Craniosynostosis and chromosome 22q11 deletion

In a recent article, Ryan et al. reported some potentially very useful data for genetic counselling in chromosome 22q11 microdeletion. This was a questionnaire based, multicentre study, also having derived data from craniofacial centres in order 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, although they have in fact referenced a different article written about cranial hemihyperplasia. 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, hypocalcemia, 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 had brachycephaly or both. We therefore subsequently investigated this family for FGFR mutation and have reported in this journal that the affected infant had a de novo pro250Arg mutation in FGFR3 (case 6 in Reardon et al.). The brachycephaly and broad thumbs seen variably in the other family members were not 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, 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 compared with 5/487 patients in the chromosome 22q11 microdeletion study 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 further 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, perhaps involving those patients with confirmed craniosynostosis for mutations in other genes (such as FGFR3), before attributing too many features to one microdeletion syndrome.

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" by Ryan et al. (1997). In this paper, we describe 22q11 deletions in a European collaborative study. 1


Clinical features of chromosome 22q11 deletion

Ryan et al. (1997) have provided 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 therefore be important to know, for example, how many had been initially ascertainment because of systemic studies in a cardiac clinic or a speech/ cleft palate clinic, etc. I hope that the authors will be able to provide these data.