

LETTERS TO THE EDITOR

Prevalence of 22q11 microdeletion

Since its first description in DiGeorge syndrome, microdeletion of chromosome 22 within the q11 region has been reported in association with various clinical pictures. The true prevalence of this submicroscopic rearrangement is unknown. In 1994, Wilson *et al*¹ reported a minimum prevalence of 1/4000 live births. Their estimation was based on the fact that chromosome 22q11 deletions were the cause of at least 5% of congenital heart defects.

The present data were extracted from the Birth Defects Registry of the Bouches-du-Rhône area in southern France. Since 1984, this Registry has covered all births to mothers resident in the department. The registration is based on voluntary notification from the maternity units. Controls are found by active case searching in the departments of paediatrics and genetics and laboratories of pathology and cytogenetics. All registered cases are reviewed by a geneticist. The total number of births is extracted from the vital statistics given by the National Institute of Statistics. In the present study, the cases recorded were those born from January 1989 to December 1993. During this five year period, the registry monitored 116 452 births and identified 12 cases of chromosome 22q11 deletions, giving a prevalence of 1/9700 livebirths. In one case, a visible microdeletion was identified on R banded chromosomes. In another one, born in 1992, the microdeletion was shown by dosage Southern blotting. In the 10 others, the diagnosis was made by FISH analysis. This prevalence varied from 1/4500 in 1993 (five cases out of 22 624 births) to 1/23 975 in 1989 (one case out of 23 975 births). Table 1 shows the annual distribution

of cases and the exact 95% confidence intervals (Poisson distribution) for the total cases.² We have used a chi-square for linear trend to compare the number of annual cases. The observed differences are not statistically significant and variations could be the result of chance. However, since FISH analyses have been available in our centre since 1993, the real prevalence is probably closer to the 1993 one. The children born before 1993 were diagnosed much later (mean age at diagnosis 34 months) when compared with those born in the last year (mean 2 months). There is a significant difference (p<0.02).

Of course, this prevalence is probably underestimated and only accounts for symptomatic cases. Most of the children included in these data exhibited prominent features of the CATCH 22 phenotype. Table 2 summarises the clinical features of the 12 patients. Of interest is the presence of a heart defect in 10 out of the 12 patients. This high percentage of CHD was confirmed in a larger series including children born in other French departments or before or after the study period (56/74). It is obvious that now most paediatricians, paediatric cardiologists, and geneticists are aware of the high percentage of 22q11 deletion in typical cases of DGS, VCFS, and more generally in any child born with a CHD and a typical face. However, an increasing number of atypical cases without any cardiac involvement have been reported recently.^{3,4} A significant number of familial cases have been described. Most of the carrier parents are almost asymptomatic or exhibit late onset disorders.⁵ Therefore, it seems likely that most of these mild cases are not diagnosed during infancy or childhood. Thus, we estimate that this prevalence of 1/9700 is significant for 22q11 deletion associated with a typical clinical picture. The true prevalence accounting for milder or atypical cases is probably higher. Systematic screening for 22q11 deletion in all newborns would be the best way to determine the exact frequency of this rearrangement. However, in the light of our partial knowledge about the long term prognosis in this condition, such screening would have important ethical implications.

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Should the 3C (craniocerebellocardiac) syndrome be included in the spectrum of velocardiofacial syndrome and DiGeorge sequence?

We read with interest the report by Lynch *et al*¹ of a 34 year old man presenting with cerebellar atrophy, neonatal hypocalcaemia, an atrial septal defect, a corrected cleft palate, and a dysmorphic face characteristic of velocardiofacial syndrome. Molecular cytogenetic studies showed a deletion of 22q11.2. The authors proposed that this man was the first reported patient with neurodegeneration, a 22q11.2 deletion, and velocardiofacial syndrome. They stated that neurological abnormalities, apart from developmental delay (present in this patient) and hypotonia, have not been commonly reported in association with either velocardiofacial syndrome or DiGeorge sequence. However, structural brain abnormalities such as a small cerebellar vermis, a small posterior fossa, and cysts have been detected by magnetic resonance imaging. Interestingly, an MRI of the head from this patient showed vermian and hemispheric cerebellar atrophy, basal ganglia calcification, a small brain stem without focal loss of volume, and white matter lucencies.

In reading their report we were impressed by the similarity between this patient and the eight published cases of patients with the 3C (craniocerebellocardiac) syndrome.² The 3C syndrome is rare and is characterised by hindbrain malformations, including cerebellar vermis hypoplasia, congenital heart defects, including tetralogy of Fallot, atrioventricular septal defect, and atrioventricular canal, along with several additional anomalies (cleft palate, micrognathia, ear and nose malformations, prominent forehead, and hypertelorism).²⁻⁷ Phenotypic variability exists for the 3C syndrome, and possibly the frequency of this syndrome is underestimated. In addition, the most recently reported patient with this syndrome² was originally suspected to have CHARGE association, a phenotypically similar condi-

Table 1 Annual distribution of prevalences of 22q11 microdeletions

	Cases		Prevalence		Total births
	No	95% CI	Per 100 000	95% CI	
89	1	0-5.6	4.2	0.1-23.2	23 975
90	2	0.2-7.2	8.6	1.0-30.9	23 341
91	3	0.6-8.8	12.7	2.6-37.2	23 559
92	1	0-5.6	4.4	0.1-24.3	22 953
93	5	1.6-11.7	22.1	7.2-51.6	22 624
Total	12	6.2-26	10.3	5.3-22.3	116 452

Table 2 Phenotype of the 12 deleted cases

	CHD	Hypocalcaemia	Hypoplasia of the thymus	Dysmorphism	Vélopharyngeal insufficiency/cleft palate
1	-	-	?	+	+
2	+	+	+	+	+
3	+	?	+	?	?
4	+	-	+	+	?
5	+	?	?	+	-
6	+	?	+	+	?
7	+	-	?	+	+
8	+	-	+	+	?
9	+	+	+	+	+
10	*	+	+	+	?
11	+	-	?	-	-
12	+	+	+	+	-

*Aberrant subclavian artery.