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## Frequency of inherited deletions of 22q11

We read with interest the report by Ryan *et al* on the spectrum of clinical features associated with 22q11 deletions, in which they aim "to increase the clinical information on which management and counselling can be based". They report a frequency of inherited deletions of 28% in their study. We have looked at the frequency of familial cases of 22q11 deletions in patients from all of Wales, none of whom was included in the European collaborative study, and have found a much lower frequency.

Since starting investigations for 22q11 deletions, it has been our policy to test both parents of all deletion cases irrespective of the reason for referral. Fifty cases with a deletion have now been detected, and these have been referred by clinicians from a range of disciplines, including medical genetics, paediatrics, cardiology, psychiatry, and nephrology. In 41 cases both parents were studied and in two cases only maternal blood was available. Most of the families who have not been studied are recent referrals. The deletion was inherited in only four out of the 41 cases, giving a frequency of approximately 10%. The four cases of parental transmission were all maternal, and all parents with the microdeletion showed facial features associated with 22q11 deletion. One patient had a corrected double outlet right ventricle, an-

other had a ventral septal defect which closed spontaneously in childhood.

The frequency of familial transmission in our group of patients of 10% is nearer the figure of 8% reported by Driscoll *et al* in the only other large study than the 28% reported by the European collaborative study.<sup>1</sup> It is difficult to explain the large discrepancy between these figures; however, we would stress that where possible we follow up all cases irrespective of parental phenotypes, and although the collaborative study is a far larger one, the authors recognise that patient selection for testing because of suggestive clinical features may have inflated their frequency. If an assumption is made that no further deletions were present in the parents not tested by Ryan *et al*,<sup>1</sup> then the minimal estimate of inherited deletion from their study is 81/558 or 15%, a value closer to our frequency.

An accurate figure for parental transmission of 22q11 microdeletions is important when counselling parents of a child recently diagnosed, helping to allay anxiety, guilt, and also fears of recurrence. A risk of 28% coming as it does from such a comprehensive and well respected study is the one most likely to be used for counselling purposes; however, in view of our findings and those of Driscoll *et al*,<sup>2</sup> we feel this may be too high and that more clinical data on non-selected patients are needed before a true frequency of familial transmission is known.

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## The annual incidence of DiGeorge/velocardiofacial syndrome

The majority of cases with either DiGeorge syndrome or velocardiofacial syndrome are caused by a submicroscopic deletion in chromosome 22q11 (del22q11).<sup>1,3</sup> Since the advent of a routine diagnostic test for this microdeletion, the number of patients diagnosed has increased dramatically, including many patients with either mild features or non-specific presenting symptoms. The del22q11 occurs much more frequently than previously thought, but precise incidence figures are not known. Wilson *et al*<sup>3</sup> found a del22q11 in approximately 5% of children with a congenital heart defect (CHD), and therefore an estimated incidence of at least 1/4000 live births. A more direct way is to

determine the annual incidence of cases with a del22q11, in a well defined region, with a known number of births. In a region in southern France, with an annual birth rate of approximately 23 000, Du Montcel *et al*<sup>4</sup> found 1/9700 as a minimum incidence of the del22q11 associated with the typical clinical picture.

In the Flemish region of Belgium, all genetic tests are performed in four genetic centres. The number of births was extracted from the annual reports of the Study Centre for Perinatal Epidemiology (Studiecentrum voor perinatale epidemiologie, SPE), which registers in Flanders over 99% of all live and stillborn children with a birth weight of over 500 g. Routine genetic testing for a del22q11 by means of FISH became available during the years 1992-1993. A total of 151 Flemish cases have been diagnosed since and, of these, 94 were born before 1992, six in 1997, and 51 in the five year period between January 1992 and December 1996. The annual birth rate in Flanders ranges from 68 613 in 1992 to 63 550 in 1996, with a total of 326 166 births during the five year study period of 1992-1996. Therefore, the estimated annual incidence of a del22q11 in 1992-1996 is 15.3/100 000 newborns (95% confidence intervals 13.3-17.2), or 1/6395 (table 1).

However, as in the study of Du Montcel *et al*,<sup>4</sup> it is evident that this represents a minimum estimate, since many cases with mild features remain undiagnosed. In the total group of patients with a del22q11, 81 of the 151 patients (54%) have a symptomatic congenital heart defect (CHD), compared to 37 of the 51 patients (72.5%) born during the last five years. This confirms the clinical experience that the diagnosis is delayed in patients without a heart defect. In our series of patients from 1992-1996, mean age at diagnosis of those with a heart defect was 8.3 months (range: day of birth-39 months). During the last three years, the majority of infants with a conotruncal heart defect and a del22q11 were diagnosed during the first weeks of life. In contrast, patients without a heart defect were diagnosed at a mean age of 25.9 months (SD 17 months), when developmental delay or speech delay becomes evident. It can be estimated, therefore, that a large proportion of the children born during the last five years with a del22q11 but without a heart defect remain to be diagnosed.

Taken together, our observation is in good agreement with a maximal annual incidence of 1/4500 found in children born in 1993 in the study of Du Montcel *et al*<sup>4</sup> and with an estimated incidence of 1/4000 as suggested by Wilson *et al*.<sup>3</sup> We conclude that a del22q11 is among the most frequent causes of genetic syndromes.

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Table 1 The minimum annual incidence of del22q11 at birth in Flanders

Year	No of cases	Annual incidence per 100 000	95% CI	Total births
1992	11	16	6.5-25.4	68 613
1993	10	15	5.2-24.7	66 780
1994	11	17.1	7-27.3	63 851
1995	11	17.2	7-27.4	63 372
1996	8	12.6	2.3-22.7	63 550
Total	51	15.3	13.3-17.2	326 166