissia Regions of Ukraine and other regions of Europe.

Categories ^(a)	Births	NTD	MIC	mOPH	CTW	BLEXTR	OM	GSTR	CL/P
Polissia (2000-2009)	72800	25.96 (51) ^(c)	6.35	3.57	0.55*	1.24	3.43 (32) ^(c)	2.34	10.71
Non-Polissia (2000-2009)	73488	16.33 (68)	3.40	1.22	0.55*	0.68	4.22 (52)	3.13	10.75
EUROCAT Registries(2005-2009) ^(b)									
Northern England (UK)	164501	14.47 (81)	1.95	0.91	0.49	1.09	2.74 (44)	6.02	10.88
Wales (UK)	172085	13.60 (84)	5.35	1.63	0.35	0.64	4.24 (58)	6.22	11.56
Paris (France)	133880	12.77 (87)	2.46	1.12	0.15	1.57	6.05 (73)	1.27	8.52
East Midlands & South Yorkshire (UK)	358590	11.60 (77)	0.92	0.39	0.31	0.84	3.99 (57)	5.21	8.84
Wessex (UK)	143432	11.36 (89)	1.46	0.84	0.35	0.70	3.21 (54)	4.81	11.5

Thames Valley (UK)	146831	11.03 (85)	0.89	0.82	0.27	0.89	5.52 (63)	3.27	8.85
South West England (UK)	240454	10.94 (82)	5.03	1.21	0.17	0.75	3.53 (59)	4.08	8.69
Basque Country (Spain)	103040	10.77 (86)	3.88	1.07	0.19	0.58	4.66 (73)	1.65	5.43
Norway	301408	10.02 (73)	0.53	0.76	0.07	0.46	2.85 (63)	3.52	12.94
Antwerp (Belgium)	100199	9.78 (53)	2.50	1.10	0.00	0.70	1.50 (40)	1.10	11.18
Hainaut (Belgium)	63349	9.47 (83)	1.89	0.16	0.00	0.63	2.21 (64)	1.89	11.84
N Netherlands (NL)	90450	8.18 (61)	2.99	1.22	0.00	1.33	2.21 (50)	1.44	13.27
Wielkopolska (Poland)	192533	8.15 (-)	1.30	0.99	0.26	0.36	1.87 (-)	1.61	9.45
Valencia Region (Spain)	165859	6.99 (79)	4.52	0.90	0.24	0.54	0.78 (-)	1.57	5.61
Hungary	493001	6.02 (64)	1.78	1.03	0.14	0.45	1.46 (43)	0.89	7.40
Dublin (Ireland)	126232	5.94 (-)	3.41	1.51	0.00	0.95	2.38 (-)	2.61	7.76
Emilia Romagna (Italy)	203283	5.71 (71)	1.18	0.98	0.00	0.69	1.87 (55)	0.89	7.03
Tuscany (Italy)	152137	5.65 (78)	0.66	0.72	0.07	0.46	2.37 (81)	0.99	5.65

* Rivne rate (8 observations).

- (a) Abbreviations: BLEXT, urinary bladder exstrophy; CL/P, cleft lip with/without cleft palate; CTW, conjoined twins; EUROCAT, European Surveillance of Congenital Anomalies; GSTR, gastroschisis; MIC, microcephaly; mOPH, microphthalmia; NTD, neural tube defects; OM, omphalocele. Births include singletons, multiple births, live and stillbirths; exclude terminations of pregnancies; all registries (including Polissia/non-Polissia) report counts of malformations (not of infants) – same infant may appear in more than one malformation category.
- (b) Rate per 10,000 births of congenital malformations (not individuals) inclusive of live births, fetal deaths of 20 or more weeks of gestation and termination of pregnancies. Rates reported by full member registries located in Europe who reported at least 30,000 births during the 2006-2008 and at least 30 instances of NTD. These criteria were met by the 19 registries shown. Excluded were registries from Zagreb (Croatia), Odense (Denmark), Strasbourg (France), Mainz (Germany), Cork and Kerry (Ireland), SE Ireland, Malta, Barcelona (Spain), Vaud (Switzerland); S Portugal. Also excluded are registries from Saxony-Anhalt (Germany) and Styria (Austria) whose data is under review. Ukraine is excluded and instead, rates from Rivne province in Ukraine subdivided as Polissia and non-Polissia regions are presented. The rates are calculated adhering to EUROCAT methods. In this table the rates are calculated on the basis of all births and individuals with multiple congenital anomalies may be included in multiple categories. In all other tables of this report, rates are calculated on the basis of live births. The series of tables 1 and S-1 show unduplicated individuals (u-rates) and in other tables individuals may be duplicated (t-rates). EUROCAT occasionally introduces data updates, the data analyzed was last accessed on November 29, 2012.
- (c) Percent of termination of pregnancies – Data accessed on November 29, 2013.

Table S-6. Teratomas – Rivne, Volyn (2000-2009) and Khmelnytsky (Kh) Provinces (2002-2009)^(a)

Category	Rivne			Volyn			Kh	All	Sex		
	P	nP	Total	P	nP	Total			M	F	U
Live births	72379	73058	145437	62882	65928	128810	104313	378560	195593	182925	42
All conjoined twins	3	6	9 ^(b)	2		2 ^(c)	3 ^(d)	14 ^(e)	4	6	4

All teratomas	7	4	11 ^(f)	3	8	11 ^(g)	7 ^(h)	29 ⁽ⁱ⁾	7	19	3
Sacro-coccygeal ^(o)	6	3	9 ⁽ⁱ⁾	3	7	10 ^(k)	6 ^(l)	25 ^(m)	7	15	3
Teratoblastoma					1 ⁽ⁿ⁾	1		1	1		
Males (M)	1		1	1	3	4	2	7	7		
Females (F)	2	3	5	2	4	6	4	15		15	
Unknown (U)	3		3					3			3
Liveborn	3	3	6	3	4	7	3	16	4	12	
Stillborn					1	1		1	1		
ToP ^(p)	3		3		2	2	3	8	2	3	3
Non-sacro-coccygeal	1	1 ^(q)	2		1 ^(r)	1	1 ^(s)	4		4	
Teratoblastoma	1 ^(t)		1					1		1	

(a) P and nP denote Polissia and non-Polissia; rates of conjoined twins include 2010 data; case-by-case clinical highlights are listed below; (b-t) respective rates are: (b) 0.55, (c) 0.14, (d) 0.25, (e) 0.33, (f) 0.76, (g) 0.85, (h) 0.67, (i) 0.77, (j) 0.62, (k) 0.78, (l) 0.58, (m) 0.66; (n) see (*vtter-11*) below; (o) all instances are not associated with other malformations except (neo-1) and (kter-7); (p) termination of pregnancy; (q-s) non-sacro-coccygeal teratomas: (q) neck (*ter-9*); (r) maxillary (*vtter-10*); (s) thymus (kter-4); (t) neck-pharynx teratoblastoma (neo-1).

Case-by-case Clinical Highlights of Individuals with Teratomas are listed in pages 33, 46.

Table S-7. Non-Syndromic NTD Associated with Omphaloceles (OM), Body Wall and Other Anomalies in Rivne, Khmelnytsky and Volyn Provinces (2000-2009)^(a)

Category	All	OM	Comment ^(a)	M-F
Cephalad	325	17		2-9
Anencephaly	223	4	Twin, acardiac (ok-1)	
Iniencephaly	17	5	CL/P, etc (ov-7)	
Cranio-rachis-schisis	85	8	Bilocular heart (f-4)	
Spina Bifida ^(b)	380 ^(b)	10 ^(b)		3-2
High	62	2	Bladder exstrophy (h-3) Conjoined twins (h-1) Hypoplastic left heart (m-5)	
Low	260	6	Ambiguous genitals (ok-7) Renal hypoplasia (m-2) Renal unilateral agenesis (m-6)	

(a) Note: For fuller clinical descriptions see particular individuals identified in parenthesis; M-F refers to male-female proportions; in Khmelnytsky Province the data was collected from 2002 to 2009; spina bifida “high” includes anomalies above the first lumbar vertebra and “low” those located at or below the first lumbar vertebra; excluded from the above table are two instances of encephaloceles (ov-2, 5). (b) The 380 instances of spina bifida include 58 lacking description regarding the locations-extent. Among these 58 instances, 2 had an associated omphalocele.

Table S-8. Gastroschisis and Maternal Age at Delivery: Rivne and Volyn Provinces (2000-2009) and Khmelnytsky Province (2002-2009)

Category	Rivne		Volyn		Khmelnysky		All	
	N	%	N	%	N	%	N	%
Total live births	145437		128810		104313		378560	
Gastroschisis	40		40		49		129	
Maternal age <20 years of age								
All	13747	9.45	13105	10.17	11889	11.40	38741	10.23
Gastroschisis	16	40.00	9	22.50	14	28.57	39	30.23
Maternal age 20-24 years of age								
All	56066	38.55	51490	39.97	40969	39.28	148525	39.23
Gastroschisis	19	47.50	23	57.50	23	46.94	65	50.39

Table S-9. Encephaloceles and Male-Female (M-F) Proportions.

Category	Rivne			Volyn+Khmelnysky			Combined					
	N	(%)	M-F	Rate ^(a)	N	(%)	M-F	Rate ^(a)	N	(%)	M-F	Rate ^(a)
All encephaloceles	31 ^(b)		9-12	2.13	36 ^(c)		12-12	1.54	67		21-24	1.77
Non-syndromic	28	(90)	7-12	1.93	35	(97)	11-12	1.50	63	(94)	18-24	1.66
Occipital	20	(71)	5- 9	1.38	21	(60)	5- 9	0.90	41	(65)	10-18	1.08

(a) Live births: 145,437 and 233,123 in Rivne, and Volyn-Khmelnysky provinces combined respectively. (b) Includes Klippel-Feil complex (n-3) and two siblings with Meckel-Gruber complex (n-1, 2). (c) Includes suspected Meckel-Gruber complex (ov-2).

FIGURES

FIGURE S-1

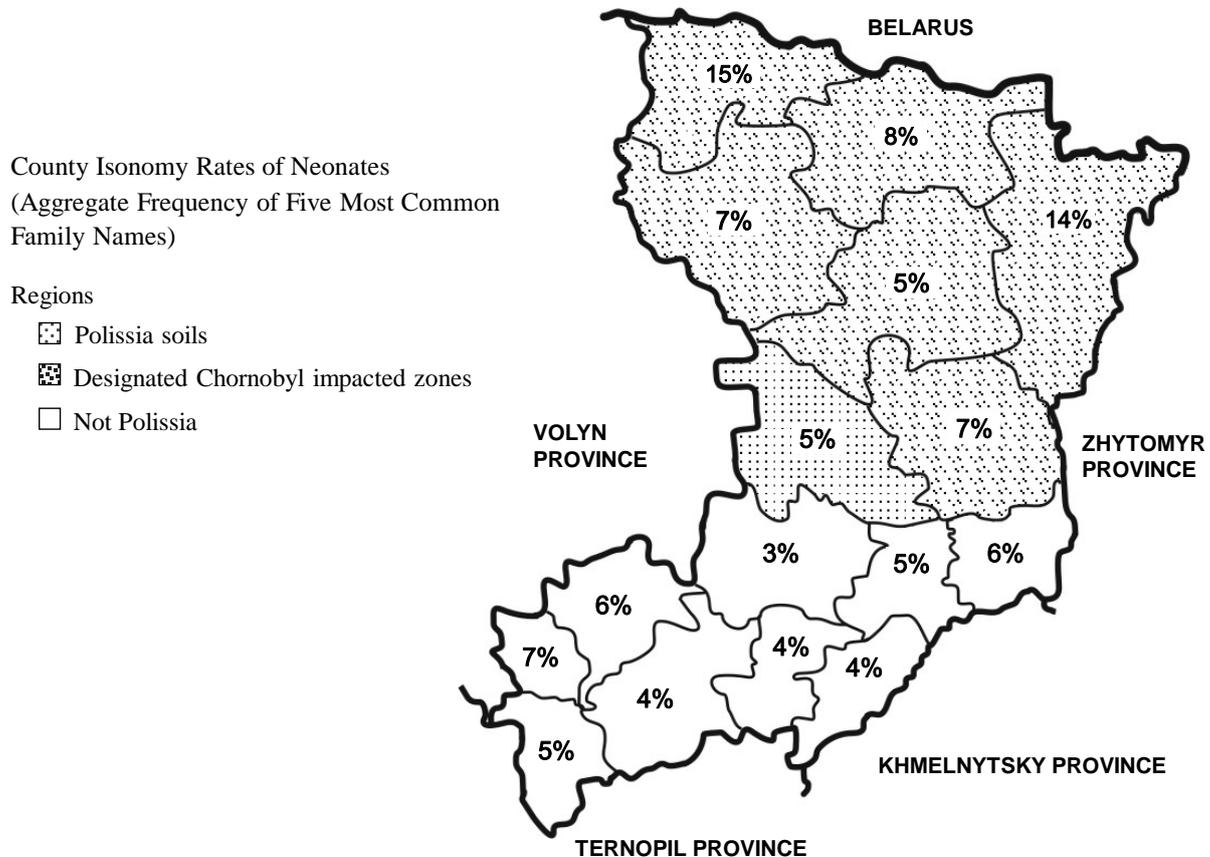


Figure S-1.

FIGURE S-2

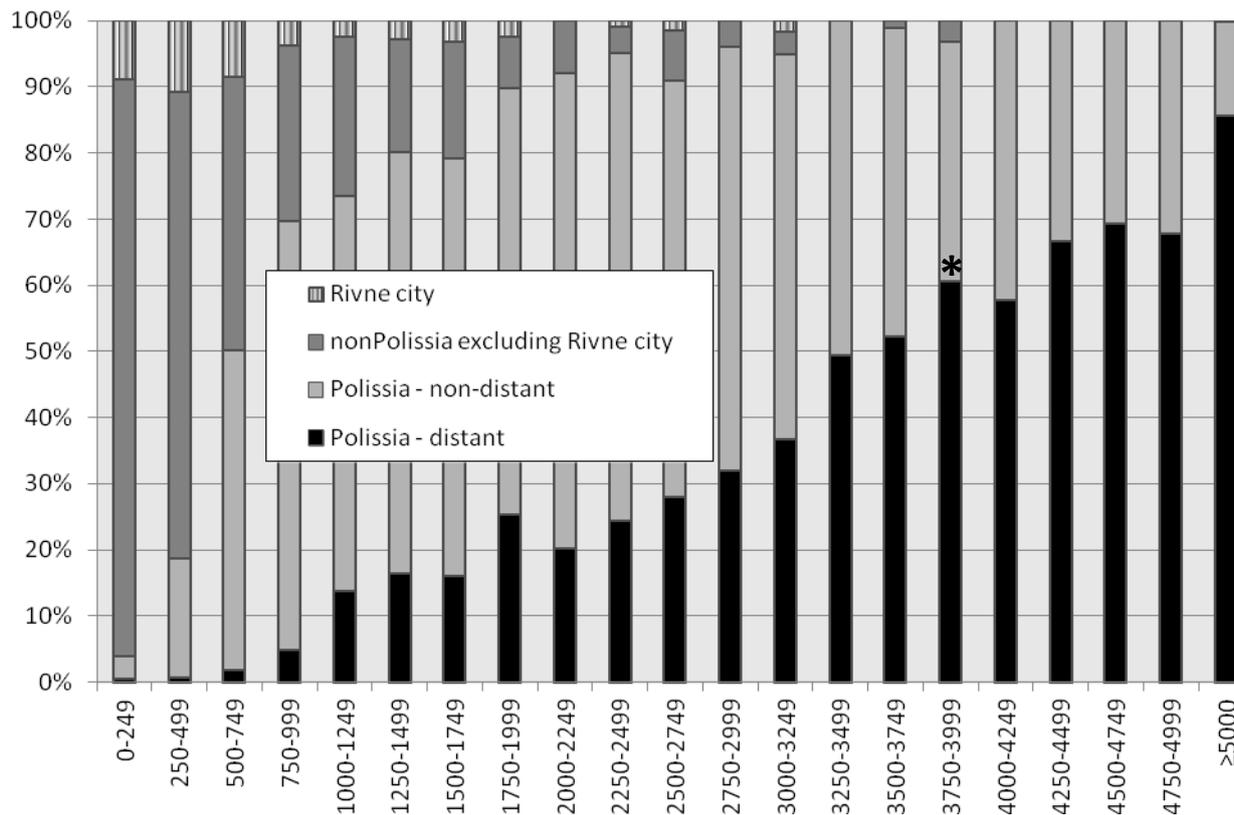


Figure S-2. Whole Body Counts of incorporated ionizing radiation (Bq ¹³⁷Cs) among 6026 pregnant women residing in Rivne Province (2008-2011). The (*) indicates the official upper norm for children under the age of 15 years (3700 Bq). (Decree #106 of Cabinet of Ministers of Ukrainian Soviet Socialist Republic of July 23, 1991. - See references).

FIGURE S-3

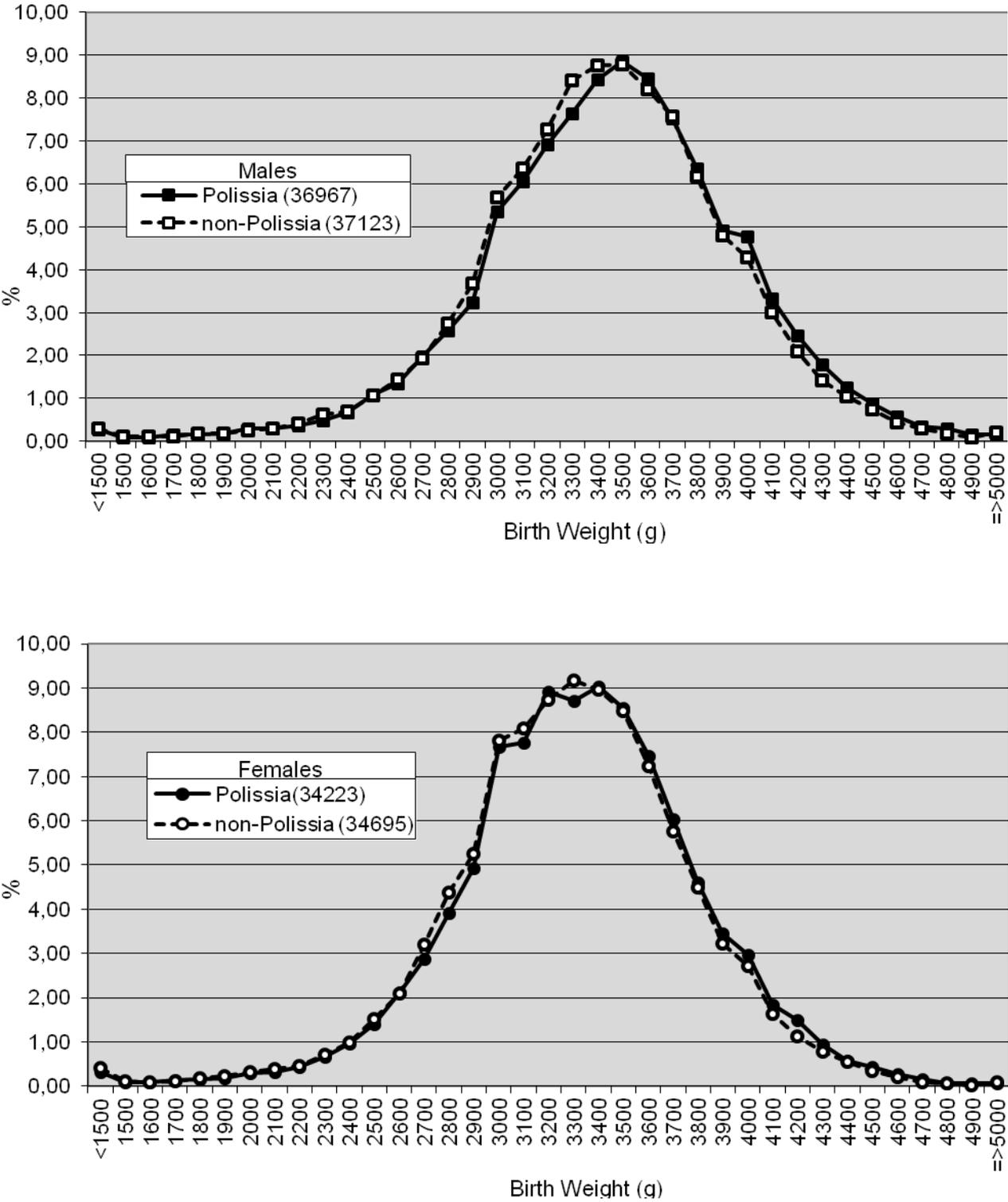


Figure S-3. Birth weight of liveborns of all gestational ages (2000-2009) in Polissia and non-Polissia regions of Rivne province of Ukraine

FIGURE S-4

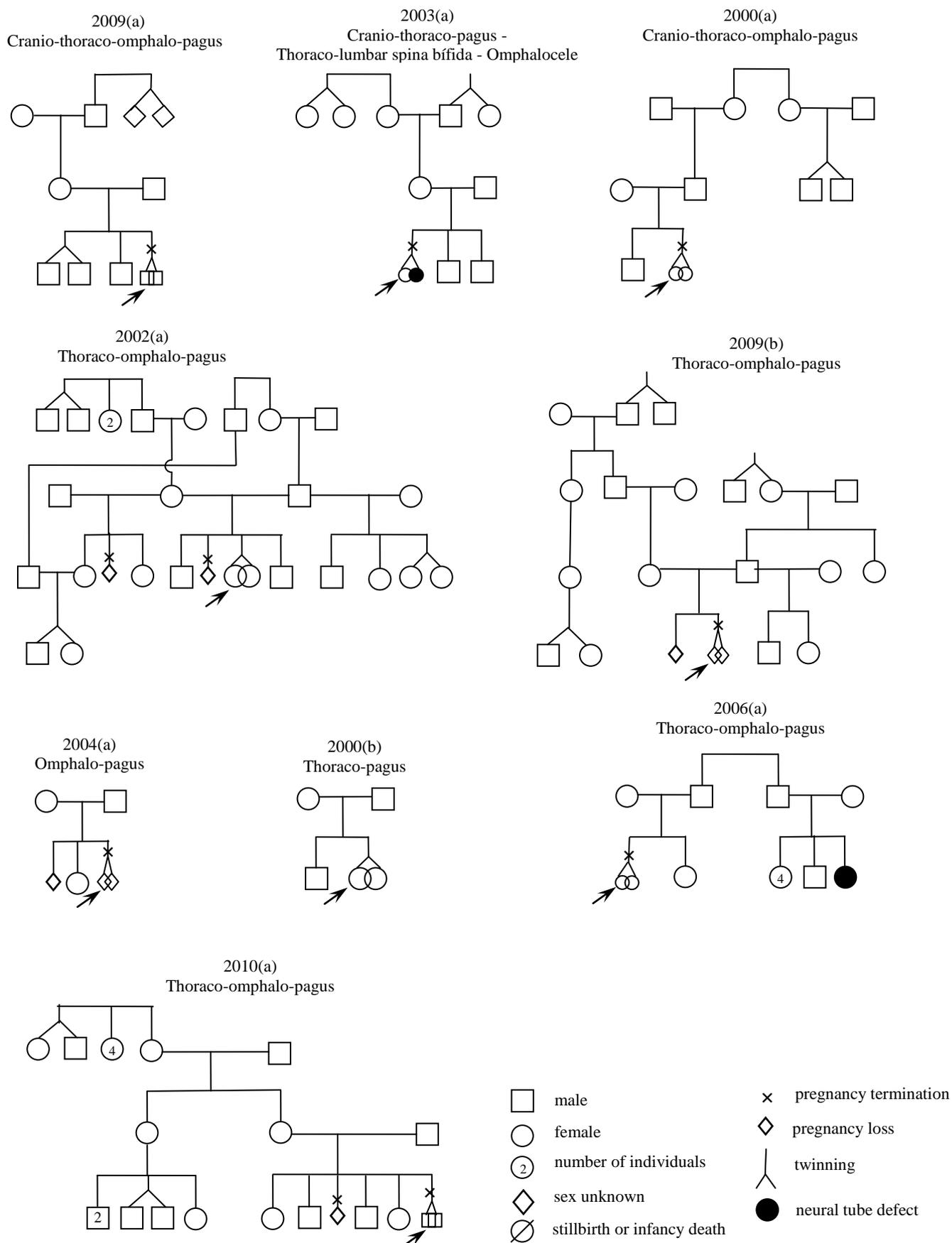


Figure S-4. Twinning Events among Relatives of Conjoined Twins (2000-2010).

SUMMARIES OF CLINICAL HIGHLIGHTS OF INDIVIDUALS INCLUDED IN THE TABLES OF THIS REPORT

Abbreviations: see below.

Congenital malformations – population-based observations.

Neural tube defects, Data Supplement page 19.

Microcephaly, page 24.

Microphthalmos, page 28.

Anterior body wall, page 29.

Omphaloceles, page 29.

Gastroschisis, page 31.

Conjoined twins, page 43.

Teratomas, page 33.

Sentinel anomalies, page 34.

Down syndrome, page 34.

Clift lip with/without cleft palate, page 34.

Supplemental survey of anterior-caudal body wall anomalies, page 36.

Ectopia cordis, page 36.

Thoraco-abdominal wall anomalies, page 36.

Exstrophy of the cloaca, page 36.

Recto anal - sirenomelia, page 37.

Additional observations, page 39.

Fetal alcohol spectrum disorder, page 39.

Holoprosencephaly, page 39.

Trisomy 13 or Patau syndrome, page 42.

Neoplasia, page 42.

All non-singleton individuals, page 42.

Observations in Rivne, Volyn and Khmelnytsky provinces, page 46.

Teratomas, page 46.

NTD-omphalocele associations, page 47.

Abbreviations:

abd(omen, omental); **abs**(ent); **agen**(esis); **amb**(iguous genitalia); **AN**(encephaly); **anom**(alies); **ant**(erior, eriorly); **apl**(asia); **ASD**, atrial septal defect; **atr**(esia); **A-V**, atrio-ventricular; **b**(irth); **bilat**(eral); **BLEXTR**, urinary bladder exstrophy; **Bwt**, birth weight; **call**(osum); **calv**(arium); **cav-sept-pel**, cavum septum pellucidum; **cerebel**(lum, lar); **cerebr**(al, um); **CHD**, cardiac malformations; **CL**, cleft lip; **clindx**, clinical diagnosis, implies no karyotype; **CL/P**, cleft lip and palate; **CM**, congenital malformation(s); **CMV**, cytomegalovirus; **conc**(ordant); **cong**(enital); **corp**(us); **CP**, cleft palate; **CRA**(niorachischisis); **CT**, computerized tomography; **CTW**, conjoined twins; **d**(ays); **def**, defect, deformed, deformation, deficiency; **diaphr**(agm); **disc**(ordant), discordant twin; **disloc**(ation); **dupl**(ication); **dysm**(orphic); **dyspl**(astic); **ECTC**, ectopia cordis; **ENC**(ephalocele); **esoph**(agus); **eventr**(ation, ated); **excl**(udes); **exophth**(almos); **ext**(ernal); **f**(emale); **fam**(ilial, family history); **FASD**, Fetal alcohol spectrum disorder; **gest**(ation, al); **GSTR**, gastroschisis; **H-SB**, cervical–thoracic spina bifida; **hemisp**(here, heric); **HOLOP**(rosencephaly); **hydroceph**(alus); **hyper**(telorism, trophy); **hypopl**(asia); **hyposp**(adias); **incl**(udes, usion); **INIEN**(cephaly); **int**(ernal); **intest**(ine, inal); **IVF**, in-vitro fertilization; **IUGR**, intrauterine growth retardation; **lat**(eral, erally); **L**(eft); **LB**, liveborn; **L-SB**, lumbar–sacral spina bifida; **m**(ale); **mal**(ormation); **mat**(ernal); **MIC**(rocephaly); **mo**(nths); **mOPH**, microphthalmia or anophthalmia; **MR**, mental retardation; **mult**(iple); **multicys**(tic); **N**, count of individuals; **NTD**, neural tube defects; **occip**(ital); **OFC**, occipito–frontal circumference; **oligohydr**(amnios); **OM**(phalocele); **OS**, ostium secundum; **pat**(ernal); **pct**, percentile; **PDA**, patent ductus arteriosus; **PFO**, patent foramen

ovale; **PKU**, phenylketonuria; **PNGR**, postnatal growth retardation; **polycys(tic)**; **polyd(actly)**; **polyhydr(amnios)**; **post(erior)**; **postax(ial)**; **preax(ial)**; **prenat(al)**; **propt(osis)**; **pulm(onary)**; **R(ight)**; **reduct(ion)**; **retard(ation)**; **S(tillbirth)**; **SA**, spontaneous abortion; **SB**, spina bifida; **sept(um)**; **short(ening)**; sir(enomelia); **sten(osis)**; **synd(rome)**; **T-E**, tracheo-esophageal fistula; **TER(atoma)**; **THAB**, thoraco-abdomino-schisis; **ToP**, termination of pregnancy; **TW(ins)**; **u(nknown gender, age)**; **umb(ilical)**; **unilat(eral)**; **ventr(icle)**; **VSD**, ventricular septal defect; **w(ith)**; **wks**, week(s), **yr**, year(s).

Notes:

Individuals are listed only once and include singletons and non-singletons.

Individuals from non-Polissia are shown in italics.

Non-singletons are also listed separately.

The sequence of the clinical summaries is: key number; year; gender; ToP or stillbirth (S) or liveborn (LB); weeks of gestation; singletons are not indicated - non-singletons are indicated, including concordance with co-twins; main clinical category in CAPS followed by prenatal and/or postnatal observations; and highlights concerning relatives including twinning events. Regarding prenatal diagnosis indicated as prenat at a given week, the detection of the anomaly subsequently confirmed is assumed - other anomalies are described.

Salient congenital malformations are shown in bold.

“**Isolated**” implies lack of associated congenital malformations.

Holoprosencephaly individuals are excluded from all core congenital malformation categories except teratomas. Holoprosencephaly individuals may be included among individuals with non-core congenital malformations.

The sequence of listed congenital malformation categories is:

Neural tube defects (below), microcephaly (page 24), microphthalmia (page 28), anterior body wall anomalies (pages 29, 36), omphaloceles (page 29), gastroschisis (page 31), urinary bladder exstrophy (page 33), teratomas (page 33), sentinel anomalies (page 34), Down syndrome (page 34), cleft lip/palate (page 34), recto-anal and cloacal (page 36), sirenomelia (page 39), fetal alcohol spectrum disorders (page 39), holoprosencephaly (page 39), trisomy 13 or Patau syndrome (page 42), neoplasia (page 42), non-singletons (page 42).

NEURAL TUBE DEFECTS (NTD)

Neural Tube Defects (NTD) in Polissia (POL) and non-Polissia (NPOL) - Prenatal Diagnosis (PD) and Terminations of Pregnancies (ToP)

Region	Years	NTD total	PD	ToP after PD	No PD
POL	2000-2004	98	68	46	30
	2005-2009	91	80	50	11
Total POL		189	148	96	41
NPOL	2000-2004	61	50	36	11
	2005-2009	59	57	44	2
Total NPOL		120	107	80	13
Total		309	255	176	54

Cephalic

Anencephaly (AN) (66 individuals)

When detected, birth status and sex:

< 15,	13	Stillborn	(S), 12		Polissia	non-Polissia
15-20,	36	Spontaneous abortion	(SA), 6	Males	12	8
21-24,	7	Termination of pregnancy (ToP),	48	Females	16	9
25-34,	6			Unknown	9	12
35-40,	1					
At birth,	3					

Isolated – Singletons (58 individuals)

When detected, birth status and sex:

< 15,	11	Stillborn	(S), 7		Polissia	non-Polissia
15-20,	33	Spontaneous abortion	(SA), 6	Males	11	5
21-24,	6	Termination of pregnancy (ToP),	45	Females	15	8
25-34,	5			Unknown	7	12
35-40,	1					
At birth,	2					

Isolated – not Singletons

- a-1 2002; m; S; 39 wks; Bwt 890 g; TW; AN, disc m-m.
- b-1 2001; m; S; 38 wks; Bwt 3000 g; TW; AN, disc m-m, monochorial; prenat 27 wks.
- b-2 2005; m; S; 38 wks; Bwt 2500 g; TW; AN, disc m-m; prenat 16 wks.
- b-3 2008; m; S; 35 wks; Bwt 1655 g; TW; AN, disc m-f, di-amniotic; prenat 12 wks.

Not Isolated – non-Syndromic – non-NTD anomalies among Singletons

- c-1 2000; f; S; 33 wks; Bwt 1000 g; AN; **mOPH**; anotia; prenat 19 wks.
- c-2 2002; u; ToP; 21 wks; Bwt 320 g; AN; **CL**; prenat 19 wks. mat fam 3 TW pairs.
- c-3 2006; u; ToP; 12 wks; AN; **OM**; prenat 12 wks. mat goiter.
- d-1 2004; f; ToP; 22 wks; AN; **esoph atr**; prenat 21 wks, polyhydr.

Anencephaly-Rachischisis (Craniorachischisis) (CRA), Includes Iniencephaly (INIEN) (50 individuals)

When detected, birth status and sex:

< 15,	12	Stillborn	(S), 7		Polissia	non-Polissia
15-20,	18	Spontaneous abortion	(SA), 4	Males	9	3
21-24,	13	Termination of pregnancy (ToP),	39	Females	19	6
25-34,	6			Unknown	6	7
35-40,	1					

Isolated – Singletons (34 individuals)

When detected, birth status and sex:

< 15,	6	Stillborn	(S), 4		Polissia	non-Polissia
15-20,	14	Spontaneous abortion	(SA), 2	Males	7	3
21-24,	9	Termination of pregnancy (ToP),	28	Females	12	4
25-34,	4			Unknown	3	5
35-40,	1					

Isolated – not Singleton

- e-1 2005; f; S; 38 wks; Bwt 1720 g; TW; CRA, disc f-f.

Not Isolated – non-Syndromic – Singletons (15 individuals)

When detected, birth status and sex:

When detected	Birth status	Sex	Polissia	non-Polissia
< 15, 6	Stillborn (S), 2			
< 15, 6	Spontaneous abortion (SA), 2	Males	2	0
15-20, 4	Termination of pregnancy (ToP), 11	Females	6	2
21-24, 3		Unknown	3	2
25-34, 2				

- f-1 2000; amb; ToP; 20 wks; Bwt 230 g; CRA; bilat **reduct forearms-legs**; CHD; R multicys renal; prenat 14 wks, IUGR, exencephaly, cervical meningocele, VSD, R multicys kidney, bilat reduct forearm-tibia, 4 fingers, oligodactyly toes.
- f-2 2001; f; ToP; 21 wks; Bwt 450 g; INIEN; thoraco-lumbar SB; **OM**; polyhydr; prenat 24 wks.
- f-3 2004; f; ToP; 27 wks; Bwt 900 g; CRA; **CL/P**; **diaphr hernia**; **esoph atr**; prenat 26 wks, polyhydr, calv not seen, exophth, rachischisis, bilat CL, cardiac disloc to R, intest loops in L thorax, diaphr hernia.
- f-4 2004; f; SA: 27 wks; Bwt 710 g; CRA; **OM**; CHD (**bilocular heart**); prenat 16 wks, polyhydr; one pair TW in mat and pat fam, both f-m.
- f-5 2005; u; ToP; 11 wks; INIEN; **OM**; prenat 10 wks, anom occipital bone w brain protrusion.
- f-6 2005; f; ToP; 20 wks; Bwt 420 g; CRA, ocular propt; **OM**; mat bronchospasms; prenat 17 wks.
- f-7 2007; m; S; 32 wks; Bwt 1500 g; CRA; **OM**; prenat 12 wks, AN, rachis-schisis, extra abd liver.
- f-8 2008; u; ToP; 13 wks; CRA; **OM**; prenat 12 wks, AN, rachis-schisis, abd organs herniation; fam mat m-m TW.
- f-9 2008; f; S; 26 wks; Bwt 280 g; CRA; **diaphr hernia**; R pulm hypopl; exophth; prenat 25 wks, polyhydr, AN, exophth, rachischisis, diaphr hernia, cardiac disloc to R, eventr abd organs.
- f-10 2008; m; ToP; 20 wks; CRA; **diaphr hernia**; prenat 19 wks, AN-rachis-schisis, exophth, dextrocardia; fam sib (1997) had AN and SB.
- f-11 2008; f; ToP; 21 wks; CRA; **esoph atr**; prenat 21 wks, polyhydr, AN-rachis-schisis.
- g-1 2002; f; SA; 22 wks; Bwt 850 g ; CRA; R **multicys renal**; prenat 20 wks.
- g-2 2002; u; ToP; 13 wks; CRA; **THAB**; S-like def spine; prenat 13 wks.
- g-3 2004; f; ToP; 25 wks; CRA; **esoph atr**; prenat 24 wks, polyhydr, one umb artery.
- g-4 2008; u; ToP; 12 wks; INIEN; **OM**; prenat 11 wks, cephalic retroflexion, cerebr anom, nuchal thickness and short spine; fam, sib (2006) cong deaf and CHD, mat fam anus atr.

Spina Bifida (SB) - Cervico-Thoracic (21 individuals)

When detected, birth status and sex:

When detected	Birth status	Sex	Polissia	non-Polissia
< 15, 1	Liveborn (LB), 9			
15-20, 10	Stillborn (S), 1	Males	10	3
21-24, 4	Spontaneous abortion (SA), 2	Females	5	1
35-40, 2	Termination of pregnancy (ToP), 9	Unknown	2	0
At birth, 4				

Isolated – Singletons (18 individuals)

When detected, birth status and sex:

When detected	Birth status	Sex	Polissia	non-Polissia
< 15, 1	Liveborn (LB), 8			
15-20, 8	Stillborn (S), 1	Males	8	3
21-24, 4	Spontaneous abortion (SA), 1	Females	4	1
35-40, 2	Termination of pregnancy (ToP), 8	Unknown	2	0
At birth, 3				

Not Isolated – non-Syndromic - Not Singletons

- h-1 2003; f-f; SA; 23 wks; Bwt 520 g; CTW, **cranio-thoraco-pagus**; SB, thoraco-lumbar; **OM**; prenat 15 wks; fam mat one f-f TW and one m-f TW.

Not Isolated – non-Syndromic – Singletons

- h-2 2003; m; ToP; 21 wks; Bwt 220 g; SB, cervico-thoracic; cong hydroceph; **reduct lower limbs**; prenat 20 wks.
- h-3 2003; m; LB; 40 wks; Bwt 2800 g; SB, thoraco-lumbar; **OM; BLEXTR**; bifid scrotum; anus atr; OEIS complex.

Spina Bifida (SB) - Lumbo-Sacral (126 individuals)

When detected, birth status and sex:

< 15,	4	Liveborn	(LB), 55		Polissia	non-Polissia
15-20,	37	Stillborn	(S), 9	Males	34	24
21-24,	18	Spontaneous abortion	(SA), 5	Females	31	21
25-34,	29	Termination of pregnancy (ToP),	57	Unknown	9	7
35-40,	3					
At birth,	35					

Isolated – Singletons (109 individuals)

When detected, birth status and sex:

< 15,	2	Liveborn	(LB), 46		Polissia	non-Polissia
15-20,	32	Stillborn	(S), 8	Males	31	20
21-24,	17	Spontaneous abortion	(SA), 5	Females	28	18
25-34,	27	Termination of pregnancy (ToP),	50	Unknown	6	6
35-40,	2					
At birth,	29					

Isolated – not Singletons

- i-1 2008; f; LB; 39 wks; Bwt 2730 g; TW, monochorionic, diamniotic; SB, lumbo-sacral, disc f-f; int hydroceph; prenat 18 wks, int hydroceph, malf post cranial fossa (Arnold-Chiari), sacral SB; fam mat one m-f TW; fam pat two cases of mental retard.
- j-1 2003; f; LB; 34 wks; Bwt 1000 g; TW; SB, lumbo-sacral, disc f-f.
- j-2 2004; f; LB; 36 wks; Bwt 2100 g; TW; SB, lumbo-sacral, disc m-f; cong hydroceph; prenat 18 wks.

Not Isolated – Syndromes – Singleton

- k-1 2004; f; LB; 35 wks; Bwt 2350 g; SB lumbo-sacral; **FASD**; cong hydroceph; Bwt 2350 g; at b OFC 31 cm; two sibs with FASD (2007, 2010).

Not Isolated – non-Syndromic – Singletons (13 individuals)

When detected, birth status and sex:

< 15,	2	Liveborn	(LB), 5		Polissia	non-Polissia
15-20,	3	Stillborn	(S), 1	Males	3	4
21-24,	1	Termination of pregnancy (ToP),	7	Females	1	1
25-34,	2			Unknown	3	1
35-40,	1					
At birth,	4					

- l-1 2000; u; ToP; 20 wks; SB, lumbo-sacral; L kidney hypopl; cardiomegaly, **R kidney agen**; prenat 19 wks, IUGR, oligohydr, lumbo-sacral SB, L kidney not seen.
- l-2 2002; m; ToP; 28 wks; Bwt 940 g; SB, lumbo-sacral; **CL/P**; prenat 27 wks, OFC 222 mm (3%).
- l-3 2002; m; LB; 40 wks; Bwt 2200 g; SB, lumbo-sacral; bilat **CL/P**; **reduct legs**; Bwt 2200 g; at b OFC 32cm; no other signs of fetal alcohol effects; mat alcohol use.
- l-4 2007; m; LB; 40 wks; Bwt 3750 g; SB, lumbar; hydroceph; L hand **preax polyd**.

- 1-5 2008; u; ToP; 13 wks; SB, lumbo-sacral; **OM**; IVF; prenat 12 wks, SB, lumbo-sacral, malf abd wall.
- 1-6 2008; f; LB; 39 wks; Bwt 2800 g; SB lumbar; hydroceph; **caudal regression** sequence; PFO; prenat 36 wks, cerebr and cerebel malf (Arnold-Chiari), SB lumbosacral.
- 1-7 2009; u; ToP; 21 wks; SB, lumbo-sacral; ventral body wall and **stalk anom; red lower limbs**; prenat 20 wks, hypoactive fetus w back tightly **adjoined to placenta**, umb cord not seen, anom body stalk, thick placenta, cardiomegaly, lumbo-sacral SB, abd wall defect and eventr liver, intest, kidneys and stomach, bilat femurs 42 mm, lower legs and feet not seen, echo-free cystic mass in distant lower limb area.
- m-1 2000; f; ToP; 22 wks; Bwt 340 g; SB, lumbo-sacral; chest deformity; **L femur reduct**; prenat 16 wks, SB lumbo-sacral - cleft vertebrae with hernia, chest malf, L femur not seen.
- m-2 2000; u, ToP; 26 wks; SB, lumbar; cong hydroceph; **OM**; **renal hypopl**; prenat 26 wks oligohydr, hydroceph, SB.
- m-3 2001; m; LB; 39 wks; Bwt 2600 g; SB, lumbo-sacral; VSD; **L tibia reduct**; fam, sib (1997) with cong scoliosis and R leg reduct.
- m-4 2004; m; S; 41 wks; Bwt 4500 g; SB, lumbar; Arnold-Chiari; **diaphr hernia**; **anus atr**; gest fetoplacental def.
- m-5 2006; m; ToP; 21 wks; Bwt 220 g; SB, sacral; **OM**; hypopl L heart; prenat 21 abd hernial sack, L heart hypopl, abd protrusion organs per umb ring.
- m-6 2009; m; LB; 30 wks; Bwt 1420 g; SB, lumbar; **OM**; unilat **renal agen**; thoracic kyphosis; died at 1 day; prenat 11 wks, nuchal thickness, abd wall malf; prenat 23 wks, oligohydr, one umb artery, lumbar SB, OM; fam sib TW (2007).

Spina Bifida (SB) - Site not Specified (15 individuals)

Isolated – Singletons (15 individuals)

- naa-1-11 (2 males, 8 females, 1 of sex unknown).
 nab-12-15 (no males, 1 female, 3 of sex unknown).

Encephaloceles (ENC) (31 individual)

Male-Female (M-F) proportions:

	All	Polissia	non-Polissia	Combined
All encephaloceles	31	4-9	5-3	9-12
Non-syndromic occipital	20	1-7	4-2	5- 9
Non-syndromic non-occipital	8	1-2	1-1	2- 3

(Also see Table S-9 (in page 13) for data from three provinces).

When detected, birth status and sex:

< 15,	5	Liveborn	(LB),	8
15-20,	16	Stillborn	(S),	3
21-24,	1	Termination of pregnancy (ToP),		20
25-34,	5			
At birth,	4			

Isolated – Singletons (23 individuals)

When detected, birth status and sex:

< 15,	3	Liveborn	(LB),	5
15-20,	13	Stillborn	(S),	3
21-24,	1	Termination of pregnancy (ToP),		15
25-34,	3			
At birth,	3			

- n-1 2003; u; ToP; 21 wks; Bwt 215 g; ENC, occip and **polycys kidneys**, bilat **postax polyd**, hands and feet (**fam Meckel-Gruber complex**, see individual n-2 below); prenat 20 wks,

- oligohydr; mat sib (2004, see below) and another sib (2006) w Meckel synd w no ENC and advanced hydroceph; fam mother also had triamniotic triplets (2012).
- n-2 2004; m; ToP; 17 wks; ENC, occip and **polycys kidneys, polyd postax (fam Meckel-Gruber coomplex**, see individual n-1 above); prenat 16 wks, oligohydr; fam sib (2003, above) and another sib (2006) w Meckel synd w no ENC and advanced hydroceph; fam mother also had triamniotic triplets (2012).
- n-3 2008; m; LB; 38 wks; Bwt 2650 g; ENC occip; int hydroceph; **Klippel-Feil complex**; chest def; R foot valgus; no polyd-renal abn.

Not Isolated – non-Syndromic – Singletons

- p-1 2003; m; LB; 38 wks; Bwt 2800 g; ENC, occip; **L multicys kidney**; prenat 33 wks; no polyd.
- q-1 2001; m; LB; 40 wks; Bwt 3400 g; ENC, occip; **VSD**; prenat 25 wks.
- q-2 2001; u; ToP; 22 wks; ENC, frontal and **amniotic bands**; **reduct limbs**; spine def; prenat 20 wks, cranio-frontal def w protruding cerebr, spine def, L forearm reduct, L hand seen, R forearm and hand not seen; L tibia and foot malf, R leg not seen; noted fetus entangled in amniotic bands.
- q-3 2009; u; ToP; 12 wks; ENC frontal; **ECTC**; **THAB**; prenat 12 wks, frontal ENC, ECTC, extra abd liver.
- q-4 2009; f; ToP; 14 wks; Bwt 150 g; ENC, temporo-parietal and unilat **reduct leg and foot**; prenat 13 wks, large def temporal bone and herniated cerebr w membrane, one femur reduct; fam mat has L dupl kidney-ureter and R renal hypopl; fam mat two m- m TW.

MICROCEPHALY (MIC) (68 individuals)

Listed in alternative CM categories (holoprosencephaly is excluded):

- tw-1 holoprosencephaly, see non-singleton twin category.
- hol-6 see holoprosencephaly category.
- hol-20 see holoprosencephaly category.

When detected, birth status and sex:

25-34,	2	Liveborn	(LB), 66		Polissia	non-Polissia
35-40,	2	Stillborn	(S), 2	Males	20	12
At birth,	31			Females	24	12
<1 st yr.,	33					

Isolated – Singletons (22 individuals, all liveborn)

Note: includes instances associated with microphthalmia or cataract.

When detected, birth weight and sex:

25-34,	1	1000-1499 g,	1		Polissia	non-Polissia
35-40,	1	1500-1999 g,	3	Males	3	3
At birth,	10	2000-2499 g,	3	Females	11	5
<1 st yr,	10	2500-2999 g,	10			
		3000-3499 g,	5			

Note: among 22 individuals 12 (55%) were born at ≥ 38 wks of gestation and had birth weights of ≤ 3000 g.

- ri-1 2001; f; LB; 37 wks; Bwt 2700 g; MIC; at b OFC 32 cm, ≤ 1.5 SD; at age 9 d 30.5 cm, ≤ 3 SD.
- ri-2 2002; f; LB; 38 wks; Bwt 2800 g; MIC; at b OFC 30 cm, ≤ 3 SD; at age 7 mo 36 cm, ≤ 3 SD; at age 46 mo 40.5 cm, ≤ 5 SD.

- ri-3 2002; m; LB; 37 wks; Bwt 2800 g; MIC; at b OFC 30.5 cm, \leq 3rd pct; at age 10 d 31 cm, \leq 3 SD.
- ri-4 2002; m; LB; 41 wks; Bwt 3200 g; MIC; at b OFC 32 cm, \leq 2 SD; at age 3 mo 36 cm, \leq 3.5 SD; at 12 mo 39 cm, \leq 5 SD.
- ri-5 2003; f; LB; 39 wks; Bwt 2850 g; MIC; at b OFC 30.5 cm, \leq 3 SD; at age 16 d 30 cm, \leq 3 SD.
- ri-6 2003; f; LB; 38 wks; Bwt 3400 g; MIC; bilat **cataract**; ovarian cyst; at b OFC 33 cm, 25th pct; at age 24 d 32 cm, \leq 3 SD; at age 7 mo 39 cm, \leq 3 SD; at age 12 mo 41 cm, \leq 3 SD; prenat polyhydr, mat anemia.
- ri-7 2003; f; LB; 35 wks; Bwt 1800 g; MIC; at b OFC 28 cm, \leq 3 SD; at age 4 wks 30 cm, \leq 3 SD.
- ri-8 2004; f; LB; 40 wks; Bwt 1200 g; MIC; **mOPH**; single umb artery; at b OFC 25 cm, \leq 3 SD; died at 3 mo.
- ri-9 2004; f; LB; 38 wks; Bwt 2800 g; MIC; at b OFC 29 cm, \leq 3 SD.
- ri-10 2007; f; LB; 40 wks; Bwt 2770 g; MIC; at b OFC 29.5 cm, \leq 3.5 SD; at age 6 mo 36.5 cm, \leq 3 SD.
- ri-11 2008; f; LB; 41 wks; Bwt 2200 g; MIC; at b OFC 30 cm, \leq 3 SD; at age 2 yrs 42 cm, \leq 3 SD.
- ri-12 2009; f; LB; 39 wks; Bwt 2300 g; MIC; bilat **mOPH**; bilat **corneal opacity**; at b OFC 29 cm, \leq 4 SD; at age 2 yrs 40 cm, \leq 4 SD.
- ri-13 2009; f; LB; 41 wks; Bwt 3400 g; MIC; hydroceph; agen corp call; at b OFC 29 cm, \leq 3 SD; prenat 36 wks, OFC 281 mm - for 30 gest wks, agen corp call, hydroceph; fam sib (2010) had MIC.
- ri-14 2009; m; LB; 40 wks; Bwt 3450 g; MIC; incomplete lissencephaly; at b OFC 32 cm, \leq 2 SD; at age 4 mo 38 cm, \leq 3 SD.
- rj-1 2000; m; LB; 37 wks; Bwt 2800 g; MIC; *acrocephaly; contracture 3-4 fingers; hypertroph shoulder girdle; at b OFC 31 cm, \leq 3rd pct; at age 4 mo 37 cm, \leq 3 SD.*
- rj-2 2002; m; LB; 40 wks; Bwt 2550 g; MIC; at b OFC 32 cm, \leq 2 SD; at age 2 mo 35.5 cm, \leq 3 SD; at age 12 mo 40.5 cm, \leq 4 SD.
- rj-3 2004; f; LB; 40 wks; Bwt 3400 g; MIC; at b OFC 32 cm, \leq 2 SD; at age 2.5 wks 33.5 cm, \leq 2 SD; at age 34 mo 43.5 cm, \leq 3.5 SD.
- rj-4 2005; f; LB; 39 wks; Bwt 2250 g; MIC; at b OFC 29 cm, \leq 4 SD; at age 9 d 30 cm, \leq 3,4 SD; at age 29 mo 38 cm, \leq 6 SD.
- rj-5 2006; f; LB; 39 wks; Bwt 2900 g; MIC; at b OFC 32 cm, \leq 1.75 SD; at age 2.5 mo 33 cm, \leq 3 SD; at age 4.5 mo 35 cm, \leq 4 SD.
- rj-6 2008; m; LB; 39 wks; Bwt 2750 g; MIC; *PFO; hypopl scrotum; 46, XY; at b OFC 31 cm, \leq 2.75 SD; at age 4.5 mo 37 cm, \leq 4 SD.*
- rj-7 2008; f; LB; 36 wks; Bwt 1750 g; MIC; at b OFC 29 cm, \leq 3 SD; at age 5 wks 31 cm, \leq 3 SD; at age 10 wks 33 cm, \leq 3 SD; at age 13 mo 40 cm, \leq 3 SD.
- rj-8 2008; f; LB; 39 wks; Bwt 1920 g; MIC; *int hydroceph; hypopl cerebel and corp call; aplasia vermis cerebelli; at b OFC 29 cm, \leq 3 SD; prenat 32 wks, int hydroceph, oligohyd, IUGR, OFC 284 mm.*

Not Isolated – Syndromes – Singletons (29 individuals)

When detected, birth status and sex:

25-34,	1	Liveborn (LB),	29	Polissia	non-Polissia	
At birth,	13			Males	10	8
<1 st yr.,	15			Females	5	6

- r-1 2000; m; LB; 33 wks; Bwt 2250 g; at b OFC 24 cm, ≤ 3 SD; at age 5 wks 26 cm, ≤ 5 SD; **FASD**; micro-hydroceph; L mega-hydro-urether, died at 5 mo; prenat 33 wks, oligohydr, MIC, hypopl umb cord.
- r-2 2002; m; LB; 39 wks; Bwt 1950 g; **FASD**; MIC; OS and ASD; at b OFC 31 cm, ≤ 3 SD; at age 1 mo 32.5 cm, ≤ 4 SD; at age 8 mo 40.5, ≤ 3 SD; at age 21 mo 43 cm, ≤ 3 SD.
- r-3 2003; m; LB; 38 wks; Bwt 2700 g; **FASD**; MIC; at b OFC 36 cm and at age 8 mo 40 cm, ≤ 3 SD; mat alcohol abuse.
- r-4 2003; m; LB; 32 wks; Bwt 2100 g; **FASD**; MIC; at b OFC 28 cm, 12th pct; at age 4 wks 29 cm, 12th pct; at age 30 mo 42.5 cm, ≤ 3 SD; mat alcohol abuse.
- r-5 2005; m; LB; 39 wks; Bwt 1400 g; **FASD**; MIC; at b OFC 29 cm, ≤ 3 SD; at age 1 mo 31 cm, ≤ 3 SD; at age 14 mo 33 cm, ≤ 7 SD; mat alcohol abuse.
- r-6 2006; m; LB; 37 wks; Bwt 2200 g; 5p- **Cri du Chat** synd; MIC; at b OFC 30.5 cm, ≤ 3 SD; at age 5 mo 36 cm, ≤ 5 SD; mat diffuse goiter; fam mat one f-f TW.
- r-7 2006; f; LB; 36 wks; Bwt 1820 g; 46,XX, **Cornelia deLange** synd; MIC; VSD; R hand ectrodactyly; hypopl L radius and hand; died at 2 yr 8 mo; at b OFC 29 cm, ≤ 3 SD; at age 14 wks 32 cm, ≤ 5 SD.
- r-8 2006; m; LB; 39 wks; Bwt 1980 g; **FASD**; MIC; at b OFC 30 cm, ≤ 3 SD; at age 10 wks 34.5 cm, ≤ 4 SD; mat smoker and alcohol abuse.
- r-9 2007; m; LB; 40 wks; Bwt 1700 g; **Angelman** synd; MIC; hypotonic, hypopl corp call; at b OFC 30 cm, ≤ 3 SD; at age 1 mo 32.5 cm, ≤ 3 SD; at age 20 wks 38.5 cm, ≤ 3 SD; at age 34 mo 44.5 cm, ≤ 3 SD.
- r-10 2008; m; LB; 37 wks; Bwt 2300 g; MIC; **PKU** fetopathy; double outlet R ventr; VSD; PFO; at b 30 cm, 3rd pct; at 30 wks gest OFC 27.5 cm, 11th pct; at age 29 mo 42 cm, ≤ 5 SD; prenat polyhydr; mat PKU; fam parents 3rd cousins.
- r-11 2008; f; LB; 36 wks; Bwt 1700 g; **FASD**; MIC; ASD; mat syphilis, fetus not infected; at age 2 wks OFC 30 cm, ≤ 3 SD; at age 7 wks 32.5 cm, ≤ 3 SD.
- r-12 2008; f; LB; 35 wks; Bwt 1850 g; **FASD**; MIC; mat syphilis positive; at b OFC 28 cm, ≤ 3 rd pct; at age 34 wks 40 cm, ≤ 3 SD; fam both parents alcohol abusers.
- r-13 2008; f; LB; 38 wks; Bwt 3240 g; 46,XY, **ring chrom** 13 synd; MIC; severe epilepsy, MR and PNGR; at b OFC 32 cm, ≤ 2 SD; at age 9 mo 36.5 cm, ≤ 3 SD.
- r-14 2009; f; LB; 38 wks; Bwt 2800 g; **CMV** synd; MIC; progressive int hydroceph; at b OFC 29.5 cm, ≤ 3 SD; at age 1 mo 32.5 cm, ≤ 3 SD; fam pat one f-f TW; fam mat one case of MR-obesity.
- r-15 2009; m; LB; 31 wks; Bwt 1300 g; **FASD**; MIC; coronal hyosp; at b OFC 27 cm, 10th pct; at age 15 wks 34 cm, ≤ 3 SD; mat alcohol abuse.
- s-1 2001; m; LB; 38 wks; Bwt 3200 g; **FASD**; MIC; at b OFC 35 cm, 50th pct; at age 7.5 mo 40 cm, ≤ 3 SD; at age 8 mo 44.5 cm, ≤ 3 SD; at age 3 yr 46 cm, ≤ 3 SD.
- s-2 2001; m; LB; 35 wks; Bwt 1650 g; **FASD**; MIC, mOPH; at b OFC 27 cm, ≤ 3 rd pct; in orphanage.
- s-3 2002; f; LB; 32 wks; Bwt 1200 g; **FASD**; MIC; seizures; MR; at b OFC 27 cm, 5th pct; at age 6 wks 31 cm, ≤ 6 SD; at age 11 mo 37.5 cm, ≤ 4 SD; at age 13 mo 39.5 cm, ≤ 3 SD; mat alcohol, tobacco and drug abuse; patient in orphanage.
- s-4 2003; f; LB; 31 wks; Bwt 2000 g; **FASD**; MIC; cong syphilis; at b OFC 31 cm, 50th pct; at age 2 mo 34 cm, 50th pct; at age 13 mo 43 cm, ≤ 3 SD; mat syphilis.
- s-5 2003; f; LB; 42 wks; Bwt 2900 g; **Down** synd typical (no karyotype); MIC; anus and rectum atr; R kidney hypopl; reduct hands; pulm hypopl; porencephaly; prenat oligohydr; at b OFC 32 cm, ≤ 2 SD; at age 3 wks 32 cm, ≤ 3 SD.
- s-6 2004; f; LB; 35 wks; Bwt 1850 g; **FASD**; MIC; unilat CP, pulm sten; at b OFC 30 cm, 10th pct; at age 15 mo 41 cm, ≤ 3 SD.
- s-7 2004; m; LB; 35 wks; Bwt 1300 g; **FASD**; MIC; at b OFC 29 cm, 3rd pct; at age 14 mo 40.5 cm, ≤ 3 SD; at age 15 mo 42 cm, ≤ 3 SD; at age 4 yr 45 cm, ≤ 3 SD; mat alcohol abuse.
- s-8 2005; m; LB; 39 wks; Bwt 2800 g; **FASD**; MIC; VSD; at b OFC 31.5 cm, ≤ 3 SD; at age 2 mo 35.5 cm, ≤ 3 SD; mat diffuse goiter and alcohol abuse.

- s-9 2006; f; LB; 35 wks; Bwt 2250 g; **FASD**; MIC; VSD, ASD-OS, pulm artery sten; at b OFC 31 cm 15th pct; at age 4 mo 36 cm, ≤ 3 SD.
- s-10 2006; f; LB; 39 wks; Bwt 2350 g; **FASD**; MIC; at b OFC 32 cm, 12th pct; at age 12 mo 40 cm, ≤ 3 SD; mat alcohol abuse.
- s-11 2006; m; LB; 38 wks; Bwt 2150 g; **PATAU** (no karyotype), MIC; bilat CL/P; ASD; VSD; bilat polycys kidneys and cryptorchidism, R hand-foot postax polyd; at b OFC 29 cm, ≤ 3 SD.
- s-12 2007; m; LB; 39 wks; Bwt 1800 g; **FASD**; MIC; PNGR; at b OFC 28 cm, ≤ 5 SD; mat alcohol hepatic cirrhosis; fam mat Down synd once.
- s-13 2009; m; LB; 31 wks; Bwt 1590 g; 46,XY; **FASD**; MIC; spastic tetraparesis and MR; at 22 wks gest OFC 18.5 cm, 43rd pct; at 29 wks gest 27.5 cm, 16th pct; at age 12 mo 38 cm, ≤ 6 SD; prenat preeclampsia, pyelonephritis, alcohol abuse, mat FAS.
- s-14 2009; m; LB; 40 wks; Bwt 2970 g; 47,XXY; **Klinefelter** synd; MIC; severe epilepsy, psychomotor delay; at 27 wks gest OFC 26 cm, 31st pct; at b 31 cm, ≤ 3 SD; at age 6 mo 39.5 cm, ≤ 3 SD.

Not Isolated – non-Syndromic – Singletons (17 individuals)

When detected, birth status and sex:

25-34,	1	Liveborn (LB),	15	Polissia	non-Polissia
35-40,	2	Stillborn (S),	2	Males	7 1
At birth,	7			Females	8 1
<1 st yr.,	7				

- t-1 2000; f; LB; 37 wks; Bwt 2900 g; MIC, microgyria; bilat **CL/P**; VSD; microtia; hand polyd; at b OFC 28 cm, <3 pct; died at 3 d.
- t-2 2000; m; LB; 37 wks; Bwt 1800 g; MIC; 46,XY; **mult dysm** signs, non-syndromic; IUGR and PNGR; severe hypertonia; dextrocardia; fingers contracture, syndactyly and hypopl distal phalanges; at b OFC 27 cm, ≤ 3 rd pct; at age 6 wks 32 cm, ≤ 3 SD.
- t-3 2002; m; LB; 38 wks; Bwt 3400 g; MIC; short sten esoph; hiatus **diaphr hernia**; at b OFC 31.5 cm, ≤ 3 SD; at age 18 wks 34 cm, ≤ 6 SD; at age 23 mo 43 cm, ≤ 5 SD.
- t-4 2004; f; LB; 40 wks; Bwt 3400 g; MIC; R **CL**; at b OFC 33 cm, ≤ 1 SD; at age 2.5 mo 36 cm, ≤ 3 SD; at age 10 mo 39 cm, ≤ 3 SD.
- t-5 2004; f; LB; 41 wks; Bwt 3300 g; MIC; micro-hydroceph and agen corp call; R descending aorta; **esoph atr** and T-E, L renal apl; at b OFC 35 cm, 75th pct; at age 6 mo 38 cm, ≤ 3 SD.
- t-6 2006; m; LB; 39 wks; Bwt 3400 g; MIC; **ASD** and OS; VSD; prenat 29 wks OFC 26.6 cm, 19th pct; at b 31 cm, ≤ 3 SD; at age 7 d 31 cm, ≤ 3 SD; at age 3 wks 31.3 cm, ≤ 3 SD.
- t-7 2007; f; LB; 39 wks; Bwt 2700 g; MIC; mult dysm signs, non-syndromic; **CP**, short umb cord w one artery, bilat renal hypopl, R foot postax polyd, died at 4 d; prenat 28 wks OFC 26.7 cm, 18th pct; at b 30 cm, ≤ 3 SD; prenat 31 wks, IUGR, polyhydr, hypopl cerebel and vermis.
- t-8 2008; f; LB; 36 wks; Bwt 1830 g; MIC; bilat **mOPH** and microcornea and cataracts, soft **CP**, short esoph, diaphr hiatus hernia, ASD, limb contractures; IUGR; PNGR; prenat 20 wks OFC 18.5 cm, 42nd pct; at b 30 cm, 3rd pct; at age 4 mo 34 cm, ≤ 6 SD.
- t-9 2008; m; LB; 37 wks; Bwt 2080 g; MIC; transposition of great vessels; **OM**; prenat IUGR; at b OFC 29 cm, <3 SD.
- t-10 2008; f; LB; 40 wks; Bwt 2000 g; MIC; **duodenal atr**, **CP**, ASD and pulm artery sten and R ventr hypertrophy, hypopl thymus, bilat syndactyly 1-2 toes, died at 2 wks; prenat polyhydr; at b OFC 30 cm, ≤ 3 SD.
- t-11 2008; f; LB; 40 wks; Bwt 2500 g; MIC; 46,XX; prominent forehead, hypopl mandible, other face dysm, hoarse voice, stridor, bilat dyspl ears, dyspl scalp hair, body hypertrichosis, bilat hand monodactyly, **hypopl L forearm** and elbow, toe syndactyly R 3-5 and L 2-5; MR; PNGR; no facial signs of Cornelia deLange synd; prenat 35 wks, agen corp call,

- cardiomyopathy, symmetric IUGR; at 35 wks gest OFC 29.9 cm, 8th pct; at b 32 cm, ≤ 2 SD; at age 6 mo 36 cm, ≤ 3 SD; at age 23 mo 38.5 cm, ≤ 6 SD.
- t-12 2008; m; LB; 36 wks; Bwt 1900 g; MIC; 46,XY; micrognathia, hypopl aortic arch; bilat undescended testicles; penile hyposp; R hand **ectrodactyly**; MR and PNGR; at b OFC 30 cm, ≤ 3 rd pct; at age 1 mo 30 cm, ≤ 3 SD.
- t-13 2008; m; S; 40 wks; Bwt 1900 g; MIC; R **renal agen**, L renal hypopl; prenat 27 wks; oligohydr, dolichocephaly, L kidney dyspl echostructure, no echoshadow of R kidney, apl of R kidney; at b OFC 29 cm, ≤ 3 SD.
- t-14 2009; m; LB; 38 wks; Bwt 2200 g; MIC; **VSD**; **PDA** and pulm hypertension; PNGR; at b OFC 30 cm, ≤ 3 SD; at age 10 mo 41.5 cm, ≤ 3 SD.
- t-15 2009; f; LB; 36 wks; Bwt 2000 g; MIC; 46,XX; occip focal skin apl; soft **CP**; lymphedema lower limbs; **PNGR**; died at 10 wks; prenat IUGR; at 19 wks gest OFC 16.3 cm, 33rd pct; at b 31 cm, 15th pct; at age 7 wks 31 cm, ≤ 3 SD; fam mat m-m TW once, an instance of VSD once.
- u-1 2001; f; LB; 39 wks; Bwt 3100 g; MIC; *dupl L renal calyx, hydronephrosis; L hand **preax polyd**; at b OFC 31 cm, ≤ 3 SD; at age 24 mo 42.5 cm, ≤ 3 SD; mat active tuberculosis.*
- u-2 2009; m; S; 36 wks; Bwt 2320 g; MIC; *bilat **CL/P**, **OM**, bilat hand postax polyd; at b OFC 27 cm, below 3rd pct; mat gest edema.*

MICROPHTHALMOS (mOPH) (24 individuals)

All holoprosencephalies are excluded and are listed in that category as: hol-6; hol-22; hol-23; hol-25; *hol-15; hol-29.*

Listed in alternative CM categories:

- ri-8 see microcephaly category.
 ri-12 see microcephaly category.
 t-8 see microcephaly category.
 c-1 see NTD category.
 s-2 *see microcephaly category.*
 z-2 *see conjoined twins category.*

Isolated – Singletons (12 individuals)

All liveborn, none detected prenatally.

	Polissia	non-Polissia
Males	5	1
Females	3	3

Not Isolated – Syndromes – Singletons

- v-1 2005; m; LB; 38 wks; Bwt 2500 g; mOPH; **PATAU** (no karyotype); bilat CL/P; polycys kidney; OM; R hand-feet postax polyd; diaphr hernia; hyposp; died at 2 d; prenat oligohydr; at b OFC 32 cm, < 1.5 SD.
- v-2 2007; f; LB; 33 wks; Bwt 1800 g; R mOPH, **Goldenhar** synd; R palpebral coloboma; hydroceph; CL/P; preauricular appendage; AV canal; L thumb hypopl; died at 7 d; prenat polyhydr; Bwt 1800 g; at b OFC 31 50th pct for 33 wk gestation; father has MR.
- v-3 2009; f; LB; 38 wks; Bwt 4390 g; L mOPH; **PATAU** (no karyotype); corp call agen; bilat renal dyspl; bilat hand polyd; died at 5 mo; prenat 21 wks, oligohydr, int hydroceph, OFC 22.4 cm; at b 48 cm, > 10 SD.
- w-1 2001; m; LB; 32 wks; Bwt 1550g; mOPH; **PATAU** (no karyotype); *agen corp call; L CL/P; OM; VSD; arthrogryposis mult; died at 3 d; at b OFC 28 cm, 12th pct.*

Not Isolated – non-Syndromic – Singletons (8 individuals)

All liveborn, none detected prenatally.

	Polissia	non-Polissia
Males	2	1
Females	5	0

- x-1 2000; m; LB; 36 wks; Bwt 2400 g; bilat mOPH; **CL**; R upper **limb reduct**; lordosis; cryptorchidism; at b OFC 30 cm, <3rd pct.
- x-2 2000; f; LB; 36 wks; Bwt 2500 g; L mOPH; **VSD**; at b OFC 32 cm, 25th pct.
- x-3 2000; m; LB; 40 wks; Bwt 3700 g; bilat mOPH and ankyloblepharon; R 3-4 fing syndactyly, died at 5 d; at b OFC 37 cm, >2 SD.
- x-4 2001; f; LB; 41 wks; Bwt 2100 g; bilat mOPH; int hydroceph; **pentalogy Fallot**; at b OFC 31 cm, <2.5 SD.
- x-5 2006; f; LB; 38 wks; Bwt 2710 g; bilat mOPH, glaucoma, and cataracts; hydroceph; bilat **ear meatus atr**, **CP**, died at 1 wks; prenat 32 wks, polyhydr; at b OFC 36 cm, >2 SD.
- x-6 2008; f; LB; 37 wks; Bwt 2860 g; bilat mOPH, corneal opacity and **ECTC** and optic disc coloboma; L severe urethero-hydronephrosis; at b OFC 32.5 cm, 25th pct.
- x-7 2009; f; LB; 37 wks; Bwt 2780 g; bilat mOPH, corneal opacity; IUGR, general **dysm**; R hydronephrosis; died at 3 mo; prenat 31 wks, oligohydr; at b OFC 34 cm, 75th pct.
- y-1 2000; m; LB; 37 wks; Bwt 2700 g; L mOPH w microcornea and R anophthalmos; **VSD**; at b OFC 34 cm, 75th pct.

ANTERIOR BODY WALL ANOMALIES

Ectopia Cordis: page 36.

Thoraco-abdominal wall anomalies: page 36.

Body stalk - umbilical cord anomalies: see l-7; arj-1; thab-1; *thab-2*.

Omphalocele: see below.

Gastroschisis: page 31.

Abdomino-caudal anomalies (urinary bladder exstrophy - cloaca, recto-anal, sirenomelia): pages 33, 36, 39.

OMPHALOCELES (OM)

(includes associated urinary bladder exstrophy and Cantrell pentalogy) (38 individuals)

Omphalocele (OM)* in Polissia (POL) and non-Polissia (NPOL) - Prenatal Diagnosis (PD) and Terminations of Pregnancies (ToP)

Region	Years	NTD total	PD	ToP after PD	No PD
POL	2000-2004	6	3	1	3
	2005-2009	9	6	1	3
Total POL		15	9	2	6
NPOL	2000-2004	9	7	3	2
	2005-2009	18	16	10	2
Total NPOL		27	23	13	4
Total		42	32	15	10

*Excluded are 14 individuals with NTD.

When detected, birth status and sex:

				Polissia	non-Polissia
< 15,	12	Liveborn	(LB), 15		
15-20,	8	Stillborn	(S), 5	Males	10 10
21-24,	7	Spontaneous abortion	(SA), 3	Females	1 5
25-34,	1	Termination of pregnancy (ToP),	15	Unknown	2 10
35-40,	1				
GA- unknown,	1				
At birth,	8				

Listed in alternative CM categories (18 individuals):

- c-3 see AN category; u; ToP; 12 wks.
- f-2 see CRA category; f; ToP; 21 wks.
- f-4 see CRA category; f; SA; 27wks.
- f-5 see CRA category; u; ToP; 10 wks.
- f-6 see CRA category; f; ToP; 20 wks.
- f-7 see CRA category; m; S; 13 wks.
- f-8 see CRA category; u; ToP; 13 wks; fam TW.
- h-1 see SB category; f-f, CTW; SA; 23 wks; fam TW.
- h-3 see SB category; m; LB; 40 wks.
- l-5 see SB category; u; ToP; 13 wks.
- t-9 see Microcephaly category; m; LB; 37 wks.
- v-1 see Microphthalmia category; m; LB; 38 wks; PATAU.
- g-4 see CRA category; u; ToP; 12 wks.
- m-2 see SB category; u; ToP; 26 wks.
- m-5 see SB category; m; ToP; 21 wks; hypopl L heart.
- m-6 see SB category; m; LB; 30 wks.
- u-2 see Microcephaly category; m; S; 36 wks.
- w-1 see Microphthalmia category; m; LB; 32 wks; PATAU.

Isolated – Singletons (22 individuals)

When detected, birth status and sex:

				Polissia	non-Polissia
< 15,	9	Liveborn	(LB), 10		
15-20,	5	Stillborn	(S), 1	Males	4 7
21-24,	2	Spontaneous abortion	(SA), 2	Females	0 3
35-40,	1	Termination of pregnancy (ToP),	9	Unknown	1 7
At birth,	5				

Not Isolated – Syndromes – Singletons

- aa-1 2004; m; LB; 40 wks; Bwt 4000 g; **Wiedemann-Beckwith** synd; OM; prenat 22 wks, polyhydr; prenat 29 wks, hydrocele, intest sack through umb ring hernia - OM; mat CMV positive; fam mat OM once and f- f TW once.
- aa-2 2008; m; ToP; 20 wks; **PATAU** by chromosome analysis; OM; prenat 13 wks, int organs of abd cavity in herniated sack – OM; prenat 20 wks, int organs in abd cavity under membrane – OM, hyperechoic kidneys.
- bb-1 2003; f; ToP; 24 wks; Bwt 480 g; OM; bilat CL/P; postax hand polyd bilat; single umb artery; prenat 21 wks; **PATAU** synd pattern of malf.

Not Isolated – non-Syndromic (12 singletons and one twin (dd-1))

When detected, birth status and sex:

				Polissia	non-Polissia
< 15,	2	Liveborn	(LB), 4		
15-20,	3	Stillborn	(S), 4	Males	4 3
21-24,	3	Spontaneous abortion	(SA), 1	Females	1 1
25-34,	1	Termination of pregnancy (ToP),	4	Unknown	1 3

GA unknown 1
At birth, 3

- cc-1 2002; f; LB; 40 wks; Bwt 2300 g; OM; common **truncus arteriosus**.
- cc-2 2004; u; SA; 17 wks; OM; unilat **CL**; trefoil skull; CHD; antenatal death; prenat 15 wks.
- cc-3 2007; m; LB; 39 wks; Bwt 4200 g; small OM; **postax polyd** hands; **penile hyosp**; mult dysm; bilat undescended testicles; **accessory spleen**; died at home at 1 mo, no autopsy.
- cc-4 2007; m; S; 35 wks; OM; **diaphr hernia**; prenat 21 wks, diaphr hernia and abd wall def w liver-intest protrusion covered with membrane - OM.
- cc-5 2008; m; S; 39 wks; Bwt 2700 g; OM; common **A-V canal**; **reduct anom arms**; prenat 15 wks, ASD, defect ant abd wall w protruding mass covered by membrane - OM, no forearm bones seen bilat and clubhands.
- cc-6 2008; m; LB; 41 wks; Bwt 3900 g; OM; **cloaca exstrophy**; rectum atr; mat acoustic nerve anom.
- dd-1 2000; amb; S; 31 wks; Bwt 1500 g; TW; **ECTC**; OM; **amb genitalia**; **S-like spine def**; **pentalogy of Cantrell**; prenat 30 wks; co-TW disc m; fam pat m-m TW once.
- dd-2 2006; u; ToP; 13 wks; OM; cyst of post cranial fossa; **diaphr hernia**; prenat 13 wks.
- dd-3 2007; m; ToP; 21 wks; Bwt 310 g; OM; bilat **CL**; **hypopl L heart**; **VSD**; unilat oligodactyly hand; chromosomal anom; prenat 21 wks, polyhydr, nuchal thickness 7 mm; fam pat MR once.
- dd-4 2007; m; S; 28 wks; Bwt 837 g; OM; **A-V septal defect**; Dandy-Walker; prenat 23 wks, abd wall anom, protruding sack; mat hypertension and smoking.
- dd-5 2008; m; LB; gest unknown; Bwt 3850 g; OM; **sten pulm artery**; **mult dysm**.
- dd-6 2008; u; ToP; 12 wks; OM; cystic hygroma; fetal hydrops; **short long bones** and small nasal bones; ant abd wall defect w intest herniation, covered w thin membrane and connected to umb cord - OM, hydrothorax; prenat 12 wks.
- dd-7 2008; f; ToP; 20 wks; Bwt 270 g; OM; **dextrocardia**; R ventr double outlet; placental hyperpl; abd wall gap and protruding mass containing liver covered by a membrane; prenat 20 wks.

GASTROSCHISIS (GSTR) (40 individuals)

When detected, birth status and weight:

< 15,	2	Liveborn	(LB), 17	<1000 g,	12
15-20,	15	Stillborn	(S), 2	1500-1999 g,	2
21-24,	8	Spontaneous abortion	(SA), 2	2000-2499 g,	9
25-34,	6	Termination of pregnancy (ToP),	19	2500-2999 g,	2
At birth,	9			3000-3499 g,	6
				Unknown,	9

Isolated – Singletons (37 individuals)

When detected, birth status and sex.

< 15,	1	Liveborn	(LB), 14	Polissia non-Polissia	
15-20,	15	Stillborn	(S), 2	Males	5 10
21-24,	8	Spontaneous abortion	(SA), 2	Females	10 7
35-40,	6	Termination of pregnancy (ToP),	19	Unknown	0 5
At birth,	7				

- ee-1 2002; m; LB; 38 wks; Bwt 3000 g; GSTR, intest eventr.
- ee-2 2003; m; LB; 38 wks; Bwt 3300 g; GSTR, intest eventr.
- ee-3 2005; f; LB; 40 wks; **Bwt 2500 g**; GSTR.
- ee-4 2005; f; LB; 33 wks; Bwt 1730 g; GSTR; small intest atr; prenat 33 wks, GSTR.

- ee-5 2005; m; LB; 38 wks; **Bwt 2400 g**; GSTR, gastro-intest eventr; prenat 32 wks, GSTR.
- ee-6 2006; f; ToP; 21 wks; Bwt 460 g; GSTR, intest eventr; prenat 21 wks GSTR.
- ee-7 2006; m; S; 40 wks; **Bwt 2400 g**; GSTR, intest eventr.
- ee-8 2006; f; LB; 39 wks; **Bwt 2200 g**; GSTR, intest eventr; prenat 21 wks, GSTR.
- ee-9 2006; f; LB; 36 wks; Bwt 2300 g; GSTR, intest eventr; prenat 19 wks, GSTR.
- ee-10 2006; f; ToP; 19 wks; Bwt 280 g; GSTR, intest eventr; prenat 16 wks, GSTR.
- ee-11 2007; f; SA; 22 wks; Bwt 400 g; GSTR, intest eventr; prenat 19 wks, GSTR.
- ee-12 2007; f; ToP; 17 wks; Bwt 220 g; GSTR, intest eventr; prenat 12 wks, GSTR.
- ee-13 2008; f; LB; 39 wks; Bwt 3200 g; GSTR, intest eventr; small intest atr.
- ee-14 2009; m; ToP; 19 wks; Bwt 320 g; GSTR, intest eventr; intest obstruction; prenat 19 wks.
- ee-15 2009; f; ToP; 20 wks; Bwt 220 g; GSTR, intest eventr; prenat 19 wks.
- ee-16 2000; f; LB; 35 wks; Bwt 2300 g; GSTR.
- ee-17 2000; u; ToP; 26 wks; GSTR, intest eventr; prenat 25 wks.
- ee-18 2001; u; ToP; 27 wks; Bwt 900 g; GSTR, intest eventr; prenat 27 wks GSTR, oligohydr.
- ee-19 2001; u; SA; 24 wks; GSTR, intest eventr; prenat 24 wks GSTR, placental hyperpl.
- ee-20 2003; m; ToP; 26 wks; Bwt 800 g; GSTR; prenat 26 wks GSTR.
- ee-21 2003; f; ToP; 22 wks; GSTR, intest eventr; prenat 22 wks, GSTR, polyhydr.
- ee-22 2003; m; ToP; 18 wks; Bwt 370 g; prenat 18 wks, GSTR.
- ee-23 2004; f; ToP; 27 wks; GSTR; prenat 27 wks, GSTR.
- ee-24 2004; u; ToP; 18 wks; GSTR, intest eventr, prenat 16 wks GSTR.
- ee-25 2004; u; ToP; 15 wks; GSTR; prenat 15 wks, GSTR.
- ee-26 2005; f; ToP; 21 wks; Bwt 300 g; GSTR, intest eventr; low intest obstruction; prenat 20 wks, GSTR, oligohydr, placental hyperpl.
- ee-27 2005; m; ToP; 21 wks; GSTR, intest eventr; low intest obstruction; prenat 21 wks, GSTR, oligohydr.
- ee-28 2005; f; ToP; 24 wks; Bwt 680 g; GSTR, intest eventr; prenat 23 wks, GSTR.
- ee-29 2005; m; ToP; 16 wks; GSTR, intest eventr; prenat 15 wks, GSTR.
- ee-30 2005; m; LB; 34 wks; Bwt 2250 g; GSTR, intest eventr; **very short umb cord.**
- ee-31 2006; m; ToP; 20 wks; GSTR, intest eventr; prenat 20 wks, GSTR, oligohydr.
- ee-32 2006; f; LB; 35 wks; Bwt 2200 g; GSTR, intest eventr; prenat 22 wks; mat bronchial asthma.
- ee-33 2008; m; ToP; 21 wks; Bwt 280 g; GSTR, intest eventr; prenat 20 wks, GSTR, oligohydr; mat chronic rheumatism, mitral valve insufficiency, smoking, alcohol use.
- ee-34 2008; m; S; 32 wks; Bwt 1780 g; GSTR, intest eventr; prenat 16 wks, GSTR.
- ee-35 2009; m; LB; 38 wks; Bwt 3160 g; GSTR, intest eventr; R undescended testicle; prenat 19 wks, GSTR, polyhydr; died at 6 wks.
- ee-36 2009; m; LB; 35 wks; Bwt 2360 g; GSTR, intest eventr; renal artery stenosis; prenat 19 wks, GSTR; died at 3 wks; mat SA TW at 10-11 wks in 2007.
- ee-37 2009; f; LB; 39 wks; Bwt 3090 g; GSTR; cong sepsis; prenat 21 wks, GSTR; died at 4 wks; mat fam one set of m-m TW.

Isolated – not Singleton Individual

- ee-38 2003; f; LB; 34 wks; Bwt 2000 g; TW, GSTR, disc m-f.

Not Isolated – non-Syndromic – Singleton

- ff-1 2004; f; LB; 37 wks; Bwt 2700 g; GSTR, intest eventr; **duodenal atr**; intest malrotation; **common mesentery** of the small and large intest; prenat 13 wks, GSTR; died at 18 d because of complications in the postoperative period.

ff-2 2000; m; LB; 38 wks; Bwt 3200 g; GSTR; **kidney hypopl**; **hyposp**.

URINARY BLADDER EXSTROPHIES (BLEXTR) (12 individuals)

Note 1: excludes omphaloceles and exstrophy of the cloaca.

Note 2: no instances of isolated episepadias were observed.

Listed in alternative CM categories:

h-3 spina bifida, omphalocele, anal atresia – see NTD category.
arj-2 see *Anal atresia associated with caudal dysplasia*.

Isolated – Sequencies (all 12 singleton individuals)

When detected, birth status and sex.

		Liveborn (LB),	12		Polissia	non-Polissia
15-20,	1			Males	3	4
25-34,	1			Females	5	0
At birth,	10					

- gg-1 2000; f; LB; 39 wks; Bwt 2940 g; BLEXTR; **epispadias**; fam sib (1990) AN and another sib (2008) SB cervical.
- gg-2 2002; m; LB; 40 wks; Bwt 3400 g; BLEXTR.
- gg-3 2003; m; LB; 39 wks; Bwt 4300 g; BLEXTR; **epispadias**.
- gg-4 2004; f; LB; 39 wks; Bwt 3650 g; BLEXTR; prenat 27 wks BLEXTR and polyhydr.
- gg-5 2006; f; LB; 37 wks; Bwt 3100 g; BLEXTR.
- gg-6 2007; f; LB; 41 wks; Bwt 3570 g; BLEXTR.
- gg-7 2009; m; LB; 39 wks; Bwt 3280 g; BLEXTR; **epispadias**.
- gg-8 2009; f; LB; 40 wks; Bwt 3000 g; BLEXTR.
- gg-9 2001; m; LB; 40 wks; Bwt 4000 g; BLEXTR; **epispadias**.
- gg-10 2003; m; LB; 38 wks; Bwt 3350 g; BLEXTR.
- gg-11 2005; m; LB; 39 wks; Bwt 3350 g; BLEXTR; **bilat undescended testicles**; prenat 19 wks, BLEXTR.
- gg-12 2009; m; LB; 40 wks; Bwt 3440 g; BLEXTR; **epispadias**; prenat 28 wks mass in genital region; mat fam m-m TW twice.

(FOR ADDITIONAL BODY WALL ANOMALIES, SEE PAGE 36)

CONJOINED TWINS (CTW) – see page 43.

TERATOMAS (TER) (10 individuals)

When detected, birth status and sex:

		Liveborn (LB),	6		Polissia	non-Polissia
15-20,	3			Males	1	0
GA unknown,	5	Stillborn (S),	1	Females	2	4
At birth,	2	Termination of pregnancy (ToP),	3	Unknown	3	0

Isolated – Singletons (10 individuals)

- ter-1 2001; u; ToP; 25 wks; TER, sacro-coccygeal.
- ter-2 2003; u; ToP; 19 wks; TER, sacro-coccygeal.
- ter-3 2003; f; LB; 40 wks; Bwt 3100 g; TER, sacro-coccygeal.

- ter-4 2003; u; ToP; 21 wks; Bwt 550 g; TER, sacro-coccygeal.
 ter-5 2004; m; LB; 37 wks; Bwt 3500 g; TER, sacro-coccygeal.
 ter-6 2007; f; LB; 31 wks; Bwt 1900 g; TER, sacro-coccygeal; prenat 18 wks, non-homogenous echogenic cystic incl in coccygeal area; at 26 wks: polyhydr and same mass, sacro-coccygeal TER; mat diabetes mellitus, non-toxic goiter.
 ter-7 2001; f; LB; 39 wks; Bwt 3090 g; TER, sacro-coccygeal.
 ter-8 2005; f; LB; 31 wks; Bwt 2700 g; TER, sacro-coccygeal.
 ter-9 2008; f; S; 25 wks; Bwt 1070 g; TER, L face-neck; prenat 20 wks, large tumor-like w cystic component, TER.
 ter-10 2009; f; LB; 39 wks; Bwt 3290 g; TER, sacro-coccygeal; prenat 20 wks, mass w cystic incl in coccygeal area, TER.

SENTINEL ANOMALIES

DOWN SYNDROME (195 individuals).

Note: no instances of holoprosencephaly were observed.

Listed in alternative CM categories:

- tw-29 See Twin pairs category.
 s-5 MIC; anus and rectum atr; - see MIC category.
 Tw-47 See Twin pairs category.

When detected, birth status and sex:

<i>< 15,</i>	4	Liveborn	(LB), 181		
15-20,	7	Termination of pregnancy (ToP),	14	Males	53
21-24,	2			Females	47
25-34,	1			Unknown	0
At birth,			181		2
				Polissia	non-Polissia

CLEFT LIP WITH OR WITHOUT CLEFT PALATE (CL/P) (134 individuals)

When detected, birth status and sex:

15-20,	19	Liveborn	(LB), 119		
21-24,	9	Stillborn	(S), 1	Males	41
25-34,	13	Spontaneous abortion	(SA), 2	Females	25
At birth,		Termination of pregnancy (ToP),	12		22
				Polissia	non-Polissia

Listed in alternative CM categories (23 individuals):

- c-2 see AN cagerory
 f-3 see CRA category
 l-2 see SB category
 l-3 see SB category
 t-4 see MIC category
 t-1 see MIC category
 v-1 see MOPH category
 v-2 see MOPH category
 x-1 see MOPH category
 cc-2 see OM category
 hol-21 see HOLOP category
 mntq-1 see PATAU category
 s-11 see MIC category
 u-2 see MIC category

w-1 see *MOPH* category
bb-1 see *OM* category
dd-3 see *OM* category
hol-27 see *HOLOP* category
hol-30 see *HOLOP* category
hol-33 see *HOLOP* category
hol-34 see *HOLOP* category
mntq-2 see *PATAU* category
mntq-3 see *PATAU* category

Isolated – Singletons (113 individuals)

Not Isolated – non-Syndromic – Singletons (21 individuals)

When detected, birth status and weight:

15-20,	7	Liveborn	(LB), 13	<1000 g,	6
21-24,	1	Stillborn	(S), 1	1500-1999 g,	2
25-34,	4	Termination of pregnancy (ToP),	7	2000-2499 g,	3
At birth,	9			2500-2999 g,	4
				3000-3499 g,	3
				3500-4000 g,	2
				Unknown,	1

clp-1 2002; f; LB; 39 wks; Bwt 2800 g; **esoph atr; CL/P**.
clp-2 2004; f; LB; 35 wks; Bwt 1600 g; CL/P; **transposition of great vessels; ASD**; at b OFC 29 cm, <3 pct.
clp-3 2005; m; LB; 38 wks; Bwt 3400 g; R CL; **VSD**; bilat undescended testicle; **micropenis**; 46XY.
clp-4 2005; f; LB; 40 wks; Bwt 2400 g; bilat CL/P; **VSD**; PFO.
clp-5 2006; f; LB; 34 wks; Bwt 1800 g; hydroceph; L CL/P; ASD-OS; **VSD**; L hand **preax polyd**; at b HC 29 cm, 3 pct; died at 2 wks; prenat 31 wks, hydroceph, **agen vermis** cerebella; unilat CL; IUGR; polyhyd; fam sib see instance *clp-12* below, and another sib with hydroceph in 2010; fam mat one case of CL, and one case of AN.
clp-6 2006; m; LB; 39 wks; Bwt 2730 g; R CL/P; **VSD**; L **renal hypopl**; umb and R inguinal hernias; prenat 20 wks, unilat cleft lip; fam mat CL.
clp-7 2006; m; LB; 35 wks; Bwt 2100 g; CL/P; **T-E**; CHD unspecified; died at 2 d.
clp-8 2007; f; LB; 37 wks; Bwt 3020 g; R CL/P; **VSD** perimembranous; PDA; mult dysm signs; prenat 33 wks, unilat CL.
clp-9 2008; f; LB; 40 wks; Bwt 2870 g; L CL/P; R **renal agen**; prenat 33 wks, R renal agen; fam sib cong cataract (2005); fam mat f-f TW once.
clp-10 2009; f; ToP; 20 wks; Bwt 340 g; CL/P; cerebel **vermis defect**; prenat 20 wks, cerebel vermis defect; bilat CL/P; fam pat TER (see instance *ter-9*).
clp-11 2009; f; ToP; 21 wks; Bwt 440 g; hydroceph; median CL/P; **VSD**; single umb artery; prenat 21 wks, hydroceph of 1st stage, median CL, hard CP, hyperechoic kidneys, single umb artery; fam sib see instance *clp-6* above, and another sib with hydroceph in 2010; fam mat one case of CL, and one case of AN.
clr-1 2000; m; S; 36 wks; Bwt 2400 g; **hydroceph**; CL.
clr-2 2000; f; LB; 40 wks; Bwt 3050 g; L CL; ASD-OS; prenat polyhyd.
clr-3 2002; m; ToP; 19 wks; **hydroceph** w macrocrania; CLP; prenat 18 wks, hydroceph, macrocrania, CL.
clr-4 2003; f; LB; 40 wks; Bwt 3500 g; **atr anus** w vag fist; bilat CL/P; R **ectopic kidney**.
clr-5 2005; m; LB; 36 wks; Bwt 2900 g; cong **cataract**; **median CL**; hydroceph; **ependymoma**; prenat 32 wks, hydroceph; mass in corp call region.
clr-6 2006; f; ToP; 21 wks; Bwt 450 g; **hypopl left heart**; CL/P; prenat 20 wks.

- clr-7* 2006; f; ToP; 21 wks; Bwt 410 g; **hypopl left heart**; A-V canal, incomplete; CL; agen vermis cerebelli; prenat 21 wks.
- clr-8* 2008; f; LB; 40 wks; Bwt 3500 g; R CL/P; R **acoustic meatus atr**; prenat 18 wks, CL.
- clr-9* 2008; f; ToP; 21 wks; Bwt 270 g; CL; bilat **reduct forearms-thumbs**; VSD; ASD and A-V canal suspected; agen corp call; choroid plexus cyst; prenat 20 wks; fam mat m-m TW once.
- clr-10* 2009; m; ToP; 20 wks; Bwt 370 g; bilat CL/P; unilat **syndactyly** 3-4 fingers; prenat 19 wks.

SUPPLEMENTAL SURVEY OF ANTERIOR-CAUDAL BODY WALL ANOMALIES

“Upper” celosomias (thoraco-abdomino-schisis w/o ectopia cordis)

Caviat:

The following categories are included to expand the scope of observations. However, population-based ascertainment may be incomplete.

Ectopia Cordis (ECTC) (includes associated thoraco-abdomino-schisis; excludes omphaloceles which, if present, are included in the omphalocele category)

Listed in alternative CM categories:

- q-3* ECTC, frontal encephalocele - see NTD category.
- dd-1* ECTC, Cantrell pentalogy, deformed spine and amb genitals - see omphalocele category.

All instances are in singletons.

- ect-1* 2003; u; ToP; 21 wks; abd ECTC and THAB; **agen of diaph**; bilat **kidney apl**; prenat 19 wks, oligohydr; placental edema; liver in pelvis, multicys masses in abd and chest, kidneys and urinary bladder not seen, ascites.
- ect-2* 2008; u; ToP; 16 wks; ECTC and THAB; prenat 15 wks, **hypopl nasal bones**, defect of thorax and ant abd wall, ECTC.
- ect-3* 2003; u; ToP; 13 wks; ECTC and THAB; hydroceph; hepatic-intest eventr; **def spine**; **reduct L arm**; R hand **syndactyly**; prenat 13 wks, brachicephaly, dilated lat ventr, hydroceph, anom entire spine, liver and intest eventr.
- ect-4* 2005; m; ToP; 21 wks; ECTC and THAB, abs ant body wall and cavities, **retroflexed spine**; fetal viscera **adjoin placenta**; prenat oligohydr.
- ect-5* 2006; u; ToP; 19 wks; ECTC and THAB, **bifid sternum** and hepatic-intest eventr.

Thoraco-Abdominal Wall Anomalies (THAB) (includes body stalk anomalies; excludes ectopia cordis and omphaloceles)

Listed in alternative CM categories

- g-2* THAB and anencephaly-rachischisis, severe “S”- like spine deformity - see NTD category.

All individuals are singletons

- thab-1* 2003; u; ToP; 16 wks; THAB; underdeveloped ribs, **body stalk not seen**; fetal spine **adjacent to uterine wall**; reduct one lower limbs; prenat 16 wks.
- thab-2* 2007; u; ToP; 12 wks; **body stalk anom**; thoracic, cardiac and abd organs not seen, severe hypopl spine; fam mat goiter; prenat 12 wks.
- thab-3* 2007; f; ToP; 19 wks; THAB; hepatic-intest eventr without membranous envelope; prenat 17 wks, anom lower chest and abd wall, **amniotic band** not connected to fetal body; mat CL/P, smoker; father mentally subnormal.

“Low” celosomias

Exstrophy of the Cloaca

One instance, cc-6, see omphalocele category.

Caudal Dysplasias (includes sacral disgenesis, sirenomelia and recto-anal anomalies)

(39 individuals).

Note: all individuals are singletons except one instance of sirenomelia (*sir-2*).

When detected, birth status and weight:

15-20,	2	Liveborn	(LB), 34	<1000 g,	1
35-40,	2	Stillborn	(S), 5	1000-1499 g,	1
At birth,	33			1500-1999 g,	5
<1 st yr.,	2			2000-2499 g,	5
				2500-2999 g,	12
				3000-3499 g,	8
				3500-3999 g,	7

Listed in alternative CM categories:

- h-3 spina bifida, omphalocele, urinary bladder exstrophy (BLEXTR), bifid scrotum, anal atresia, OEIS complex – see SB category
- cc-6 omphalocele, urinary bladder and cloaca exstrophy, rectum atresia – see OM category
- m-4 spina bifida, diaphragmatic hernia, anal atresia – see SB category
- s-5 Down syndrome, microcephaly, ano-rectal atresia – see MIC category
- clr-4 anal atresia, cleft lip/palate and ectopic kidney - see CL/P category
- hol-29 holoprosencephaly, microphthalmia, anal atresia – see HOLOP category

Recto-Anal Anomalies (37 individuals)

Isolated recto-anal atresia, includes fistulas and dystopic anus (20 individuals):

Note: 5 (25%) among the 20 instances were born at ≥ 38 wks of gestation and had birth weights ≤ 3000 g.

Note: the M-F proportion 6-8 and 5-1 among those with and without fistulas respectively.

- ari-1 2001; f; LB; 40 wks; Bwt 2800 g; **atr anus w recto-vag fist.**
- ari-2 2002; m; S; 28 wks; Bwt 1000 g; **atr anus**; prenat fever in the 1st trimester; polyhydr; fam mat CHD.
- ari-3 2002; f; LB; 40 wks; Bwt 2900 g; **atr anus w recto-vag fist** (see relative, individual ari-11 below).
- ari-4 2004; f; LB; 38 wks; Bwt 3570 g; **recto-vag fist.**
- ari-5 2004; m; LB; 35 wks; Bwt 2300 g; **atr anus and rectum w perineal fist.**
- ari-6 2007; m; LB; 39 wks; Bwt 3100 g; **atr anus w perineal fist**; mother is TW, member of f-f pair.
- ari-7 2009; m; LB; 42 wks; Bwt 3550 g; **atr anus and rectum**; 46XY.
- ari-8 2000; m; LB; 40 wks; Bwt 2490 g; **atr rectum, high; atr anus**; died at 10 d; prenat polyhydr.
- ari-9 2001; f; LB; 40 wks; Bwt 2300 g; **atr anus and rectum w perineal fist.**
- ari-10 2001; f; LB; 36 wks; Bwt 2950 g; **atr anus**; prenat 32 wks, low intest obstruction; polyhydr.
- ari-11 2002; m; LB; 40 wks; Bwt 3500 g; **atr anus w perineal fist.**
- ari-12 2002; m; LB; 39 wks; Bwt 3820 g; **atr anus.**
- ari-13 2003; m; LB; 39 wks; Bwt 3415 g; **atr anus and rectum.**
- ari-14 2003; m; LB; 40 wks; Bwt 3600 g; **atr anus w perineal fist.**
- ari-15 2005; f; LB; 39 wks; Bwt 3480 g; **atr anus w recto-vag fist**; died at 4 mo.
- ari-16 2006; m; LB; 42 wks; Bwt 3720 g; **atr anus w perineal fist.**

- ari-17 2007; f; LB; 40 wks; Bwt 3180 g; **atr rectum (high, supralevatoric) and anus w recto-vag fist.**
- ari-18 2008; m; LB; 39 wks; Bwt 2800 g; **atr anus and rectum w perineal fist.**
- ari-19 2008; f; LB; 40 wks; Bwt 3050 g; **atr anus w perineal fist.**
- ari-20 2009; f; LB; 37 wks; Bwt 3360 g; **atr anus w recto-vag fist.**

Recto-anal atresia associated with other malformations (15 individuals):

- ari-21 2000; m; LB; 39 wks; Bwt 2700 g; posteriorly **shifted anus; horseshoe kidney, R hydronephrosis.**
- ari-22 2001; f; LB; 37 wks; Bwt 2000 g; **atr anus w recto-vag fist; L pulm hypopl; Valsalva sinus aneurysm; dysm face; 46XX; autopsy L bronchus atr; at b OFC 31 cm, ≤ 2.5 SD; at age 2 wks 32.5 cm, ≤ 2.5 SD; died at 2 mo.**
- ari-23 2002; m; LB; 40 wks; Bwt 3500 g; **atr anus w perineal fist; R kidney dupl; L hydronephrosis of 2nd stage.**
- ari-24 2002; f; LB; 33 wks; Bwt 1800 g; **atr anus; esoph atr; died at 3 mo.**
- ari-25 2007; m; LB; 41 wks; Bwt 2700 g; **atr anus and rectum; soft CP; L multicys kidney; mult dysm signs; died at 2 mo; no autopsy; prenat 35 wks, L multicys kidney, R hydronephrosis; father's brother is parent of ari-7, see above.**
- ari-26 2008; f; LB; 36 wks; Bwt 2340 g; **atr anus and rectum; duodenal atr; single umb artery; Meckel's diverticulum; ASD; prenat 35 wks, duodenal atr, single umb artery, polyhydr.**
- ari-27 2000; m; LB; 38 wks; Bwt 2950 g; **esoph atr w T-E; atr anus; CHD, unspecified; micropenis; died at 1 d.**
- ari-28 2000; m; LB; 36 wks; Bwt 2500 g; **atr anus; duodenal atr; small intest atr; preauricular tags; died at 2 d; prenat polyhydr.**
- ari-29 2000; m; LB; 37 wks; Bwt 2850 g; **atr anus and rectum; R cranial def; scoliosis; R undescended testicle; short neck; died at 1 d post-surgery.**
- ari-30 2001; f; LB; 39 wks; Bwt 2350 g; **anus atr w recto-perineal fist; diaphr hernia; Meckel's diverticulum.**
- ari-31 2003; f; LB; 39 wks; Bwt 2700 g; **atr rectum, anterior displacement of imperforated anus, no gluteal folds, f ext genitals, vag atr, sigmoid-urethral fist; L pelvic kidney; hypopl of pelvic floor musculature and anal sphincter. No evidence of exstrophy.**
- ari-32 2004; m; LB; 40 wks; Bwt 2550 g; **atr anus; empty scrotum; died at 4 d; no autopsy report.**
- ari-33 2004; f; LB; 40 wks; Bwt 3050 g; **atr anus w recto-vag fist; esoph atr; died post-surg at 7 d; no autopsy report.**
- ari-34 2008; m; LB; 34 wks; Bwt 3200 g; **esoph atr w T-E; anal sten; annular pancreas; died at 6 wks.**
- ari-35 2009; f; LB; 38 wks; Bwt 2530 g; **ectopic-stenotic anus; VSD, perimembranous; ASD-OS; R torticollis.**

Anal Atresia Associated with Body Stalk Anomalies

- arj-1 2000; amb; S; 40 wks; Bwt 1900 g; **anus and rectum atr and anom body stalk; caudal regression sequence; esoph atr; pulm hypopl; VSD; bilat renal and urinary bladder agen; Potter sequence; adrenal apl; L hip and tibia hypopl; L foot apl; R foot preax polyd; R leg def; asplenia; thick nasal tip; prenat oligohydr; mat flu in the 1st trimester.**

Anal Atresia Associated with Caudal Dysplasia

- arj-2 2000; f; LB; 38 wks; Bwt 2200 g; **anal sten; BLEXTR; L agen kidney, pelvic bones and leg; epispadias, normal mental development, at 11 yrs of age is bilingual, attends standard school, is among the best students.**

Sirenomelia (SIR) and Anal Atresia

- sir-1* 2002; *amb*; *S*; 31 wks; Bwt 1700 g; *SIR*, fused legs entire length; **renal hypopl**; *pulm hypopl*; **atr anus**; *ureters open into intestine*; *abs external genitalia*; *abs urinary bladder*; rudimentary abdominal gonads; cardiac dilatation; **nephroblastoma** of R kidney; *prenat 15 wks, oligohydr*; 22 weeks, renal hypopl, severe oligohydr; 26 wks, R renal nephroblastoma, Wilms' tumor, hypopl thorax.
- sir-2* 2008; *amb*; *S*; 36 wks; Bwt 591 g; **TW diamniotic, dichorionic, disc u-m set**; *SIR*, webbed legs, **anal atr**, *bilat renal agen*; *abs external genitalia*; **abs L arm**; *co-TW, m, S*, Bwt 2530 g, *no malf noted*; *prenat at 15 wks, one fetus no CM, co-TW w oligohydr, legs not visualized*.

ADDITIONAL OBSERVATIONS

Caviat:

Although the number of observations shown approaches complete population ascertainment, the variability of expression of these disorders render complete population ascertainment uncertain.

FETAL ALCOHOL SPECTRUM DISORDER (FASD)

Clinical highlights of 58 individuals are summarized in the Table S-2b above.

One individual (k-1) is included in the NTD category.

Twenty individuals (r-1-5, 8, 11, 12, 15; s-1-4, 6-10, 12, 13) are included in the Microcephaly category.

Note: Not all individuals reported below are represented in the text or tables of the report. Their ascertainment is mostly by prenatal diagnostic services.

HOLOPROSENCEPHALY (HOLOP) (34 individuals)

Note: included are individuals with a single cerebral ventricle and lack of cerebral hemispheres; lobar HOLOP implies partial development of the anterior cerebral hemisphere and incomplete separation of frontal lobes and ventricles; semi-lobar implies partial development of posterior cerebral hemispheres and ventricles. Excluded are instances of arrhinia.

Note: includes holoprosencephaly associated with microphthalmia, microcephaly, and PATAU or trisomy 13 syndrome.

When detected, birth status and sex:

< 15,	3	Liveborn	(LB), 17	Polissia	non-Polissia
15-20,	11	Stillborn	(S), 4	Males	7
21-24,	2	Termination of pregnancy (ToP),	13	Females	4
25-34,	4			Unknown	0
<1 st yr.,	14				4

Listed in alternative CM categories:

tw-1 see twins category.

neo-1 see neoplasia (NEO) category.

z-2 see conjoined twins category.

Isolated – Singletons (20 individuals)

When detected, birth status and sex:

< 15,	1	Liveborn	(LB), 13	Polissia	non-Polissia
15-20,	5	Termination of pregnancy (ToP),	7	Males	4
21-24,	1			Females	2
25-34,	2			Unknown	0
					2

<1st yr., 11

- hol-1 2007; m; LB, 40 wks; Bwt 3260 g; HOLOP, semilobar; at b OFC 35 cm, 50th pct; at age 3 wks 34.5 cm, ≤ 1.75 SD; at age 1 yr 43 cm, < 2.5 SD; at 4 mo, lat cerebr ventr noted to be merged ant and cav-sept-pel not seen.
- hol-2 2008; m; LB, 25 wks; Bwt 990 g; HOLOP, semilobar; died at 3 d.
- hol-3 2008; f; ToP, 21 wks; Bwt 250 g; HOLOP, lobar, incompletely defined; prenat 19 wks, polyhydr, brachycephaly, broad cisterna magna, banana-shaped cerebel, transcerebel diameter 19 mm, cav-sept-pel 4 mm wide, lat ventr widely separated, 6 mm wide; mat syphilis before pregnancy.
- hol-4 2009; m; LB, 40 wks; Bwt 3660 g; HOLOP, lobar; prenat 39 wks, cav-sept-pel not seen, 5 mm wide ant horns, post horns 11 mm wide, probable ventriculomegaly, 8 mm cisterna magna, 37 mm transverse cerebel diameter, fused ant ventr, absent cav-sept-pel.
- hol-5 2009; f; ToP, 20 wks; Bwt 360 g; HOLOP, lobar; prenat 20 wks, single frontal lobes, cav-sept-pel not seen; father had CL.
- hol-6 2009; m; LB, 35 wks; Bwt 1700 g; HOLOP, semilobar; **mOPH**; **MIC**, at b OFC 28 cm, $< 3\%$; at age 36 d OFC 30 cm, < 3 SD; **central CL/P**; **R corneal opacity**; bilat preauricular tags; no polyd; no renal abn; died at 2 mo.
- hol-7 2003; f; LB, 40 wks; Bwt 2700 g; HOLOP, semilobar; **central-CL**; **midface hypopl**; **nasal sept not seen**; **big ears**; **frontal ethmoidal sinuses underdeveloped**; **acoustic meatuses underdeveloped**.
- hol-8 2003; m; LB, 30 wks; Bwt 1450 g; HOLOP, lobar; single brain ventr; at age 1 mo, cav-sept-pel not seen, merge ant horns of lat ventr, smooth cerebr gyri and sulci.
- hol-9 2004; m; ToP, 18 wks; HOLOP, semilobar; nasal bone hypopl; cav-sept-pel and ant cerebr horns not seen, cerebr falx not seen; separate post cerebr hemisp; single crescent-shaped frontal ventr; mat 46,XX; prenat 18 wks.
- hol-10 2004; u; ToP, 20 wks; HOLOP, semilobar; lat shifted post horns of lat cerebr ventr; cerebr falx partially seen separating cerebr hemisp in post regions and not in frontal lobes region, cav-sept-pel and ant ventr not seen, single crescent-shaped frontal lobes ventr, upper lip intact; prenat 20 wks.
- hol-11 2004; m; LB, 40 wks; Bwt 3200 g; HOLOP, semilobar; single brain ventr.
- hol-12 2006; f; LB, 40 wks; Bwt 3900 g; HOLOP, lobar; 46,XX; one cong tooth; at age 3 d, merged lat ventr at their ant horns and bodies, and R and L post ventr seen, post interhemisp fissure seen and partially seen in frontal lobes area, cav-sept-pel and corp call not seen, separate thalami seen; at age 2 mo, examination confirms previously noted anom, psycho-motor development delay.
- hol-13 2007; f; LB, 41 wks; Bwt 2780 g; HOLOP, lobar; at age 10 d, lat cerebr ventr merged at level of ant horns, cav-sept-pel not seen.
- hol-14 2007; m; LB, 39 wks; Bwt 3500 g; HOLOP, lobar; agen corp call; prenat 29 wks, cav-sept-pel not seen, corp call not seen, internal hydrocephalus; mat duodenal ulcer.
- hol-15 2008; m; ToP, 20 wks; Bwt 190 g; HOLOP, semilobar; bilat **mOPH**; prenat 19 wks, cav-sept-pel and frontal horns of lat ventr not seen, thalami and nasal bones seen, orbital diameter 3 mm (normal 5-9 mm), intraorbital diameter - 5 mm (normal 6-15 mm), extraorbital diameter - 15 mm (normal 19-34 mm), measurements consistent w **mOPH**.
- hol-16 2008; f; ToP, 21 wks; HOLOP, alobar, 46,XX; prenat 14 wks, anom cerebr hemisp and post cranial fossa structures; int hydroceph; prenat at 21 wks, cerebr falx and corp call not seen; intact upper lip, symmetric IUGR; fam pat m-m TW once.
- hol-17 2009; u; ToP, 13 wks; HOLOP; prenat 12 wks, middle brain structures not seen, single crescent-shaped ventr.
- hol-18 2009; m; LB, 39 wks; Bwt 3460 g; HOLOP, semilobar; agen corp call; at age 3 d OFC 33.5 cm; at age 2.5 mo 37 cm, < 1.5 SD; at age 2 mo, single crescent-shaped ventr; partially fused and abs corp call.

hol-19 2009; f; LB, 28 wks; Bwt 1400 g; HOLOP, semilobar; at age 6 d, ant merged lat ventr; partially merged lat ventr; cav-sept-pel not seen.

hol-20 2009; m; LB, 36 wks; Bwt 2540 g; HOLOP, semilobar; MIC; at b OFC 30 cm, 3%; at age 1 w 31 cm, 3%; 46,XY; at b and at age 2 wks, single cerebr ant ventr.

With Associated Malformations – Singletons (14 individuals)

When detected, birth status and sex:

				Polissia non-Polissia	
< 15,	2	Liveborn	(LB), 4	Males	3
15-20,	6	Stillborn	(S), 4	Females	2
21-24,	1	Termination of pregnancy (ToP),	6	Unknown	0
25-34,	2				2
<1 st yr.,	3				

hol-21 2007; f; ToP, 20 wks; Bwt 300 g; HOLOP; PATAU; agen corp call and vermis cerebelli; bilat CL; hypopl L heart; aortic sten; postax R hand polyd; R kidney dupl; IUGR, oligohydr, cav-sept-pel and ant horns not seen, post horns lat located; prenat 20 wks.

hol-22 2007; m; LB, 38 wks; Bwt 2790 g; HOLOP, lobar; bilat mOPH; PATAU; esoph atr; died at 8 d.

hol-23 2008; m; S, 33 wks; Nwt 1500 g; HOLOP; mOPH; PATAU; penis hypopl; prenat 18 wks, single hemisp and crescent-shaped ventr, mOPH, orbital diameter 5 mm; fam sib see HOLOP individual (*hol-24*).

hol-24 2008; m; LB, 32 wks; Bwt 1900 g; HOLOP, semilobar; PATAU; hydroceph; died at 1 d; prenat at 23 wks, cav-sept-pel and ant horns not seen, macrocephaly and hydroceph; at 13 wks, cav-sept-pel not seen; cerebr hemisp not separated in frontal area, ant horns and lat ventr not seen, single crescent-shaped echonegative area in frontal lobe, interpretation as single ventr, cerebr hemisp separation in post lobes; fam sib HOLOP see *hol-23*.

hol-25 2009; f; ToP, 21 wks; Bwt 360 g; HOLOP, semilobar; PATAU; mOPH, orbital diameter at 20 wks 5 mm vs. 7-12 mm norm; prenat at 20 wks, cerebr hemisp incompletely separated, single ventr, cerebr falx not seen.

hol-26 2003; amb; LB, 40 wks; Bwt 2550 g; HOLOP, lobar, agen corp call, cav-sept-pel not seen, hypopl thalami; common vaginal-urinary bladder opening (**urogenital sinus**).

hol-27 2003; m; LB, 40 wks; Bwt 3700 g; HOLOP, semilobar; PATAU; agen corp call; bilat CL/P; died at 5 mo, post mortem, semilobar HOLOP, incomplete frontal lobe separation, agen of corp call, dyspl fronto-nasal bones, CL/P, prenat polyhydr.

hol-28 2007; m; ToP, 21 wks; Bwt 250 g; HOLOP, semilobar; PATAU; L renal agen, R renal hypopl; cerebr anom, separated brain lobes except frontally, common sickle-shaped ventr, cav-sept-pel not seen, anom R and agen L kidneys; prenat 21 wks.

hol-29 2007; f; S, 38 wks; Bwt 2550 g; HOLOP, lobar; mOPH, orbital diameter 10 mm vs. 15-20 mm norm; hydroceph; anus atr; prenat 33 wks, polyhydr, corp call not seen.

hol-30 2007; m; S, gest unknown; HOLOP, semilobar; 46,XY,der(13;14)(q10;q10),+13, PATAU; agen corp call; bilat CL/P; postax polyd hands and feet; prenat 18 wks, brachycephaly, cav-sept-pel not seen, bilat CL, nephromegalic, hyperechogenic and hydronephrotic kidneys, polyhydr.

hol-31 2008; u; ToP, 13 wks; HOLOP, alobar, PATAU; limbs reduct and short trunk; prenat 13 wks, cerebr anom, single ventr, cerebr falx not seen, nasal bones not seen; fam father has polycys kidneys, anom hips, and coxoarthrosis.

hol-32 2009; m, S, 38 wks; Bwt 2800 g; HOLOP, lobar; agen corp call; **tetralogy of Fallot**; hydronephrosis; prenat 31 wks, polyhydr, cav-sept-pel, frontal and ant horns of lat ventr not seen, anom frontal cerebr, tetralogy of Fallot, L hydronephrosis; fam mat renal anom, f-m TW once.

hol-33 2009; m; ToP, 21 wks; Bwt 400 g; HOLOP, PATAU; hypopl L heart and aorta, VSD; unilat CL; prenat 19 wks, cav-sept-pel and ant horns of lat ventr not seen.

hol-34 2009; f; ToP, 18 wks; Bwt 340 g; HOLOP, alobar, PATAU; CL, median; VSD; bilat renal hypopl; prenat 18 wks, oligohydr, crescent-shaped ventr, cerebr hemisp not separated.

TRISOMY 13 or PATAU SYNDROME (PATAU)

Note: all individuals were detected by clinical diagnosis.

Listed in alternative CM categories:

s-11, see microcephaly category.

v-1,3; w-1, see microphthalmia category.

aa-2; bb-1, see omphalocele category.

hol-21-25, 27, 28, 30, 31, 33, 34, see holoprosencephaly category.

mntq-1 2002, f; SA; 27 wks; PATAU; agen corp call; CL/P; hypopl left heart; L hand postax polyd; prenat 23 wks OFC 219 mm.

mntq-2 2002; m; LB; 38 wks; PATAU; CL/P; intest malrotation; trilocular heart; L foot polyd; died at 1 d.

mntq-3 2009; m; ToP; 20 wks; 47,XY+13, PATAU; bilat CL/P; R diaphr hernia; prenat 20 wks, orbital dm 10 mm; spine normal; R diaphr hernia, intest in the thoracic cavity; L hydropericardium, myocardial hypertrophy, mult hyperechoic inclusions in cardiac ventricles; hyperechoic kidneys.

NEOPLASIA (NEO) (3 individuals)

Comment: these two observations are incidental and not representative of cancer rates.

Listed in alternative CM categories:

clr-5 ependymoma, see CL/P category.

sir-1 nephroblastoma, see Sirenomelia category.

Not Isolated – non-Syndromic – Singleton

*neo-1 2007; f; LB, 34 wks; Bwt 2450 g; **teratoblastoma**, histology similar to a metastatic ovarian tumor, neck and trachea impacted; **HOLOP**, lobar; died at 2 wks; gestation in vicinity of nuclear power plant; prenat 33 wks, polyhydr; biparietal diameter 90 mm, calculated OFC=324 mm, cav-sept-pel 8 mm wide, post horns 6 mm wide, cisterna magna 10 mm, transcerebel diameter 45 mm, tumour-like multichambered structure 110x87 mm on neck L surface.*

ALL NON-SINGLETON INDIVIDUALS

Note: The listing includes all non-singleton individuals with congenital malformations including those reported above.

QUADRUPLETS

Qdr-1 2007; f-f-m-m; LB; 28 wks; structural malf not noted.

TRIPLETS

Without associated malformations (8 sets).

- trpl-1 2004; f-f-f; LB; 34 wks; structural malf not noted.
 trpl-2 2008; m-m-m; LB; 33 wks; structural malf not noted.
 trpl-3 2003; f-f-f; LB; 35 wks; structural malf not noted.
 trpl-4 2004; m-m-m; LB; 31 wks; structural malf not noted.
 trpl-5 2007; f-f-f; LB; 33 wks; structural malf not noted.
 trpl-6 2007; f-f-f; LB; 30 wks; structural malf not noted.
 trpl-7 2009; f-f-f; LB-S-S; 38 wks; structural malf not noted.
 trpl-8 2009; f-f-f; LB; 35 wks; all survived; structural malf not noted.

Associated with malformations

trpl-9 2008; f; LB; 31 wks; Bwt 1330 g; one of IVF triplet, disc f-f-f (co-twins: one died at 1 d; another – died at 8 wks gest); **cataract** bilat; hydroceph; fam mat Down synd m.

CONJOINED TWIN SETS (CTW) (8 sets)

Without associated malformations (6 sets)

- ctw-1 2000; f-f; S; 31 wks; Bwt 2940 g; CTW, thoraco-pagus; pat M-M twins once.
 ctw-2 2004; u-u; ToP; 13 wks; CTW, omphalo-pagus.
 ctw-3 2000; f-f; ToP; 26 wks; CTW, cranio-thoraco-omphalo-pagus.
 ctw-4 2006; f-f; ToP; 18 wks; CTW, thoraco-omphalo-pagus; pat brother had one daughter with anencephaly-rachis-schisis and another with hypopl L heart .
 ctw-5 2009; u-u; ToP; 18 wks; CTW, thoraco-omphalo-pagus; prenat 18 wks, noted fetal demised estimated at 14 wks; fam pat 2 singleton individuals had fatal malformations suggestive of diabetic fetopathy; m-f TW once; fam mat m-m TW and m-f TW once.
 [ctw-6 2010; m-m; ToP; 21 wks; CTW, thoraco-omphalo-pagus; common heart and liver, two gastro-intest tracts; prenat 21 wks, polyhydr, one 4-chamber heart, 2 stomachs, 2 urinary bladders, 4 kidneys; fam mat m-m TW once and m-f TW once.]

Associated with malformations

- h-1 f-f, **spina bifida, OM**, see NTD category.
 z-1 2002; f-f; LB; 40 wks; Bwt 6000 g; CTW, thoraco-omphalo-pagus; **bilocular heart**; fam mat m-m TW once; fam pat f-f TW once; fam mat-pat m-f TW once.
 z-2 2009; m-m; ToP; 20 wks; CTW, cranio-thoraco-omphalo-pagus; R TW with **proboscis**, **single orbit**, abs oral opening and **short umb cord**; L TW with malf face and **reduct anom of R leg**; prenat 20 wks, oligohydr; 3 brothers incl m-m TW; fam mat TW once.

TWIN PAIRS

Without associated malformations - See Table S-3.

Holoprosencephaly (HOLOP)

- tw-1 2009; m; LB; 38 wks; Bwt 3080 g; TW, disc m-m (co-twin: fetal death at 20 wks), diamniotic, monochorionic, symmetrical; **MIC**, at b OFC 29 cm, <4SD; at age 3.5 mo 30.5 cm, <7SD; **HOLOP**, lobar; ileum atr; int hydroceph; prenat 16 wks, two fetuses, amniotic sept between fetuses, diamniotic, monochorionic, symmetrical TW; at 35 wks, fetus A: no cardiac motion, growth arrested at 20-21 wks level; fetus B: at 29-30 wks gest size, MIC noted, cav-sept-pel not seen, single crescent-shaped ventr, intest obstruction, unilat hydrocele, interpretation, lobar HOLOP, MIC, intest obstruction; fam pat m-f TW once.

Neural Tube Defects (8 individuals)

See individuals a-1, e-1, i-1, b-1, b-2, b-3, j-1, j-2.

Ectopia Cordis (ECTC)

See individual dd-1 (ECTC, **pentalogy of Cantrel**) in omphalocele category.

Acardia (5 individuals)

When detected, birth status and sex:

< 15,	1	Stillborn	(S), 3	Polissia	non-Polissia
15-20,	2	Spontaneous abortion (SA),	2	Males	3 1
21-24,	1			Females	1 0
At birth,	1				

- tw-2 2007; m; SA; 21 wks; TW, monochorial, asymmetric, disc m-m, co-TW SA; acephaly; acardia; reduct legs; prenat 18 wks, fetus A (on L): no anom, amniotic sept seen, vascular connections between fetu; fetus B anom shape, no cephalon, no spine, no heart and no limbs, no blood flow, interpretation is monochorionic twins, asymmetric development, acardia, reversed arterial flow, severe polyhydr, feto-placental insufficiency.
- tw-3 2008; f; SA; 21 wks; TW, disc f-f, co-TW SA; acardia; acephaly; prenat 15 wks, severe polyhydr, fetus A - no anom, fetus B - cranial bones, heart, heart motion not seen; interpretation, acephalic acardia.
- tw-4 2008; m; S; 32 wks; Bwt 400 g; TW, monochorial, diamniotic, disc m-m, co-TW S; acardia; abs arms; prenat 13 wks, fetus B, edematous, heart, arterial flow, upper limbs not seen; amniotic sept between fetu; interpretation, acardia, monochorial diamniotic TW with reversed arterial flow, malf upper limbs, and hydrops.
- tw-5 2008; m; S; 37 wks; Bwt 430 g; TW, disc m-m, co-twin LB; fetus acardius amorphous.
- tw-6 2008; m; S; 32 wks; TW, disc m-m, co-TW L has VSD of unknown significance; acardia; prenat 22 wks, fetus A – anom not seen; fetus B, undifferentiated head, trunk, limbs, no heart motion seen.

Cardiac Malformations (21 individuals)

The prenatal-postnatal detection proportion is 1-20.

Liveborn (LB), 20	Stillborn (S), 1 (see tw-8)	Polissia	non-Polissia
		Males	9 5
		Females	3 4

- tw-7 2002; m; LB; 37 wks; TW, disc m-m, co-TW LB; muscular **VSD**.
- tw-8 2002; m; S; 31 wks; TW, disc m-m, co-TW LB; **trilocular heart**.
- tw-9 2003; f; LB; 37 wks; TW, disc f-f, co-TW LB; **CHD**, unspecified.
- tw-10 2003; m; LB; 39 wks; TW, disc m-m, co-TW LB; **CHD**, unspecified.
- tw-11 2003; m; LB; 39 wks; Bwt 1700 g; TW, disc m-f, co-TW LB; **VSD**.
- tw-12 2003; m; LB; 36 wks; Bwt 3060 g; TW, disc m-m, co-TW LB; **Tetralogy of Fallot; esoph atr**; polycys kidney; cong tracheomalacia; dolichocephaly; polyhydr; pectus excavatum; died at 6 mo.
- tw-13 2004; m; LB; 39 wks; TW, disc m-m, co-TW LB; **VSD**.
- tw-14 2005; m; LB; 40 wks; TW, disc m-m, co-TW LB; **VSD**.
- tw-15 2008; m; LB; 33 wks; Bwt 2760; TW, monochorionic, diamniotic, disc m-m, co-TW LB; **pulm artery atr**; aneurism of atrial sept; prenat 20 wks, fetus A, no malf seen; fetus B, polyhydr, R atrium large, myocardial hypertrophy; amniotic sept between fetu seen; Ebstein anom, microgastria; mat diffuse goiter; fam mat f-f TW once; fam pat m-f TW once.
- tw-16 2008; f; LB; 37 wks; TW, disc f-f, co-TW LB; **CHD**, unspecified.
- tw-17 2009; f; LB; 37 wks; Bwt 2410 g; TW, disc f-f, co-TW LB; **VSD**.
- tw-18 2009; m; LB; 34 wks; Bwt 2210 g; TW, disc m-m, co-TW LB; **Tetralogy of Fallot**.
- tw-19 2000; f; LB; 38 wks; Bwt 2300 g; TW, disc f-f, co-TW LB; **hypopl R heart; ASD**.
- tw-20 2002; m; LB; 31 wks; TW, disc m-f, co-TW LB; **CHD**, unspecified.
- tw-21 2002; m; LB; 39 wks; TW, disc m-m, co-TW LB; muscular **VSD**; bilat inguinal hernia.
- tw-22 2005; f; LB; 40 wks; TW, disc f-f, co-TW LB; muscular **VSD**.
- tw-23 2008; f; LB; 36 wks; Bwt 2680 g; TW, disc m-f, co-TW LB; **pulm valve sten**.
- tw-24 2008; f; LB; 39 wks; TW, disc f-f, co-TW LB; **pulm artery sten; PFO**.
- tw-25 2009; m; LB; 34 wks; Bwt 1440 g; TW, disc m-m, co-TW LB; **VSD**.

tw-26 2009; m; LB; 37 wks; Bwt 2600 g; TW, conc m-m, co-TW LB (see tw-27); **VSD**.
 tw-27 2009; m; LB; 37 wks; Bwt 2600 g; TW, conc m-m, co-TW LB (see tw-26); **VSD**.

Gastroschisis

See individual ee-38.

Other Malformations (24 individuals)

Reported under an alternative category

Sirenomelia and nephroblastoma – see *sir-2* in Sirenomelia category.

When detected, birth status and sex:

21-24,	1	Liveborn	(LB), 23		Polissia	non-Polissia
25-34,	1	Spontaneous abortion (SA),	1	Males	8	7
Unknown,	22			Females	4	4
				Unknown	0	1

- tw-28 2000; m; LB; 33 wks; TW, disc m-m, co-TW LB; **R acoustic meatus atr**; R microtia.
- tw-29 2000; m; LB; 38 wks; TW, disc m-m, co-TW LB; **Down** synd (no karyotype); died; mat schizoprenia.
- tw-30 2001; m; LB; 36 wks; TW, disc, m-f, co-TW LB; **amniotic bands** synd; bilat clubfoot; prenat polyhydr.
- tw-31 2001; f; LB; 35 wks; TW, disc f-f, co-TW LB; **polycys kidney**.
- tw-32 2001; m; LB; 36 wks; TW, disc m-m, co-TW LB; balanic **hyposp**.
- tw-33 2004; m; LB; 40 wks; TW, disc m-f, co-TW LB; cong **hydroceph**.
- tw-34 2006; f; SA; 25 wks; TW, disc m-f, co-TW S; **abs shoulder, forearm, femur**; cystic hygroma; IVF.
- tw-35 2006; m; LB; 36 wks; Bwt 2900 g; TW, disc m-f, co-TW LB; L **uretherohydronephrosis**; prenat 30 wks, L kidney enlarged, 60x45 mm, pelvi-calyceal system 36 mm - hydronephrosis of the 4th stage; fam mat f-f TW once.
- tw-36 2007; m; LB; 28 wks; TW, disc m-m, co-TW LB; **ileum atr**; died at 6 d; prenat polyhydr.
- tw-37 2009; m; LB; 34 wks; TW, disc m-m, co-TW LB; **hydranencephaly**; fam mat m- m TW twice and f- f TW once.
- tw-38 2009; f; LB; 34 wks; TW, disc f-f, co-TW LB; R **cataract**.
- tw-39 2009; f; LB; 31 wks; Bwt 700 g; TW monochorial diamniotic, disc f-f, co-TW LB; extensive **intest sten**; died at 2 d.
- tw-40 2002; m; LB; 38 wks; TW, disc m-m, co-TW LB; balanic **hyposp**.
- tw-41 2002; m; LB; 38 wks; TW, disc m-m; co-TW LB; balanic **hyposp**.
- tw-42 2002; m; LB; 34 wks; TW, disc m-m; co-TW LB; balanic **hyposp**.
- tw-43 2003; m; LB; 35 wks; TW, disc m-m, co-TW LB; **peno-scrotal hyposp**; prenat polyhydr.
- tw-44 2004; m; LB; 37 wks; TW diamniotic, symmetrical, disc m-m, co-TW LB; **reduct R arm**.
- tw-45 2004; m; LB; 28 wks; TW, disc m-m, co-TW LB; **jejunal atr**; died at 20 d.
- tw-46 2004; f; LB; 37 wks; TW, disc f-f, co-TW LB; **Dandy-Walker malf**.
- tw-47 2006; m; LB; 34 wks; TW conc m-f; co-TW LB (see tw-48); **Down** synd, 47,XY+21; **ASD**, secondary; prenat chronic fetal hypoxia.
- tw-48 2006; f; LB; 34 wks; TW conc m-f; co-TW LB (see tw-47); **hydroceph**; prenat chronic fetal hypoxia.
- tw-49 2008; amb, LB; 35 wks; TW, disc m-amb, co-TW LB; **amb genitalia**; bifid scrotum; urogenital sinus; perineal **hyposp**.
- tw-50 2009; f; LB; 33 wks; TW, diamniotic, disc f-f, co-TW LB; **abd wall def**; neonatal death; prenat 21 wks, fetus A, malf not noted; fetus B, large abd wall def and organs eventr covered w membrane; mat smoking.

tw-51 2009; f; LB; 36 wks; Bwt 1760; TW monochorial diamniotic, disc f-f, co-TW LB; **arthrogryposis mult cong**; prenat 34 wks, IUGR, ascitic; fam mat f-f TW once, fam pat m-m TW once.

Observations in Rivne, Volyn and Khmelnytsky provinces

Case-by-case Clinical Highlights of Individuals with Teratomas

Rivne Province

Isolated – Singletons (10 individuals)

- ter-1 2001; u; ToP; 25 wks; TER, sacro-coccygeal.
ter-2 2003; u; ToP; 19 wks; TER, sacro-coccygeal.
ter-3 2003; f; LB; 40 wks; Bwt 3100 g; TER, sacro-coccygeal.
ter-4 2003; u; ToP; 21 wks; Bwt 550 g; TER, sacro-coccygeal.
ter-5 2004; m; LB; 37 wks; Bwt 3500 g; TER, sacro-coccygeal.
ter-6 2007; f; LB; 31 wks; Bwt 1900 g; TER, sacro-coccygeal; prenat 18 wks, non-homogenous echogenic cystic incl in coccygeal area; at 26 wks: polyhydr and same mass, sacro-coccygeal TER; mat diabetes mellitus, non-toxic goiter.
ter-7 2001; f; LB; 39 wks; Bwt 3090 g; TER, sacro-coccygeal.
ter-8 2005; f; LB; 31 wks; Bwt 2700 g; TER, sacro-coccygeal.
ter-9 2008; f; S; 25 wks; Bwt 1070 g; TER, L face-neck; prenat 20 wks, large tumor-like w cystic component, TER.
ter-10 2009; f; LB; 39 wks; Bwt 3290 g; TER, sacro-coccygeal; prenat 20 wks, mass w cystic incl in coccygeal area, TER.

Other

- neo-1 2007; f; LB, 34 wks; Bwt 2450 g; TER-**teratoblastoma**, histology similar to a metastatic ovarian tumor, neck and trachea impacted; HOLOP, lobar; died at 2 wks; gestation in vicinity of nuclear power plant; prenat 33 wks, polyhydr; biparietal diameter 90 mm, calculated OFC=324 mm, cav-sept-pel 8 mm wide, post horns 6 mm wide, cisterna magna 10 mm, transcerebel diameter 45 mm, tumour-like multichambered structure 110x87 mm on neck L surface.

Volyn Province

Isolated – Singletons (11 individuals)

- vter-1 2000; f; LB; 42 wks; Bwt 3200 g; TER, sacro-coccygeal; died at 10 d, postmortem diagnosis: immature teratoma 15x16x16 cm with bleeding ulcer at the top. Mat age 32 yrs, gravidity 3.
vter-2 2002; f; LB; 39 wks; Bwt 3560 g; TER, sacro-coccygeal (10x15 cm, skin unchanged, with cystic vaginal fistula, surgery: thin-walled cystic formation filled with transparent yellow liquid); prenat at 36 wks, sacro-coccygeal TER. Mat age 24 yrs, gravidity 2.
vter-3 2006; m; LB; 40 wks; Bwt 4100 g; TER, sacro-coccygeal. Mat age 19 yrs, gravidity 1.
vter-4 2002; f; LB; 31 wks; Bwt 1930 g; TER, sacro-coccygeal (38 cm in diameter with hemangiomatosis areas and bleeding ulcers; anus is displaced forward, overstretched and deformed); died at 1 d; prenat at 22 wks, SB; prenat at 26 wks, coccygeal hygroma. Mat age 19 yrs, gravidity 1.
vter-5 2004; m; LB; 40 wks; Bwt 3500 g; TER, coccygeal (15x12x11 cm, paste consistency, with fluctuation; skin is unchanged). Mat age 26 yrs, gravidity 1.

- vter-6 2006; m; S; 31 wks; Bwt 3650 g; TER, sacro-coccygeal giant; prenat at 20 wks, polyhydr, sacro-coccygeal TER. Mat age 30 yrs, gravidity 1.
- vter-7 2008; f; ToP; 19 wks; TER, sacro-coccygeal; prenat at 19 wks, sacro-coccygeal TER. Mat age 28 yrs, gravidity 3.
- vter-8 2008; f; ToP; 20 wks; Bwt 400 g; TER, sacro-coccygeal (11x6x4 cm); prenat at 19 wks, sacro-coccygeal TER. Mat age 32 yrs, gravidity unknown.
- vter-9 2009; f; LB; 40 wks; Bwt 3800 g; TER, sacro-coccygeal (10x7 cm); prenat at 39 wks, sacro-coccygeal TER. Mat age 24 yrs, gravidity 2.
- vter-10 2009; f; LB; 41 wks; Bwt 3000 g; TER, maxillary. Mat age 27 yrs, gravidity 1.

Other

- vter-11 2005; m; LB; 38 wks; Bwt 4690 g; **terato-blastoma** sacro-coccygeal malignant (surgery: solid tuberous pear-shaped tumor, 10x11x10 cm, top of the tumor is like fish meat with degradation and contains regional lymph nodes 0.5 cm in diameter); prenat at 38 wks, urinary bladder anomaly. Mat age 19 yrs, gravidity 1.

Khmelnysky province

Isolated – Singletons (6 individuals)

- kter-1 2002; f; LB; 37 wks; Bwt 1800 g; TER, sacro-coccygeal. Mat age 22 yrs, gravidity 1.
- kter-2 2002; m; ToP; 25 wks; Bwt 220 g; TER, sacro-coccygeal; prenat at 18 wks, TER in coccygeal area of spine, breech presentation. Mat age 28 yrs, gravidity 1.
- kter-3 2003; f; LB; 40 wks; Bwt 3200 g; TER, sacro-coccygeal; prenat oligohydr. Mat age 19 yrs, gravidity 1.
- kter-4 2004; f; LB; 38 wks; Bwt 3750 g; TER of thymus; prenat at 37 wks, polyhydr, hydrothorax, ascites. Mat age 33 yrs, gravidity 3.
- kter-5 2005; f; ToP; 18 wks; Bwt 220 g; TER, sacro-coccygeal; prenat at 18 wks, TER in coccygeal area of spine 58x43 mm. Mat age 30 yrs, gravidity 2.
- kter-6 2008; f; LB; 39 wks; Bwt 4370 g; TER, sacro-coccygeal. Mat age 28 yrs, gravidity 2.

Other

- kter-7 2005; m; ToP; 18 wks; Bwt 220 g; **THAB R**, R liver lobe eventrated; TER, sacro-coccygeal (7 cm in diameter, incl liver, cerebral, cartilaginous tissues); apl diaphr; prenat at 18 wks, fetal death, sacro-coccygeal TER. Mat fibromyoma of uterus, carbon monoxide poisoning. Mat age 30 yrs, gravidity 3.

Case-by-case Clinical Highlights of Individuals with NTD, Omphaloceles, Body Wall and Other Anomalies

Volyn Province

- ov-1 2002; u; SA; 17 wks; **AN; OM**; prenat 15 wks; mat age 48 yrs.
- ov-2 2003; m; LB; 35 wks; Bwt 2100 g; at b OFC 30 cm, 3rd pct; suspected **Meckel-Gruber** complex; **ENC frontal; sacral rachischisis; OM; MIC; CL/P** central; **Meckel diverticulum; bilat polycys kidney**; bilat cryptorchidism; hyposp penile; micropenis; prenat 25 wks, oligohydramnios, chorioamnionitis; died at 9 d post surgery; autopsy: same malformations plus creberal edema; mat age 38 yrs, gravida 5; placenta 390 g.
- ov-3 2004; f; ToP; 24 wks; **AN; OM**; prenat 20 wks; mat age 18 yrs, gravida 1.
- ov-4 2005; u; ToP; 18 wks; **SB** unspecified, meningoencephalocele; **OM**; prenat at 14 wks; mat age 20 yrs, gravida 1.

- ov-5 2008; m; ToP; 20 wks; Bwt 650 g; **ENC occipital; OM**; int hydroceph; prenat at 18 wks, hydroceph, hypopl cerebellum, ENC, OM; mat age 35 yrs, gravida 3.
- ov-6 2009; f; ToP; 22 wks; Bwt 320 g; **CRA** (AN+rachischisis); **OM**; prenat at 20 wks, AN, rachischisis, OM; mat age 27 yrs, gravida 1.
- ov-7 2000; f; ToP; 25 wks; Bwt 530 g; **INIEN; OM; CL/P bilat; pulm hypopl; trilocular heart; ectopic spleen and kidney; L clubfoot**; prenat at 22 wks; mat age 22 yrs, gravida 2.
- ov-8 2001; u; ToP; 23 wks; **SB; OM**; prenat at 20 wks; mat fam two ectopic pregnancies and infertility; mat age 26 yrs, gravida 1.

Khmelnysky Province

- ok-1 2004; m; ToP; 19 wks; **TW** dichorionic; **acardia**; AN, **OM**; agen spleen; amelia, upper L; mOPH; liver agen; anotia L; tetraoligodactyly; prenat at 19 wks; mat age 22 yrs.
- ok-2 2006, f; ToP; 22 wks; **SB** lumbar; **OM**; prenat at 19 wks; prev preg 2005 - TOP (SB lumbo-sacral); mat age 39 yrs, gravida 5.
- ok-3 2008, u; ToP; 14 wks; **CRA; OM**; prenat at 12 wks; mat age 26 yrs, gravida 1.
- ok-4 2006, f; ToP; 16 wks; **CRA; OM**; prenat at 16 wks; mat age 23 yrs; gravida 2.
- ok-5 2003, f; ToP; 19 wks; **INIEN; OM**; prenat at 19 wks; mat age 26 yrs, gravida 3.
- ok-6 2003; f; ToP; 20 wks; **CRA; OM**; prenat at 20 wks; mat age 24 yrs, gravida 2.
- ok-7 2009; u; SA; 20 wks; **SB, lumbar; OM; amb genitalia**; talipes calcaneovalgus; prenat at 18 wks; mat age 27 yrs, gravida 3.

Rivne Province

2000-2009 observations: c-3; f-2, 4-8; g-4; h-1; h-3; l-5; m-2; m-5; m-6 described in previous pages.

END