Oral-facial-digital syndrome type VI: is C5orf42 really the major gene?

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Abstract Oral-facial-digital type VI syndrome (OFDVI) is a rare phenotype of Joubert syndrome (JS). Recently, C5orf42 was suggested as the major OFDVI gene, being mutated in 9 of 11 families (82 %). We sequenced C5orf42 in 313 JS probands and identified mutations in 28 (8.9 %), most with a phenotype of pure JS. Only 2 out of 17 OFDVI patients (11.7 %) were mutated. A comparison of mutated vs. non-mutated OFDVI patients showed that preaxial and mesoaxial polydactyly, hypothalamic hamartoma and other congenital defects may predict C5orf42 mutations, while tongue hamartomas are more common in negative patients.

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Fig. 1 Schematic representation of C5orf42 protein structure and distribution of all reported mutations. The two predicted transmembrane domains (TM, amino acids 592–612 and 631–651) and the two predicted coiled coil domains (CCD, amino acids 2,457–2,487 and 2,691–2,724) are shown. Mutations found in patients with pure Jou-
and eight fetuses), suggesting that \textit{C5orf42} could represent the major causative gene for OFDVI (Lopez et al. 2014).

As part of a ciliopathy research project, we sequenced \textit{C5orf42} in 313 JS probands, and identified pathogenic mutations in 28 (8.9 %) (Fig. 1). Only two out of 17 OFDVI probands in our cohort (11.7 %) carried \textit{C5orf42} mutations, while one was mutated in \textit{OFD1}. No mutations were detected in the remaining 14 (82.3 %) OFDVI patients in all tested genes (see Supplementary material online for methods, characterization of mutations and clinical features of mutated OFDVI patients).

To explain the striking discrepancy between our findings and those reported by Lopez et al., we compared clinical features in \textit{C5orf42} mutated (\(n = 14\)) vs. non-mutated (\(n = 17\)) OFDVI patients (Table 1). Preaxial and mesoaxial polydactyly, hypothalamic hamartomas and other congenital abnormalities were significantly more frequent in the mutated group, while tongue hamartomas or multiple lingual frenula occurred more commonly in non-mutated patients.

Despite the limited number of patients, these findings suggest that \textit{C5orf42} is the major causative gene, and another with less severe presentation and prevalent oral-facial involvement, which genetic causes still remain to be identified.

Twenty-seven \textit{C5orf42} mutated patients (from 23 families) in our study had pure JS (with retinopathy in one),

| Mutated | Non-mutated | \(p\) |
|---------|-------------|-------|
| Any oral-facial feature | 7/12 (58 %) | 17/17 (100 %) | 0.006 |
| Tongue hamartomas/multiple lingual frenula\(^a\) | 6/12 (50 %) | 17/17 (100 %) | 0.002 |
| Other oral-facial features\(^b\) | 4/12 (33 %) | 5/17 (29 %) | n.s. |
| Any polydactyly | 14/14 (100 %) | 13/17 (76 %) | n.s. |
| Mesoaxial polydactyly\(^d\) | 7/14 (50 %) | 1/17 (6 %) | 0.01 |
| Preaxial polydactyly | 14/14 (100 %) | 5/17 (29 %) | 0.0001 |
| Postaxial polydactyly | 9/14 (64 %) | 10/17 (59 %) | n.s. |
| Any CNS abnormality besides MTS | 8/14 (57 %) | 4/17 (24 %) | n.s. |
| Hypothalamic hamartoma\(^a\) | 6/14 (43 %) | 1/17 (6 %) | 0.03 |
| Occipital encephalocele | 2/14 (14 %) | 1/17 (6 %) | n.s. |
| Other CNS abnormalities\(^c\) | 4/14 (29 %) | 2/17 (12 %) | n.s. |
| Retinal/renal/hepatic involvement | 0/14 | 4/17 (24 %) | n.s. |
| Retinopathy (only living patients) | 0/2 | 3/17 (18 %) | n.s. |
| Nephronophthisis (only living patients) | 0/2 | 2/17 (12 %) | n.s. |
| Cystic dysplastic kidneys | 0/14 | 0/17 | n.s. |
| Congenital liver fibrosis | 0/14 | 0/17 | n.s. |
| Other congenital abnormalities outside the CNS\(^d\) | 8/14 (57 %) | 1/17 (6 %) | 0.004 |

\(\text{C5orf42}\) mutated patients include the 12 patients from 9 families reported by Lopez et al. (2014) and the two patients from the present paper; \(\text{C5orf42}\) non-mutated patients (\(n = 17\)) are all from the present cohort, and include one patient mutated in \textit{OFD1} (see text) and 16 patients from 14 families. Statistical comparisons were made by Fisher’s exact test.

\(\text{a}\) Sufficient for diagnosis of OFDVI in association with the MTS
\(\text{b}\) Cleft lip and/or palate, tooth abnormalities, lobulated tongue, short frenula
\(\text{c}\) Porencephaly, nodular heterotopia, polymicrogyria, corpus callosum abnormalities, hydrocephalus, arhinencephaly
\(\text{d}\) Abnormal ribs or long bones, cubitus valgus, heart or aortic defects, uterus septation, common mesentery, coloboma, microphthalmia, Hirschsprung disease, scoliosis
\(\text{e}\) Includes two siblings

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while clinical data were unavailable in three. Considering all reported C5orf42 mutated patients (n = 58), over two-thirds showed a pure JS phenotype while only 24% has OFDVI (Supplementary Table 1). Kidney or liver involvement was never noted, while polydactyly (mainly preaxial) was present in nearly half of mutated patients regardless of the phenotype. These findings delineate a specific C5orf42-related phenotype, and suggest a major role for this gene in limb development.

Overall, the identification of mutations in 28 of 313 JS probands makes C5orf42 a major contributor to the pathogenesis of this ciliopathy. How mutations in the same gene may cause pure JS or a much more severe oral-facial-digital syndrome remains an open question. Genotype–phenotype correlations seem to fail, since truncating and missense mutations affecting the entire length of the protein are detected in patients with either pure or OFDVI presentations (Fig. 1). As suggested for other ciliopathies, it is conceivable that additional, yet unidentified variants in distinct genes may act as genetic modifiers able to influence the penetrance and expression of oral-facial and digital features in patients bearing C5orf42 mutations.

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