

LETTERS TO THE EDITOR

Craniosynostosis and chromosome 22q11 deletion

In a recent article, Ryan *et al*¹ reported some potentially very useful data for genetic counselling in chromosome 22q11 microdeletion. This was a questionnaire based, multicentre study, combining data from the various centres to try to minimise ascertainment bias. However, the authors admitted that this approach may have contributed some bias, because of the difficulty in obtaining consistency of clinical description between centres, and the associated variability in completeness of data with regard to the investigation and reporting of certain clinical features in different body systems. In discussing the occurrence of craniosynostosis with this deletion, we believe they intended to quote the small series of patients which two of us reported in 1995,² although they have in fact referenced a different article written about cranial hemihyperplasia.³ In our series of seven patients from three families, one infant had bilateral coronal and sagittal craniosynostosis and broad thumbs, in addition to an interrupted aortic arch, thymic aplasia, hypocalcaemia, a bifid uvula, and a chromosome 22q11 deletion. His mother (also deleted) had brachycephaly and broad thumbs, but other adult family members without 22q11 deletion also had unusually broad thumbs or brachycephaly or both. We therefore subsequently investigated this family for FGFR3 mutation and have recently reported in this journal that the affected infant had a de novo pro250arg mutation in FGFR3 (case 6 in Reardon *et al*⁴). The brachycephaly and broad thumbs seen variably in the other family members were neither associated with the FGFR3 mutation nor with chromosome 22q11 deletion and presumably represent private familial traits which were identified because of the findings in the proband.

Thus, we believe that the craniosynostosis in our patient did not result from chromosome 22q11 deletion, but rather from a de novo FGFR3 mutation.

To try to define further the relationship between chromosome 22q11 microdeletion and craniosynostosis, it is worth considering the underlying frequency of craniosynostosis in the general population. In one epidemiological study,⁵ the birth incidence of craniosynostosis was found to lie between about 1/3225 and 1/735 livebirths, depending on the rigour with which the diagnosis was defined. Taking the upper end of the 95% confidence interval for the loose definition of craniosynostosis (infants ascertained because a cranial x ray had been ordered to investigate suspected craniosynostosis), the higher estimate of incidence in this study was 1/518. This compares with 5/548 patients in the chromosome 22q11 microdeletion study¹ reported to have craniosynostosis, although no details were given about the diagnostic criteria or severity. We believe that the relationship between craniosynostosis and chromosome 22q11 microdeletion requires

further evaluation. It would be useful to document the clinical basis of the diagnosis of craniosynostosis in the chromosome 22q11 patients and, given the relatively high frequency of the pro250arg mutation in FGFR3 in our phenotypically diverse series of patients (5.5%), some of whom had unilateral non-syndromic craniosynostosis,⁴ perhaps investigate those patients with confirmed craniosynostosis for mutations in other genes (such as FGFR3), before attributing too many features to one microdeletion syndrome.

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Spectrum of clinical features associated with interstitial chromosome 22q11 deletions

We read with great interest the paper "Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study".¹ Despite juvenile rheumatoid arthritis (JRA) being reported in many patients with 22q11 deletion,²⁻⁴ this disease was not considered as part of this clinical spectrum.

We have recently diagnosed an additional patient with this association. She is a 4 year old girl, who was admitted to hospital in the first month of life because of velopharyngeal insufficiency and left multicystic kidney. At the age of 9 months she had hypocalcaemic seizures and at the age of 3½ years she developed polyarticular JRA, which responded poorly to treatment with non-steroidal anti-inflammatory drugs; she was therefore treated with steroids and methotrexate.

Immunological study showed IgA deficiency, high IgG, and normal IgM; T cell subset and lymphocytic response to mitogens were normal. FISH study with D22S75 (ONCOR) DNA probe showed deletion of chromosome 22 in the region 22q11.2.

The number of case reports published suggests that this deletion and polyarthropathy do not occur together by chance. Three of 80 patients enrolled in the chromosome 22q11 deletion syndrome cohort at The Children's Hospital of Philadelphia have developed JRA polyarthritides. Thus, the prevalence of polyar-

thritis in this cohort is 50 times that seen in the general population and 150 times that seen specifically for polyarticular JRA in the general population. This calculation is probably an underestimate because of the young age of patients in this series.⁴

It is possible that there is an immunoregulatory gene in the region 22q11 that, when altered, may predispose to development of autoimmune diseases. In fact, apart from JRA, other autoimmune conditions have been observed in 22q11 deletion syndrome (Graves disease, autoimmune haemolytic anaemia, and autoimmune thrombocytopenia).¹

Therefore, we propose enlarging the spectrum of 22q11 deletion syndrome to include polyarticular JRA and to follow with care all patients with this deletion for the possibility of developing an autoimmune disease.

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Clinical features of chromosome 22q11 deletion

Ryan *et al* (*J Med Genet* 1997;34:798-804) provide a great deal of valuable clinical information concerning the spectrum of chromosome 22q11 deletions. However, there is one important category of data whose absence raises concerns about the generalisability of the findings. Specifically, there is no information as to the specific ascertainment of the patients in the various centres. It would be important to know, for example, how many had been initially ascertained because of systematic studies in a cardiac clinic or a speech/cleft palate clinic, etc. I hope that the authors will be able to provide these data.

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