Evaluation of the distal 22q11 deletion syndrome. A highly variable phenotype.

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Introduction

Chromosome 22 is rich in segmental duplications that mediate recurrent genomic rearrangements, notably the 22q11 deletion associated with velocardiofacial syndrome (diGeorge syndrome). Over the last few years, a number of patients with recurrent atypical distal deletions have been described. These genomic aberrations are located distally to the common recurrent ~3Mb region implicated in the velocardiofacial syndrome. However, the observed phenotypes within the atypical distal deletion regions do not seem to be consistent. The copy number changes have been observed in phenotypically normal individuals. The inconsistencies in clinical presentation and the presence of the copy number change in unaffected family members could be due to factors such as incomplete penetrance, variable expressivity or a failure to recognize more subtle manifestations of a phenotype. Therefore, this region poses a challenge for diagnostic interpretation. Due to the diversity of published clinical features for these recurrent rearrangements and reports of asymptomatic parental inheritance, we present a retrospective evaluation of a case series of patients with 22q11 distal deletion syndrome with additional prenatal cases to identify the common clinical features and to discuss the difficulties of genetic counseling the 22q11 distal deletion syndrome.

Discussion

Our patients were all carriers of atypical distal deletions of the 22q11 region, of comparable and overlapping sizes. These deletions were not associated with a clear mental retardation, but presented more subtle neurodevelopmental problems such as attention-deficit hyperactivity syndrome, behavioural and learning difficulties. In some cases, no signs of neurodevelopmental problems were present. Microcephaly, suggested to be associated with haploinsufficiency of BCR, was only present in case B and absent in her carrier mother. The atypical distal deletion may be associated with congenital cardiac anomalies (case D) even while the TBX1 gene is outside the deleted region.

In conclusion, patients with a atypical distal 22q11 deletion syndrome may present neurodevelopmental problems. Asymptomatic parental inheritance presents difficulties in the genetic counseling of this chromosomal condition.

Facial appearance of patients with distal 22q11.2 deletions

Case A
Case B
Case C
Case D

Array profile of case E

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