Haploinsufficiency of TBX1 is not responsible for facial dysmoprhology in patients with 22q11.2 deletion syndrome

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Aim: We report two cases with an atypical deletion located in the 22q11.2 region, to elucidate the role of *TBX1* haploinsufficiency in the facial dysmorphology in 22q11DS.

Method: In this prospective study, a family presented with velopharyngeal insufficiency, inherited in an autosomal dominant way. A small atypical 22q11.2 deletion was detected by microarray-CGH. Sanger Sequencing indicated a deletion of the first five exons of *TBX1*. *In silico* analysis using 'SIFT InDel' indicated that the partly deleted *TBX1* is no longer functional. Phenotypically, they did not share any of the other characteristics of the 22q11.2DS and facial features were unremarkable.
Secondly, a boy aged 14 was referred to the Department for Human Genetics for refractory epilepsy and mild intellectual disability. Microarray-CGH and Sanger sequencing showed another atypical 22q11.2 deletion including *CRKL*, but not containing the *TBX1* gene. The boy had facial features reminiscent of the 22q11DS.
All study subjects underwent 3D morphometric facial analysis, with comparison to faces of patients with a complete 3Mb 22q11.2 deletion.

Results: Objective 3D analysis confirmed that the affected family members with the *TBX1* deletion did not have the characteristic facial features of 22Q11DS, whereas the 14 year-old male with an atypical deletion including *CRKL* did.

Conclusion: Based on these observations, we can conclude that the craniofacial phenotype in 22q11DS is not solely explained by *TBX1* haploinsufficiency. *CRKL* is alternative candidate gene for this phenotype.