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ARTICLE

Rare chromosome abnormalities, prevalence and prenatal diagnosis rates from population-based congenital anomaly registers in Europe

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The aim of this study is to quantify the prevalence and types of rare chromosome abnormalities (RCAs) in Europe for 2000–2006 inclusive, and to describe prenatal diagnosis rates and pregnancy outcome. Data held by the European Surveillance of Congenital Anomalies database were analysed on all the cases from 16 population-based registries in 11 European countries diagnosed prenatally or before 1 year of age, and delivered between 2000 and 2006. Cases were all unbalanced chromosome abnormalities and included live births, fetal deaths from 20 weeks gestation and terminations of pregnancy for fetal anomaly. There were 10 323 cases with a chromosome abnormality, giving a total birth prevalence rate of 43.8/10 000 births. Of these, 7335 cases had trisomy 21,18 or 13, giving individual prevalence rates of 23.0, 5.9 and 2.3/10 000 births, respectively (53, 13 and 5% of all reported chromosome errors, respectively). In all, 473 cases (5%) had a sex chromosome trisomy, and 778 (8%) had 45,X, giving prevalence rates of 2.0 and 3.3/10 000 births, respectively. There were 1 737 RCA cases (17%), giving a prevalence of 7.4/10 000 births. These included triploidy, other trisomies, marker chromosomes, unbalanced translocations, deletions and duplications. There was a wide variation between the registers in both the overall prenatal diagnosis rate of RCA, an average of 65% (range 5–92%) and the prevalence of RCA (range 2.4–12.9/10 000 births). In all, 49% were liveborn. The data provide the prevalence of families currently requiring specialised genetic counselling services in the perinatal period for these conditions and, for some, long-term care.
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INTRODUCTION

Chromosome abnormalities account for approximately 15% of the major congenital anomalies diagnosed before the age of 1 year in Europe, and are associated with 25% of perinatal deaths due to congenital anomalies.[1] In the European Union in 2004, about one-quarter of all early neonatal deaths were due to congenital anomalies, and of these, in the European Surveillance of Congenital Anomalies (EUROCAT) database regions, 18% were chromosomal.[1] The most common chromosome abnormalities are trisomies 21, 18 and 13, and the sex chromosome abnormalities.[2] Little detailed information is available on rarer chromosome abnormalities diagnosed prenatally or in infancy.

In the 1960s and 1970s, cytogenetic surveys of all newborns[3–6] established the prevalence of babies born with chromosome abnormalities surviving to live births, irrespective of whether they would normally have been diagnosed in early infancy. Not all babies with chromosome abnormalities surviving to live births are diagnosed under normal health care conditions. Children with sex chromosome abnormalities may not have problems requiring investigation until later in life, if at all.[7,8] Marker chromosomes are known to vary widely phenotypically, with apparently normal babies at birth remaining unkaryotyped.[9–11] Thus, the prevalence from cytogenetic surveys does not tell us the diagnosed prevalence among babies. On the other hand, the advent of prenatal screening has led to earlier detection of some babies with chromosome abnormalities who would not survive to live births, and to the increased detection of chromosomal abnormalities, which result in phenotypically normal children.

Since these cytogenetic surveys, average maternal age has risen across Europe and with it the prevalence of chromosomal abnormalities. In the last few decades, increasing recognition of microdeletions

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as a cause of structural anomalies and ease of detection using the PCR and other techniques have led to more chromosomal abnormality diagnoses that would not have been included in the cytogenetic surveys. Taking all these factors together, it is impossible to extrapolate from the cytogenetic surveys to find the current prevalence of chromosome abnormalities diagnosed prenatally or up to 1 year of life.

EUROCAT is a network of population-based congenital anomaly registers in Europe.[1,12] Full-member registries send case data on all congenital anomalies in their region. Data are collected in a standardised format and subjected to rigorous validation checks to ensure high quality. EUROCAT surveys >1.5 million births per year (24.3% of the annual European birth population), including information on live births, fetal deaths from 20 weeks gestation and terminations of pregnancy for fetal anomaly (TOPFA). One of the main EUROCAT objectives is to assess the prevalence of congenital anomalies and the impact of prenatal screening.

The aim of this study is to assess the prevalence and types of rare chromosome abnormalities (RCAs) detected prenatally or in the first year of life, using population-based data from EUROCAT registers. This study provides data useful for the planning of services for affected children and their families, and to contribute to the ongoing debate as to whether routine prenatal screening with increasingly sensitive techniques may be leading to the overdiagnosis of some chromosome abnormalities which have no, or minor, health consequences.[13] The wide variation in prenatal screening policies in Europe[14] serves as a 'natural experiment' resulting in variation in the prevalence of prenatally detected RCA.

METHODS

Full member registries were invited to participate in the study if their cytogenetic reporting was complete. In all, 16 registries from 11 countries agreed to take part. Most congenital anomaly registries cover a local region of variable size and so represent only part of a country, this area is described in the title of each registry, as shown in Table 1.

For the main analysis, cases were extracted from the EUROCAT central database using the following selection criteria:

- Live birth, fetal death from 20 weeks gestation or TOPFA
- Birth year 2000–2006

An ICD-10 code of Q9* or D82.1 or an ICD-9 code of 758* (Codes Q9* and 758* are the codes assigned, in either system, to cover all cases with any chromosome abnormality and D82.1 ensures that all cases with a diagnosis of DiGeorge syndrome are also included).

A search was also made of the anomaly text fields to ensure all relevant cases had been captured.

All chromosome abnormalities were extracted and categorized according to the type of error, with a more detailed analysis performed on those cases with an RCA. RCAs were defined as cases with triploidy, other trisomy, marker chromosomes, unbalanced translocation, deletions and duplications, and excluded trisomies 21,18,13, 45,X and sex chromosome trisomies.

RESULTS

Table 1 shows the countries and their contributing EUROCAT registers, the number of births in 2000–2006 covered by participating registries, the observed prevalence of both total chromosome abnormalities and RCAs. The percentage of all cases with a chromosome abnormality that were prenatally detected is also shown.

There were approximately 2.4 million births in the registry areas, representing 9% of total births in the 11 countries, during the 7-year study period, of which 10 323 were diagnosed as having a chromosome abnormality within the first year of life. The overall prevalence rate of an unbalanced chromosome abnormality was 43.8/10 000 births, ranging from 25.6 in Antwerp to 75.1 in Paris.

The rate of RCA was 7.4/10 000 births with a range from 2.4 in South East Ireland to 12.9 in Northern England. The percentage of RCAs prenatally detected varied widely from 4.9% in South East Ireland to 92.3% in Paris. Most centres, however, were nearer to the average of 65.2%. The method of chromosome ascertainment is also noted in Table 1, clarifying whether the register obtains routine downloads of all data (preferred) or not.

Table 1 The number of cases and prevalence of all, and rare, chromosome abnormalities and the percent of these prenatally detected for each EUROCAT register included in this study

Country	*EUROCAT register(s)*	*Number of births in the EUROCAT registry areas 2000–2006*	*Number of all chromosome abnormalities reported to EUROCAT 2000–2006*	*% of all chromosome abnormalities prenatally detected*	*Prevalence of all chromosome abnormalities per 10 000 births*	*Number of rare chromosome abnormalities reported to EUROCAT 2000–2006*	*Prevalence of rare chromosome abnormalities per 10 000 births*
Austria	Styria[a]	62 667	228	76.4%	36.4	35	5.6
Belgium	Antwerp[b]	127 871	327	60.1%	25.6	47	3.7
Denmark	Odense[c]	37 346	137	70.9%	36.7	22	5.9
England and Wales	East Midlands[b]	432 568	1564	68.6%	36.2	234	5.4
	Northern England	214 037	1030	58.8%	48.1	277	12.9
	Thames Valley	88 814	458	73.9%	51.6	66	7.4
	Wales	222 991	946	66.6%	42.4	184	8.3
	Wessex	185 616	983	63.7%	53.0	231	12.4
France	Paris	247 661	1860	92.3%	75.1	226	9.1
	Strasbourg[b,d]	64 276	285	81.8%	45.4	37	5.8
Germany	Saxony-Anhalt[b]	123 241	366	54.6%	29.7	57	4.6
Ireland	South East Ireland[b]	45 135	118	4.9%	26.1	11	2.4
Italy	Emilia Romagna	218 178	797	80.9%	36.5	118	5.4
Netherlands	N Netherlands	137 278	411	48.5%	29.9	73	5.3
Spain	Barcelona	96 912	491	88.1%	50.7	61	6.3
Switzerland	Vaud	50 275	322	83.8%	64.0	58	11.5
Total		2 354 668	10 323	65.2%	43.8	1737	7.4

[a]Data from 2000–2005 only.
[b]No routine downloads from cytogenetic labs.
[c]Only prenatal cytogenetic downloads.
[d]Data from 2000–2004 only.

Figure 1 gives the total number of all unbalanced chromosome abnormalities with the rare ones classified as 'other'. Figure 2 subdivides these rare abnormalities by type.

RCAs

Table 2 and Figure 2 summarise the results for each chromosome abnormality group. These are described in more detail below.

Triploidy. There was a total of 296 cases of triploidy, giving a prevalence rate of 1.26/10 000 births, of which 92% were prenatally detected (Table 3). There was no association with increased maternal age. Fewer than 5% were alive at birth.

Other trisomies (non-21, 18, 13). There were 58 full trisomies notified to EUROCAT, none of whom survived. The trisomic chromosomes were: 21% with chromosome 22, 11% each with chromosome 9 and 16 and 1 or 2% each with chromosomes 1, 4, 5, 7 and 12. They were all identified by prenatal testing or at late fetal deaths ($\geq$20 weeks). Of the 141 mosaic trisomies (0.60/10 000 births), 78% were prenatally detected (Table 3). Of these, 41% were liveborn, 7% resulted in a

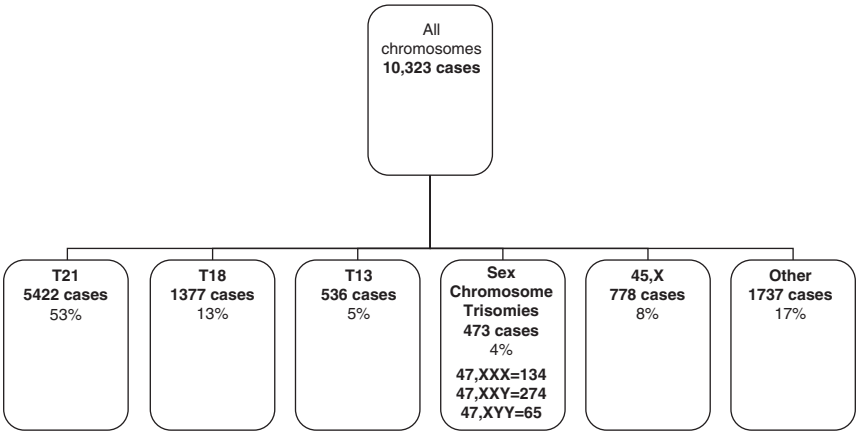

Figure 1 All unbalanced chromosome cases, diagnosed <1 year of age, from 16 registers, 2000–2006.

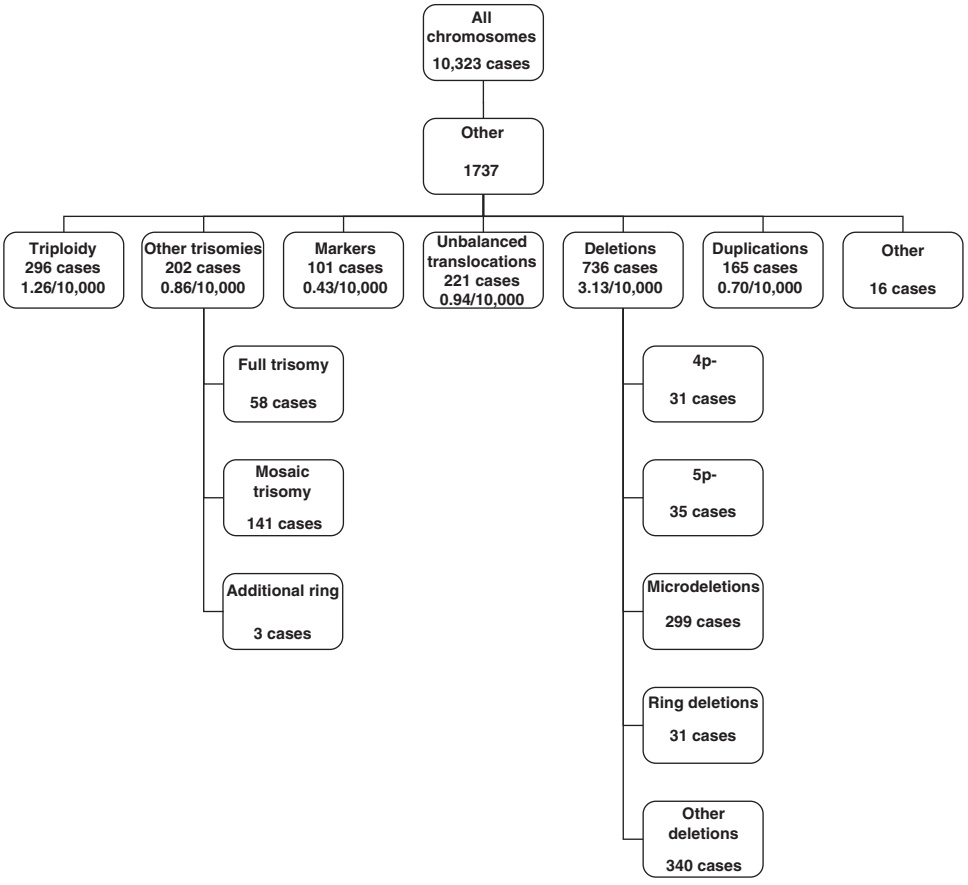

Figure 2 Numbers, rates and categories of RCAs.

Table 2 Summary of cases, live births, prevalence, prenatal detection rate and maternal age for each rare chromosome group

Type of chromosome error	*No. of cases*	*Liveborn (%)*	*Total prevalence per 10 000 births*	*% Prenatally detected*	*% Maternal age ≥35 years*	*Other findings of interest*
Triploidy	296	10 (3%)	1.26	92%	20%	
Other trisomies (non-21,18,13)	202		0.86	82%	46%	Of 63% full trisomies with chromosomal origin specified:
Full trisomies	58	0				21%=T22, 11%=T9, 11% =T16
Mosaic trisomies	141	58 (41%)				Of 62% mosaic trisomies (MT) 25%=MT 8, 22%=MT 9
Markers	101	52 (52%)	0.43	77%	53%	53% chromosome 15 (Of 17 cases with chromosome specified)
Unbalanced translocations	221	138 (62%)	0.94	52%	12%	27% *de novo*, 73% 'familial' (Specified in 49 cases)
Deletions, not including microdeletions (see Table 3)	437	261 (60%)	1.86	43%	23%	
Microdeletions	299	269 (90%)	(1.27)			
22q11	227	197	0.96	38%	16%	
7q11 (Williams)	26	26		3%		
	28	28		0%		
15q11 (Prader–Willi)				0%		
	9	9		78%		
15q11 (Angelman)	9	9				
11p15 (Beckwith–Wiedemann)						
Duplications	165	101 (61%)	0.70	48%	28%	Of the 73% with chromosome specified: 14%=chromosome 15, 6%=chromosome 12, rest <5% (nil chromosome 21, Y)

Table 3 Gestational age at detection in those prenatally diagnosed

		% Prenatally detected			
Chromosome abnormality	*% Prenatally detected*	*% <14/40*	*% 14–21/40*	*% ≥22/40%*	*% Gestation unknown*
Triploidy	92	18	53	7	22
Other trisomies	83	25	45	14	16
Markers	76	9	61	17	13
Unbalanced translocations	52	35	45	7	13
Deletions	43	11	49	20	20
22q11 del	37	3	47	41	9
Duplications	48	14	51	18	17

stillbirth and 49% had a TOPFA. Details of which mosaic chromosome was involved were reported in 62%, with chromosomes 8 and 9 each accounting for 25% of these. In all, 33% of the prenatally detected cases and 73% of those postnatally detected were reported to have structural anomalies. There was no pattern to these anomalies except perhaps for trisomy 9, where three cases had spina bifida and at least two had a cleft palate.

Marker chromosomes. There were 101 additional marker chromosomes identified (a birth prevalence rate of 0.43/10 000 births), of which 77 were prenatally detected, 9 diagnosed at birth, 1 after the 1st week of life and 14 with age at diagnosis not recorded. Of the prenatally diagnosed cases, 43 (56%) resulted in a TOPFA, 30 (39%) were liveborn, two were stillborn and in two the outcome is unknown. In only 17 cases, the chromosomal origin of the marker was reported, of these, nine were from chromosome 15 and three from chromosome 22. Significant congenital anomalies, including cleft lip and palate, diaphragmatic hernia, agenesis of the corpus callosum, Dandy–Walker malformation, VSD and craniosynostosis, were reported in 17 cases, but there were insufficient details to link these to the marker detected. A further three cases had nuchal oedema recorded. Cases were reported from 11 centres.

Unbalanced translocations. There were 221 unbalanced translocations reported (0.94/10 000 births). Of these, 115 (52%) were diagnosed prenatally, 33 (15%) within the first week of life, 15 (7%) between 1 week and 1 year, 6 (3%) at miscarriage and in 52 (24%) the time of diagnosis was not reported. In all, 62% were liveborn. There was no evidence that maternal age was linked to the prevalence of an unbalanced translocation and the sex ratio of the fetus/baby was also within the normal range. The origin of the translocation was specified in 49 cases. Of these, 27% were *de novo*, 35% maternal, 20% paternal and 20% 'familial'.

Of those prenatally detected, 35% were diagnosed by 14 weeks gestation (number of inherited cases not known), 45% between 15 and 21 weeks and 7% ≥22 weeks.

Deletions, not including microdeletions. There were 437 cases, giving a prevalence rate of 1.86/10 000 births reported with a chromosome deletion, including those configured as a ring, but not including microdeletions. The vast majority of these would have been detected by a routine karyotype, perhaps clarified by FISH, but array CGH was not in regular use during the case years of this study. Forty-three percent were detected prenatally, a quarter of these following first trimester screening, about half due to anomalies detected at a routine anomaly scan and the remainder after 24/40. Sixty-nine percent were liveborn. There was no evidence that maternal age was linked to the prevalence of a deletion and the sex ratio of the fetus/baby was also within the normal range.

Microdeletions. A total of 299 microdeletions were reported, of which 227 were cases of 22q11 deletion from nine centres, giving a prevalence rate of 0.96/10 000 births. For the other microdeletions, there were too few cases from too few centres to comment on prevalence, the details are shown in Table 2.

22q11 deletion. Of the 227 cases reported with 22q11 deletion, 180 had a heart defect. Of these, 54 (30%) were Fallot's tetralogy, 24 (13%)

had truncus arteriosus and 28 (16%) had an abnormality of the aorta. In all, 61 (34%) had a ventricular septal defect and 28 (16%) had an atrial septal defect, some in association with additional cardiac anomalies. Eighty-one percent of cases were liveborn (Table 2). In all, 37% were prenatally detected (Table 3), of whom 84% had a heart defect, 8% talipes, 4% cleft lip and palate, and 6% a cleft palate alone. The number of familial cases is not recorded.

Duplications. There were 165 cases with a chromosomal duplication (prevalence rate 0.7/10 000 births), of which 48% were detected prenatally (Table 3). There were 23 cases of dup(15), of which 16 were female and 7 male. Ten cases were duplications of chromosome 12 and there were <10 cases of duplication from each of the other chromosomes and none from chromosomes 21 and Y. In 44 cases, the chromosomal origin was unspecified. Considering all chromosomes together, the sex ratio and maternal age distribution were within the normal range. 61% were liveborn.

Others. The 16 cases in this category include those with diagnoses, such as chimera, hermaphrodite and non-specific microdeletion or uniparental disomy. Of these, 10 were liveborn.

Survival. There were 899 live births, of which 40 were known to have died within the first year of life, 778 were known to have survived and in 81 one-year survival was unknown. This gives a prevalence of 3.3–3.7 children/10 000 births potentially in need of long-term care.

DISCUSSION

Population-based congenital anomaly register data are derived from both prenatal and postnatal sources. With the advent of prenatal screening in the first trimester, many fetuses that would have miscarried or been stillborn are diagnosed with a chromosome error. Our rate of 43.6/10 000 births, for all chromosome abnormalities, is therefore, as expected, higher than that found in newborn studies[3,15–17] where rates of 17–31/10 000 were found.

There are very few data on the frequency of the less common and non-maternal age-dependent chromosome errors detected perinatally. One other report using congenital anomaly register data is from Baena *et al*[18] who looked at all babies diagnosed prenatally or within 7 days of life and found a rate of 26.2/10 000 births for all chromosome abnormalities. The 6.6% cases that were classified as rare (deletions, duplications, trisomies, unbalanced translocations, markers and apparently balanced rearrangements with a congenital anomaly) gave a prevalence rate of 1.7/10 000 births, much lower than our figure of 7.4/10 000 births. Apart from the study by Baena *et al*, we are aware of no other studies looking at the total prevalence of rare chromosome errors, so the data will be compared with the published subgroup findings.

Triploidy is estimated to occur in 1–2% of all clinically recognised conceptions[19] with two-thirds miscarrying before 15 weeks of gestation. Our rate of 1.26/10 000 births reflects this early loss and is very close to the prevalence rate of 1.34/10 000 births from Hawaii.[20]

Regarding marker chromosomes, Liehr and Wiese[21] reviewed 132 studies on small supernumerary marker chromosomes (sSMC) and found an averaged prevalence rate of 7.5/10 000 births in unselected prenatal cases and 4.4/10 000 births in consecutively studied newborns. Our rate of 0.43 is therefore lower than might be expected. A recent study by Crolla *et al*[9] showed that 68% are derived from acrocentrics, and of these 51% are from chromosome 15. With significant variability in the phenotype associated with many sSMCs, it is likely that only those considered significant were reported to the registers. This is supported by the high rate (17%) of anomalies present in our prenatally detected cases and 30% in our postnatally detected cases with a sSMC compared with a study by Warburton,[10] who found that 13% of those detected by amniocentesis had one or more anomaly. Our predominance of markers derived from chromosome 15, in the few that were further analysed, is entirely in keeping with other reports.[9,22,23]

There are no comparable studies on the prevalence of non-21, 13 or 18 mosaic and non-mosaic trisomies, but Forabosco *et al*[24] found a rate of 0.22/10 000 births. Our rate of 0.86 included the 22% of cases not reported to be detected prenatally. Mosaic trisomy 8 was the most common diagnosis in liveborn cases with the chromosome of origin specified, although many of these would be expected to be diagnosed in later childhood and therefore not registered.

Duplications are rare abnormalities and there are no studies offering a birth prevalence for this group of chromosome abnormalities. Our rate of 0.7/10 000 births with a duplication that represents 1.6% of all our reported chromosome abnormalities therefore stands alone.

The reported prevalence of chromosomal deletions from congenital anomaly register data ranges from 0.3 to 2/10 000 births[18,25–28] with newborn studies suggesting a similar rate of 0.5–1/10 000.[3,15] More recent studies include that of Forrester and Merz from Hawaii,[27] who looked at all deletions reported to a congenital anomaly register within an 8-year period. In all, 4.7% of all chromosome abnormalities reported were deletions, including microdeletions, giving a prevalence of 1.99/10 000 births. Twenty-seven percent were diagnosed prenatally. Just over 7% of all our chromosome abnormalities were deletions, giving a rate of 3.27/10 000 births with 43% of our cases reported prenatally.

Our data cover a more recent time period when the detection of microdeletions is more routine and frequently considered clinically. Forrester and Merz[27] found 14% of their deletion cohort to have 22q11 deletion, whereas in our cohort the proportion was 31%. Swerdlow *et al*[29] analysed the mortality rate in all deletions ever reported postnatally to all the UK cytogenetic laboratories. It is not possible to derive a prevalence rate from these data, as only postnatally detected cases were included, but 20% of their cases had a 22q11 deletion.

Genetic testing for 22q11 deletion became available in 1993–1994, and increased awareness of this syndrome means that children with congenital anomalies within the expected spectrum are now likely to be diagnosed with this chromosome deletion. Oskarsdottir *et al*[30] studied the incidence and prevalence of this condition in live births in a hospital catchment area in Western Sweden for the period 1991–2000. Their 1.32–2.33/10 000 birth rates varied by district, depending on experience and awareness. Our inclusive rate of 0.96/10 000 births varied from 0.2–1.8/10 000 births for different registers and reflects the largely perinatal ascertainment of cases by registers. The rate found by Forrester and Merz[27] was 0.28/10 000 births.

Other microdeletions are included in this report as they are an RCA; however, as most of them were reported from only a few registers, no prevalence figures can be given. The poor reporting is likely to be due to the age of presentation of these conditions as many are not detected perinatally. It may also be related to the variation in genetic expertise available to individual registers.

There are some limitations to this study. Although the variation in prevalence rates between registers may be due to real differences, there are inherent local policy issues that contribute to these variations. For instance, the low prevalence rate in Ireland in part reflects their minimal rates of prenatal diagnosis as TOPFA is illegal, and in Paris ascertainment only includes infants up to 1 week of age. Also relevant

is the link between congenital anomaly registers and the cytogenetic laboratories in their area of coverage. For those with regular and routine downloads, complete ascertainment can be expected, but for those registers with partial (for example, prenatal only) or no routine reports, lower prevalence rates can be expected, which we generally found to be the case (Table 1).

Reporting the prevalence rates by register as well as overall, allows the use of comparable data for future studies, while maintaining the spectrum offered by covering several regions of Europe.

Those chromosome abnormalities that lead to significant developmental disability may be detected within the first year of life, but many such children do not present until later. Most of the registers in this study only collect cases that are diagnosed by one year of age, thus we have excluded all cases diagnosed after this age for consistency. Therefore, the figure of 7.4/10 000 births is certainly an underestimate of the true prevalence of all RCAs in a population.

Only limited data about prenatal diagnosis are currently reported to EUROCAT. Although there is robust information on whether a case was prenatally detected or not, details such as the reason for karyotyping and associated anomalies are not recorded by all EUROCAT registers.

The strength of this study is that EUROCAT registries are population-based, use similar methodology and thus can provide data on prevalence and prenatal diagnosis for rare anomalies. It also enables comparisons between regions to be made.

In spite of the stated limitations of this study, these data provide the only baseline prevalence figures currently available for health service planning for the management and care of people with a rare chromosome abnormality. The live birth prevalence rate of 3.7/10 000 births of long-term survivors with an RCA is significant and may be used to guide long-term healthcare for affected individuals.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DISCLAIMER

The views expressed are not necessarily those of the Department.

1 Zeitlin J, Mohangoo A, Cuttini M *et al*: The European Perinatal Health Report: comparing the health and care of pregnant women and newborn babies in Europe. *J Epidemiol Community Health* 2009; **63**: 681–682.
2 Boyd PA, Loane M, Garne E, Khoshnood B, Dolk H: Sex chromosome trisomies in Europe: prevalence, prenatal detection and outcome of pregnancy. *Eur J Hum Genet* 2010.
3 Hamerton JL, Canning N, Ray M, Smith S: A cytogenetic survey of 14 069 newborn infants. I. Incidence of chromosome abnormalities. *Clin Genet* 1975; **8**: 223–243.
4 Nielsen J, Sillesen I: Incidence of chromosome aberrations among 11148 newborn children. *Humangenetik* 1975; **30**: 1–12.
5 Bell J, Pearn J, McCarthy C *et al*: A total population study of diagnosed chromosome abnormalities in Queensland, Australia. *Clin Genet* 1982; **22**: 49–56.
6 Lubs HA, Ruddle FH: Chromosomal abnormalities in the human population: estimation of rates based on New Haven newborn study. *Science* 1970; **169**: 495–497.
7 Nielsen J, Wohlert M: Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. *Hum Genet* 1991; **87**: 81–83.
8 Jacobs PA: The incidence and etiology of sex chromosome abnormalities in man. *Birth Defects Orig Artic Ser* 1979; **15**: 3–14.
9 Crolla JA, Youings SA, Ennis S, Jacobs PA: Supernumerary marker chromosomes in man: parental origin, mosaicism and maternal age revisited. *Eur J Hum Genet* 2005; **13**: 154–160.
10 Warburton D: *De novo* balanced chromosome rearrangements and extra marker chromosomes identified at prenatal diagnosis: clinical significance and distribution of breakpoints. *Am J Hum Genet* 1991; **49**: 995–1013.
11 Hook EB, Cross PK: Extra structurally abnormal chromosomes (ESAC) detected at amniocentesis: frequency in approximately 75,000 prenatal cytogenetic diagnoses and associations with maternal and paternal age. *Am J Hum Genet* 1987; **40**: 83–101.
12 EUROCAT. 2011, http://www.eurocat-network.eu.
13 Ogilvie CM: Prenatal diagnosis for chromosome abnormalities: past, present and future. *Pathol Biol (Paris)* 2003; **51**: 156–160.
14 Boyd PA, Devigan C, Khoshnood B *et al*: Survey of prenatal screening policies in Europe for structural malformations and chromosome anomalies, and their impact on detection and termination rates for neural tube defects and Down's syndrome. *BJOG* 2008; **115**: 689–696.
15 Dolk H, Loane M, Garne E: The prevalence of congenital anomalies in Europe. *Adv Exp Med Biol* 2010; **686**: 349–364.
16 Baena N, De Vigan C, Cariati E *et al*: Prenatal detection of rare chromosomal autosomal abnormalities in Europe. *Am J Med Genet A* 2003; **118A**: 319–327.
17 Jacobs PA, Browne C, Gregson N, Joyce C, White H: Estimates of the frequency of chromosome abnormalities detectable in unselected newborns using moderate levels of banding. *J Med Genet* 1992; **29**: 103–108.
18 Hook EB, Cross PK, Schreinemachers DM: Chromosomal abnormality rates at amniocentesis and in live-born infants. *JAMA* 1983; **249**: 2034–2038.
19 Hook EB, Schreinemachers DM, Willey AM, Cross PK: Inherited structural cytogenetic abnormalities detected incidentally in fetuses diagnosed prenatally: frequency, parental-age associations, sex-ratio trends, and comparisons with rates of mutants. *Am J Hum Genet* 1984; **36**: 422–443.
20 Forrester MB, Merz RD: Epidemiology of triploidy in a population-based birth defects registry, Hawaii, 1986–1999. *Am J Med Genet A* 2003; **119A**: 319–323.
21 Liehr T, Weise A: Frequency of small supernumerary marker chromosomes in prenatal, newborn, developmentally retarded and infertility diagnostics. *Int J Mol Med* 2007; **19**: 719–731.
22 Karaman B, Aytan M, Yilmaz K *et al*: The identification of small supernumerary marker chromosomes; the experiences of 15,792 fetal karyotyping from Turkey. *Eur J Med Genet* 2006; **49**: 207–214.
23 Huang B, Solomon S, Thangavelu M, Peters K, Bhatt S: Supernumerary marker chromosomes detected in 100 000 prenatal diagnoses: molecular cytogenetic studies and clinical significance. *Prenat Diagn* 2006; **26**: 1142–1150.
24 Forabosco A, Percesepe A, Santucci S: Incidence of non-age-dependent chromosomal abnormalities: a population-based study on 88965 amniocenteses. *Eur J Hum Genet* 2009; **17**: 897–903.
25 Baird PA, Anderson TW, Newcombe HB, Lowry R: Genetic disorders in children and young adults: a population study. *Am J Hum Genet* 1988; **42**: 677–693.
26 Ten Kate LP, Dolk H, Cornel MC *et al*: Frequency of births with potentially avoidable serious chromosomal anomalies in EEC countries, 1979-1982. *J Epidemiol Community Health* 1988; **42**: 266–270.
27 Forrester MB, Merz RD: Patterns of chromosomal deletions identified by a birth defects registry, Hawaii, 1986-2003. *Congenit Anom Kyoto* 2007; **47**: 58–62.
28 De VC, Baena N, Cariati E, Clementi M, Stoll C: Contribution of ultrasonographic examination to the prenatal detection of chromosomal abnormalities in 19 centres across Europe. *Ann Genet* 2001; **44**: 209–217.
29 Swerdlow AJ, Schoemaker MJ, Higgins CD, Wright AF, Jacobs PA: Mortality risks in patients with constitutional autosomal chromosome deletions in Britain: a cohort study. *Hum Genet* 2008; **123**: 215–224.
30 Oskarsdottir S, Vujic M, Fasth A: Incidence and prevalence of the 22q11 deletion syndrome: a population-based study in Western Sweden. *Arch Dis Child* 2004; **89**: 148–151.