ORIGINAL ARTICLE

Incidence and prevalence of the 22q11 deletion syndrome: a population-based study in Western Sweden

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Backgound: Almost all cases of DiGeorge syndrome, velo-cardio-facial syndrome and conotruncal anomaly face syndrome result from a common deletion of chromosome 22q11.2. These syndromes are usually referred to as the 22q11 deletion syndrome (22q11DS), which has a wide phenotypic spectrum and an estimated incidence of one in 4000 births.

Aims: To assess the incidence and prevalence of the 22q11 deletion syndrome in the Western Götaland Region of western Sweden

Methods: Children below 16 years of age with 22q11DS in a well defined catchment area and population of the Western Götaland Region were recruited. Diagnosis of 22q11DS was confirmed using a FISH (fluorescence *in situ* hybridisation) test. Proven 22q11 deletion was the demonstration of one signal in 11 metaphase spreads with fair quality.

Results: During the study period in the Western Götaland Region the mean annual incidence of 22q11DS was 14.1 per 100 000 live births. During the first five years the incidence was 18.1 per 100 000 live births for the whole region and 23.4 per 100 000 live births in Gothenburg, where a multidisciplinary specialist team for 22q11 DS is based. The prevalence was 13.2 per 100 000 children below 16 years of age in the whole region and 23.3 per 100 000 in Gothenburg.

Conclusion: The number of individuals diagnosed depends on the experience and awareness of the syndrome among specialists who encounter these children and also the severity of the phenotype. The higher frequency of 22q11DS found in Gothenburg is an example of increased awareness.The true incidence and prevalence of this syndrome will only be found through population-based screening, but this would be too expensive and ethically questionable. Screening of specific risk populations would be more justified.

In the early 1990s it was recognised that almost all cases of DiGeorge syndrome, velo-cardio-facial syndrome and conotruncal anomaly face syndrome resulted from a common deletion of chromosome 22q11.2.[1–4] Consequently, all these syndromes are today most often referred to as the 22q11 deletion syndrome (22q11DS). Routine genetic testing for the 22q11 deletion, which became available in 1993–94, has resulted in increased awareness of the syndrome and in a rapidly growing group of patients.

The phenotypic spectrum of the 22q11DS includes a wide variety of malformations and abnormalities occurring in different combinations and with widely differing severity. The typical clinical picture includes congenital heart defects, recurrent infections, velopharyngeal insufficiency, learning difficulties, behavioural abnormalities, and characteristic facial features. Many other abnormalities and malformations may, however, also be associated with the syndrome. The incidence of the 22q11DS has been estimated at one per 4000 live births, thus placing this syndrome among the most frequent causes of genetic syndromes and being the most common microdeletion syndrome known in man.[5 6] The 22q11 deletion is found in an increasing number of individuals with mild features, which indicates that the syndrome is more common than previously thought.[7] Because of the wide phenotypic spectrum, it may be many years before we know its true incidence. Similarly, we do not know if the incidence varies in different populations. In recent years awareness of the syndrome has increased in Sweden following the setting up of a multidisciplinary 22q11DS team in Gothenburg. The aim of this study was to assess the incidence and prevalence of 22q11DS in the Western Götaland Region of western Sweden, where Gothenburg is the main city.

SUBJECTS AND METHODS

Study design

A hospital-based prospective study of children below 16 years of age with 22q11DS was performed at the Queen Silvia Children's Hospital, a national reference centre for primary immunodeficiencies, congenital heart defects, and certain rare neurological and neuropsychiatric disorders. The Regional Cleft Palate Team at Sahlgrenska University Hospital is also affiliated to this study.

Study period

The 10 year period 1991–2000 was chosen for the incidence study. The prevalence date was set at 31 December 2000.

Study area

The catchment area and population were well defined and consisted of the Western Götaland Region (Region Västra Götaland)—a recent merger of three counties and the city of Gothenburg in western Sweden. In Sweden, children undergo regular health checks at the local child health centres as well as by a doctor and/or a nurse at school. In cases of symptoms of disease, patients are referred to a paediatric clinic.

Abbreviations: 22q11DS, 22q11 deletion syndrome; FISH, fluorescence *in situ* hybridisation

Study population
All children below 16 years of age diagnosed with 22q11DS living in the Western Götaland Region of Sweden during the study period were recruited into the study. During the study period, 177 047 infants were born in the study area and as of 31 December 2000 the number of children below 16 years of age was 295 495. The corresponding figures for the city of Gothenburg were 56 072 and 81 421, respectively.[8]

Within the Western Götaland Region all children with 22q11DS were referred to the multidisciplinary team at the Queen Silvia Children's Hospital. Confirmation of the diagnosis was made at the only genetic laboratory performing 22q11 deletion analysis in this region and all investigations for 22q11 deletion were scrutinised retrospectively in order to detect cases that had possibly not been referred to the multidisciplinary team.

Case ascertainment
A confirmatory FISH (fluorescence *in situ* hybridisation) test for the 22q11 deletion was requested by many different specialists at the hospitals and outpatient clinics in the region. Nineteen patients (19/41) (46%) were referred by cardiologists, 11 (27%) by paediatric neurologists or child psychiatrists, and seven (17%) by speech pathologists. Two patients were referred by paediatric immunologists and one by an audiologist. One patient was diagnosed antenatally.

FISH test for 22q11 deletion
The FISH analyses were performed on metaphase spreads from standard lymphocyte cultures.[9] Two different, commercially available FISH probes were used for the detection of the deleted 22q11 chromosome region. The N25 (ONCOR) cosmid probe was used until March 1997, when it was replaced by the 32–191028 (Vysis) cosmid probe. A chromosome 22-identifier probe mapping to the 22q13 chromosome region was an integral part of FISH analysis during both periods. The requirement for proven 22q11 deletion was the demonstration of one signal in 11 metaphase spreads with fair quality. Accordingly, the presence of two signals in 11 metaphases was taken to be proof of a normal 22q11 region.

Ethics
Informed consent was obtained from both parents and children. The study was approved by the Research Ethics Committee at Göteborg University.

Statistical methods
Fisher's exact two-tailed test was used to compare the proportion of children with and without a heart defect during the two 5 year periods of the study. The sign test was used to make a comparison of age at diagnosis of children with and without a heart defect.

RESULTS
Incidence
During the 10 year period 1991–2000, 22q11 deletion was confirmed in leucocytes from 24 children born during the study period in the Western Götaland Region and in one fetus diagnosed antenatally, corresponding to a mean annual incidence of 14.1 per 100 000 live births (9.1–20.8, 95% CI) (table 1). Ten of these 24 children were born in Gothenburg, which corresponds to a mean annual incidence of 17.8 per 100 000 live births (8.6–32.8, 95% CI) in the city population. Eighteen (18/24, 75%) were born during the 5 year period 1991–95 and the median age at diagnosis in this group was 5.4 years. Eight of these (8/18) had a heart defect (44%) (table 2). The annual incidence during this period was 18.1 per 100 000 in the Western Götaland Region and 23.4 per 100 000 in Gothenburg.

A retrospective control of FISH analysis performed during the study period revealed a family with two deceased children diagnosed as suspected DiGeorge syndrome. The 22q11 deletion could not be confirmed, as FISH was yet not available. Later the mother was tested positive for 22q11 deletion. Her next pregnancy was terminated following a positive prenatal FISH test for 22q11 deletion. This case with confirmed 22q11 deletion was included in this study.

During the study period, children without a heart defect were diagnosed more often if they were born during the period 1991–95 compared with 1996–2000 ($p<0.024$, Fisher's exact two-tailed test). Children with heart defects were younger at diagnosis compared with those without heart defects ($p<0.006$, sign test) (table 2). The diagnosis was delayed in six out of 14 children with a heart defect. Five of these children were born before the FISH test became available in late 1994, when the level of awareness of this syndrome still was low. One child born in 1996 with patent ductus arteriosus, who was operated on through lateral thoracotomy, was diagnosed at 4 years of age, when other clinical features of the syndrome became apparent. Two children, born in 1993 and 1994, with a heart defect and delayed diagnosis had neither aplasia nor hypoplasia of the thymus at heart surgery, which was otherwise a common reason for suspecting this syndrome.

The median age at diagnosis of children referred by child neurologists or psychiatrists was almost twice as high as that of children referred by cardiologists and speech pathologists (9.6 years and 4.9 years respectively). Clinical signs and symptoms, which prompted referral from neurologists and psychiatrists, were developmental and/or behavioural abnormalities and other symptoms typical for 22q11 deletion (most commonly speech abnormalities, but in most cases also at least one more, such as heart defect, recurrent infections, or characteristic facial features).

Prevalence
The total number of children younger than 16 years of age in the Western Götaland Region of Sweden on 31 December 2000 was 295 495. Chromosome 22q11 deletion was found in 39 children in the region, corresponding to a prevalence of 13.2 per 100 000 children below 16 years of age. For the city of Gothenburg the prevalence was higher. Nineteen children were found with 22q11 deletion, giving a prevalence of 23.3 per 100 000 children younger than 16 years of age. One child died during the study period. Another case was diagnosed antenatally and the pregnancy was terminated.

DISCUSSION
Our study could be seen as a population-based study. The number of individuals diagnosed depends on the experience and awareness of the syndrome among specialists who encounter these children. It also depends on the severity of the phenotype. Individuals with very mild phenotype may not attract medical attention and we could therefore miss cases exhibiting ''soft'' signs. It must also be remembered that only about a decade has elapsed since the discovery of the aetiology of this syndrome and the availability of diagnostic testing.

In recent years an effort has been made to increase awareness of the 22q11 deletion syndrome in Sweden through lectures, courses, and publications. Information in Swedish and English is also available at the Swedish database for rare diseases.[10] A multidisciplinary specialist team has been in place in Gothenburg since 1997, and it was the only team of its kind in Sweden during the study period. Patients were referred to the team from the whole country, offering the opportunity to see many patients and acquire good experience of the syndrome. The team includes a wide

Table 1 The minimum annual incidence of 22q11 deletion in the Western Götaland Region and the city of Gothenburg during the 10 year period 1991–2000

	Western Götaland Region			City of Göteborg		
Year	No of cases	No of births	Annual incidence per 100 000 newborns	No of cases	No of births	Annual incidence per 100 000 newborns
1991	4	21 162	18.9	0	6220	0
1992	5	21 119	23.7	2	6104	32.7
1993	4	20 202	19.8	1	6035	16.6
1994	4	19 336	20.7	3	6044	49.6
1995	1	17 528	5.7	1	5549	18.0
1991–95			**18.1**			**23.4**
1996	1	16 127	6.2	0	5341	0
1997	0	15 494	0	0	5095	0
1998	0	15 372	0	0	5264	0
1999	1	15 216	6.6	0	5128	0
2000	5	15 491	32.3	3	5292	58.5
1996–2000			**10.3**			**11.5**
Total: 1991–2000	**25**	**177 047**	**14.1**	**10**	**56 072**	**17.8**

range of specialisms: cardiology, speech pathology, neurology, psychiatry, psychology, immunology, endocrinology, ENT, odontology, ophthalmology, and clinical genetics.

The referring specialisms represent most of the main specialisms that these patients meet. More than 90% of the patients were ascertained through cardiology, neurology/psychiatry, and speech pathology (46%, 27%, and 17% respectively). Compared with other reports, an unusually high percentage of the patients were ascertained through neurology/psychiatry.[11] The proportion of patients without a heart defect was as high as 40%.

In this study we found a higher incidence among children born during the first 5 year period (1991–95) than during the second 5 year period (1996–2000). The reason for this difference was a delayed diagnosis of children without a cardiac defect (0.6 *v* 6.9 years) (table 2) The most typical heart defects associated with 22q11 deletion are conotruncal heart defects, usually confirmed early in life. All 10 children without a heart defect were born during the first 5 year period and the median age at diagnosis for these children was almost 7 years. The main presenting symptoms were speech abnormalities, learning difficulties, behavioural abnormalities, or developmental delay. Children without a heart defect born during the period 1996–2000 probably still wait to be diagnosed. Assuming that the incidence during the years 1991–95 is more close to the true incidence, it could mean that between eight and 12 children remain undiagnosed. This also implies that a long follow up is needed to find the true incidence.

Table 2 Number of children with and without a congenital heart defect and age at diagnosis, in children born in 1991–95 and 1996–2000 in the Western Götaland Region, Sweden

	Children with a heart defect		Children without a heart defect	
Year of birth	N (%)	Median age at diagnosis Years (range)	N (%)	Median age at diagnosis N (range)
1991–95	8 (44)	3.9 (0.01–6.4)	10 (56)	6.7 (4.1–10.6)*
1996–2000	6 (100)	0.2 (0.01–4.8)	0	–
1991–2000	14 (58)	0.6 (0.01–6.4)†	10 (40)	6.9 (4.1–10.6)†

*The proportion of children without a heart defect was significantly higher during the period 1991–95 compared with 1996–2000 ($p<0.024$, Fisher's exact two-tailed test).
†Children with a heart defect were diagnosed significantly earlier than those without a heart defect ($p<0.006$, sign test).

The incidence was higher in Gothenburg, the main city in the region, than in the whole of the Western Götaland Region. The incidence in Gothenburg during the first 5 year period (23.4 per 100 000) was almost the same as the estimated incidence of one in 4000 often referred to in the literature. This figure is based on three previous reports.[5 12 13]

Wilson *et al* reported 10 patients with 22q11 deletion and a heart defect, born during 1993 in the north of England, and estimated a minimum incidence of 25 per 100 000 based on the number of births and children with congenital heart defects born during the previous 5 years.[12] In a population-based study from the same region covering the following 2 years and including children with and without a heart defect, Goodship *et al* found a much lower annual incidence of 13 per 100 000 live births.[14] In a population-based survey from southern France, covering the 5 year period 1989–93, DuMonchel *et al* found an annual incidence ranging from 4.2 to 22.1 per 100 000 live births and a mean annual incidence of 10.3 per 100 000.[13] During the 5 year period 1992–96, Devriendt *et al* found an annual incidence of 15.3 per 100 000 newborns in Flanders in Belgium.[5] They observed a delay in diagnosis of children without a heart defect and agreed to the highest annual incidence of 22.1 per 10 000 (one per 4500) found by DuMonchel *et al* and the estimated incidence of 25 per 100 000 (1 per 4000) suggested by Wilson *et al*.[12]

The only way to find the true incidence and prevalence of this syndrome is through population-based screening, but this is hardly feasible as it would be too expensive and ethically questionable to screen a large population. Screening of specific risk populations would be more justified. Tobias *et al* proposed useful guidelines to facilitate early diagnosis of 22q11DS.[15] Increased awareness and good experience of the syndrome, diagnostic guidelines and a long follow-up time, are probably the most important factors if more correct incidence and prevalence data are to be obtained. In our study the higher frequency of 22q11DS in Gothenburg is an example of such increased awareness.

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Adoption and Children Act 2002

Just as the Children Act 1989 gave primacy to the welfare of the child so does the Adoption and Children Act 2002 which received royal assent in November 2002 (Frank Roper. National Children's Bureau. Highlight no199. May 2003). The Act revises the legal basis for adoption in England and Wales and some parts apply to Scotland and Northern Ireland. The main provisions are expected to come into force in 2004.

The intentions behind the Act are to safeguard the welfare of the child, to improve adoption practice, to shorten the adoption process, and to promote fairness and efficiency. It provides a ''welfare checklist'' and requires courts and adoption agencies to consider the wishes of the child as far as is possible. Local authorities will have to maintain an adoption service and provide adoption support services. Adoptive families and others involved will have a right to ask for an assessment of needs for support services and adoption support agencies will be required to register under the Care Standards Act 2000. The appropriate Minister will be able to set up an independent mechanism to review decisions such as refusal to approve a person as an adopter and unmarried couples, same sex couples, and single people will be able to apply to adopt. Step-parents will also have this right and may be granted parental responsibility. The Act also provides for improved access for courts and the Registrar General to agency records, for improvements in procedures for adoption of children from other countries, and for restriction of adoptions other than through adoption agencies. Courts will have to draw up timetables to ensure that adoption cases are resolved as quickly as possible. The Secretary of State will be able to set up an Adoption and Children Act Register to facilitate matching of prospective adopters and children waiting to be adopted. Unmarried fathers will acquire parental responsibility when they register the birth together with the mother.

Other recent initiatives have included the setting up of an Adoption Register for England and Wales, which includes details of all children awaiting adoption and all approved adopters (www.adoptionregister.net), and the establishment of an Adoption and Permanence Task force (www.doh.gov.uk/adoption/improvingpractice/index.htm).

Government targets for 2004–05 are to increase the number of looked-after children who are adopted by 40%, and preferably by 50%, compared with 1999–2000 and to increase the proportion of looked-after children who are placed for adoption within 12 months of the decision that the child should be adopted to 95%.