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

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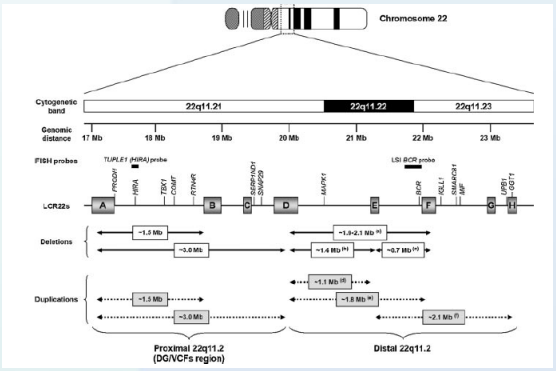
Introduction

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.



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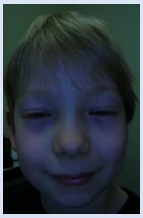
Case A: This 8 year old boy was referred for learning problems and a borderline IG of 79. His four sibs and both parents had been diagnosed with learning problems. Array-CGH analysis showed a deletion of 642 kb at 22q11.22-q11.23 (23,012,013-23,654,222 – hg19). Familial analysis is ongoing.
Case B. A two year old girl referred for microcephaly (OFC -3 DS) with a normal psychomotor development. The normal father had an OFC of -2.5SD and the carrier mother had a normal psychomotor development with an OFC of -1.5DS. Array-CGH analysis revealed a 22q11.22-q11.23 maternal deletion of 419 kb (23,228,870-23,648,103 – hg19).
Case C. A 7 year old boy presenting with dysphasia, borderline macrocephaly and an otherwise normal development. The development of both parents had been normal. Array-CGH analysis showed a paternal deletion of 640 kb at 22q11.22-q11.23 (23,002,709-23,643,223 – hg19).
Case D. This 7 year old boy diagnosed with a congenital cardiac defect developed behavioural problems necessitating medical treatment. One of his five sibs presented with a developmental delay. His mother and one of her brothers had been diagnosed with ADHD. Array-CGH analysis showed a maternal deletion of 640 kb at 22q11.22-q11.23 (23,002,709-23,643,223 – hg19). Further familial analysis is ongoing.
Case E. A prenatal array-CGH analysis (indication: previous child with trisomy 21) showed a paternal deletion of 631 kb at 22q11.22-q11.23 (23,012,013-23,643,223– hg19). Utrasound investigations did not reveal any congenital anomalies; the father was phenotypically normal. One sister presented learning problems; she was not tested for the presence of the deletion.

Facial appearance of patients with distal 22q11.2 deletions

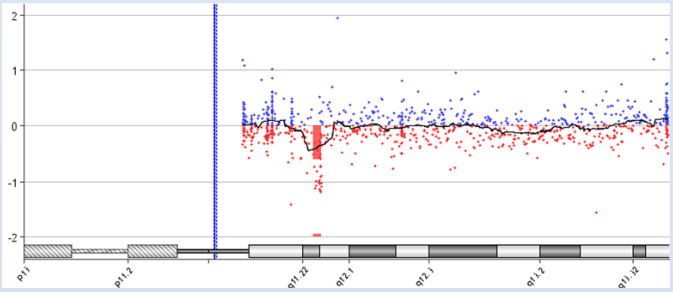

Case A


Case B


Case C


Case D

Array profile of case E



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.

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