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Exome Sequencing Identifies a Homozygous *C5orf42* Variant in a Turkish Kindred With Oral-Facial-Digital Syndrome Type VI

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Abstract

Oral-facial-digital syndrome type VI (OFDVI) is a rare ciliopathy in the spectrum of Joubert syndrome (JS) and distinguished from other oral-facial-digital syndromes by metacarpal abnormalities with central polydactyly and by a molar tooth sign on cranial MRI. Additional characteristic features include short stature, micrognathia, posteriorly rotated low-set ears, hypertelorism, epicanthal folds, broad nasal tip, tongue hamartoma, upper lip notch, intraoral frenula, cleft lip/palate, and renal anomalies. Recently, novel mutations in *C5orf42* were identified in 9 out of 11 OFDVI families. In a subsequent study *C5orf42* was found to be mutated in only 2 out of 17 OFDVI probands while 28 patients with a pure JS phenotype also had pathogenic mutations of *C5orf42*.

We report on two affected cousins diagnosed with OFDVI who were born from first degree cousin marriages. Whole exome sequencing (WES) identified a homozygous predicted damaging missense mutation (c.4034A >G; p.Gln1345Arg) in the *C5orf42* gene. Our data contribute to the evidence that *C5orf42* is one of the causative genes for OFDVI.

Keywords

oral-facial-digital syndrome type VI; C5orf42; ciliopathy

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INTRODUCTION

Oral-facial-digital syndrome type VI (OFDVI) (OMIM#277170), or Varadi–Papp syndrome, is a rare disorder in the Joubert syndrome (JS) spectrum and distinguished from the other types of OFD syndromes by metacarpal abnormalities with central polydactyly, molar tooth sign (MTS) on cranial magnetic resonance imaging (MRI), tongue hamartoma, upper lip notch, and intellectual disability [Varadi et al., 1980; Doss et al., 1998; Poretti et al., 2012]. Associated clinical findings include short stature, micrognathia, posteriorly rotated low-set ears, hearing loss, hypertelorism, epicanthal folds, broad nasal tip, intraoral frenula, lingual or sublingual nodules, cleft lip/palate, and renal anomalies. Hypothalamic hamartomas in OFDVI patients have also been described in previous studies [Stephan et al., 1994; Poretti et al., 2012]. A characteristic neuroradiologic feature of OFDVI is the MTS visualized by cranial MRI and this feature links OFDVI and JS in the same spectrum [Gleeson et al., 2004]. In addition to MTS on cranial MRI, one or more of the following findings is/are necessary for the clinical diagnosis of OFDVI: (i) tongue hamartoma and/or additional frenula and/or upper lip notch, (ii) mesoaxial polydactyly of one or more limbs, or (iii) hypothalamic hamartoma [Poretti et al., 2012].

Previously, mutations of *TMEM216* and *OFD1* have been reported in a few OFDVI patients [Coene et al., 2009; Valente et al., 2010; Darmency-Stamboul et al., 2013]. Despite these findings, the exact molecular etiologic basis of OFDVI remained uncertain. Recently, Lopez et al. [2014] described 14 novel mutations in *C5orf42* in 9 out of 11 families meeting OFDVI clinical diagnostic criteria and concluded that *C5orf42* is the major gene responsible for OFDVI. However, in a more recent study Romani et al. [2015] sequenced *C5orf42* in 313 JS patients and pathogenic mutations were identified in 28 probands (8.9%) with a pure JS phenotype while only 2 out of 17 patients (11.7%) with the diagnosis of OFDVI were found to have *C5orf42* mutations. These results suggest that *C5orf42* might not be the major causative gene for all OFDVI subtypes. Additionally, Romani et al. [2015] compared clinical features between their patients and those reported by Lopez et al. [2014]. Their findings suggested that *C5orf42* mutations are responsible for a phenotypic subgroup, specifically distinguished by preaxial and/or mesoaxial polydactyly and other congenital anomalies (e.g., skeletal, cardiac), whereas the non-mutated group is characterized by a less severe presentation with more prominent oral-facial features.

Here we report on whole exome sequencing (WES) results for an extensively characterized family in which affected cousins fulfill criteria for the clinical diagnosis of OFDVI.

CLINICAL REPORT AND GENETIC STUDIES

Patients

An 11-year-old girl was referred to the Center for Genetics Diagnosis at Zeynep Kamil Women's and Children's Diseases Training and Research Hospital because of intellectual disability and multiple congenital anomalies. She was the second daughter of consanguineous parents and her mother had a history of one spontaneous abortion. On physical examination her weight was 41 kg (50th–75th centile), her length was 152 cm (75th–90th centile), and her occipito-frontal diameter was 55 cm (75th–90th centile). Her

distinctive facial features included broad forehead, hypertelorism, epicanthal folds, strabismus, short nose, and long philtrum. Examination of extremities revealed mesoaxial polydactyly of the left hand (operated) and bilateral pre-axial polydactyly of the feet (operated) (Fig. 1A,B). Ataxic gait, mild intellectual disability (IQ: ~60), and history of seizures associated with fever (generalized tonic–clonic) were noted on neurologic examination. Genitourinary examination revealed that she had hypoplasia of external genitalia and a surgically repaired inguinal hernia. There were no significant findings on the examination of the other organ systems. Cranial MRI study showed molar tooth sign, mild cortical atrophy, and thin corpus callosum (Fig. 1C,D,E). A clinical diagnosis of OFDVI was rendered.

After a careful search within the kindred a 51-year-old male cousin of the index patient's father was also found to meet some of the diagnostic criteria of OFDVI. On clinical examination he had mild intellectual disability (IQ: ~60) frontal bossing, hypertelorism, strabismus, mesoaxial scar on left hand, and pre-axial scars on both feet due to surgical repair of polydactyly. Cranial MRI study could not be performed and the patient was presumptively diagnosed with OFDVI.

Whole-Exome Sequencing of the Index Case

After obtaining informed consent, we applied WES to the index case at Baylor College of Medicine Human Genome Sequencing Center (BCM-HGSC) through the Baylor Hopkins Center for Mendelian Genomics. A genomic DNA sample was isolated from a blood sample obtained from the patient and processed according to protocols previously described [Lupski et al., 2013]. Briefly, DNA sample was prepared into Illumina paired-end libraries and underwent whole exome capture using BCM-HGSC core design (52 Mb, Roche NimbleGen, Inc.), followed by sequencing on the Illumina HiSeq 2000 platform (Illumina, Inc.) with an ~150× depth of coverage. Data produced were aligned and mapped to the human genome reference sequence (hg19) using the Mercury pipeline. Variants were called using the ATLAS (an integrative variant analysis pipeline optimized for variant discovery) variant calling method and SAMtools (The Sequence Alignment/Map) and annotated using the in-house-developed "Cassandra" annotation pipeline that uses ANNOVAR [Li et al., 2009; Wang et al., 2010; Bainbridge et al., 2011].

PCR Amplification and Sanger Sequencing

To confirm the identified WES detected variant, exon 23 of *C5orf42* was amplified from genomic DNA using conventional end-point PCR and analyzed by Sanger sequencing. We successfully amplified the target exons in all available family members and also in the affected cousin. PCR amplification products of all available samples were sequenced by using the following primers: Forward: 5′-TCCAAAGAAAGGCAACATCA-3′ and reverse: 5′-GGACCTT-GAAGTGGAGTTTGA-3′.

RESULTS

Targeted exome capture identified a homozygous NM_023073: c.4034A >G; p.Gln1345Arg missense variant in *C5orf42* in the index patient (BAB4030). This identified novel variant is

predicted to be deleterious by PolyPhen-2, LRT, and Mutation Taster computational algorithms and was not reported in the 1000 Genomes Project (http://www.1000genomes.org), NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS/), dbSNP, Atherosclerosis Risk in Communities Study (ARIC) dataset which contains exome data from ~4,000 individuals (https://www2.cscc.unc.edu/aric/) our internal exome database (>3,000 exomes) including more than 600 persons of Turkish ancestry (MGL; http://www.bcm.edu/geneticlabs/).

DNA samples from the parents of the index case (BAB4031 and BAB4032) and the unaffected sister (BAB4033) were analyzed by Sanger sequencing. Consistent with Mendelian expectations the parents were found to be heterozygous carriers and the unaffected sister found to be wild type (Fig. 2A). Additionally, the affected cousin (BAB6503) was also analyzed by Sanger sequencing and the same homozygous variant was observed (Fig. 2A).

Because of the consanguinity between parents we examined the AOH (Absence of Heterozygosity) regions in the index patient. Haplotype block analysis based on single nucleotide polymorphisms data culled from exome sequencing (i.e., B-allele frequency) showed that this identified novel variant was found in a ~29.05 Mb block of AOH as shown in Figure 2B.

DISCUSSION

In this study, we identified a homozygous *C5orf42* variant in a Turkish family with a clinical diagnosis of OFDVI; an affected cousin was also found to harbor this homozygous variant. The index case met OFDVI diagnostic criteria including MTS and mesoaxial polydactyly of the left hand. Although cranial MRI study could not be performed in the affected cousin to assess for MTS, his other clinical findings, which he shared with the index patient, suggested an OFDVI clinical diagnosis and the homozygous variant identified by Sanger sequencing confirmed this diagnosis. Because OFDVI is considered within the spectrum of JS and ciliopathy disorders, we examined WES data for all previously described JS and ciliopathy genes (including *TMEM216* and *OFD1*) to find any evidence that may allow us to consider a potential oligogenic model such as triallelic inheritance [Katsanis et al., 2001] or other mutational burden model, but no other potential disease causing or modifying variant was found. Additionally, we screened WES data for copy number variant (CNV) alleles and no pathogenic CNV was detected including the absence of evidence for the *NPHP1* deletion which was previously associated with ciliopathies [Lindstrand et al., 2014] (Fig. 2C).

C5orf42 (chromosome 5 open reading frame 42) contains 52 exons and encodes a 3,198-amino acid protein; very little knowledge about its function is available. The C5orf42 protein (Synonym: FLJ13231) encoded by this gene has putative coiled-coil domains and may be a transmembrane protein [Srour et al., 2012]. Interestingly, most of the *C5orf42* variants (59 out of 63: ~94%) identified in JS and OFDVI patients in previous studies (including the homozygous variant identified in our study) were found to occur outside of these predicted coiled-coil and trans-membrane domains [Romani et al., 2015]. Analysis of

the proteomics databases reveal that *C5orf42* is widely expressed in a variety of tissues, including brain and close orthologs are detected in other vertebrates [Srour et al., 2012]. The identification of *C5orf42* mutations in JS as well as in OFDVI suggests that the C5orf42 protein is involved in cilia function and perturbed signaling through receptors whose optimal signal mediated function requires cilia may be the underlying cause of the facial dysmorphology and polydactyly as proposed for Bardet–Biedl syndrome (OMIM#209900) [Tobin et al., 2008; Davis and Katsanis, 2012].

The common clinical findings of our patients were distinct facial features, intellectual disability, mesoaxial polydactyly of the left hand, and bilateral pre-axial polydactyly of the feet. We compared the clinical features of our patients with those reported in most recent studies (Table I) and the findings support the contention of a specific genotype–phenotype correlation for *C5orf42* mutated versus non-mutated OFDVI cases.

To date, 63 different pathogenic *C5orf42* mutations (44 in patients with JS or cerebellar malformations and 19 in OFDVI patients) have been reported [Srour et al., 2012; Lopez et al., 2014; Romani et al., 2015]. The identified mutation in our study (Gln1345Arg) has also been reported by Romani et al. [2015] but in a compound heterozygous state. Lopez et al. [2014] suggest that at least one truncating mutation is necessary to induce JS or OFDVI as suggested by the high rate of mutations of this type (~70%), contrasting with most JS causative genes. In our study we report on homozygous *C5orf42* missense mutation in Turkish patients with a clinical diagnosis of OFDVI.

The recent identification of the mutations in *C5orf42* including our study strongly confirms that OFDVI syndrome and JS are allelic disorders. However, the exact genotype–phenotype correlation still remains unclear. The identification of new mutations in ciliopathy protein pathway genes or in the modifier genes will provide further insights into the broad clinical spectrum of OFDVI and JS.

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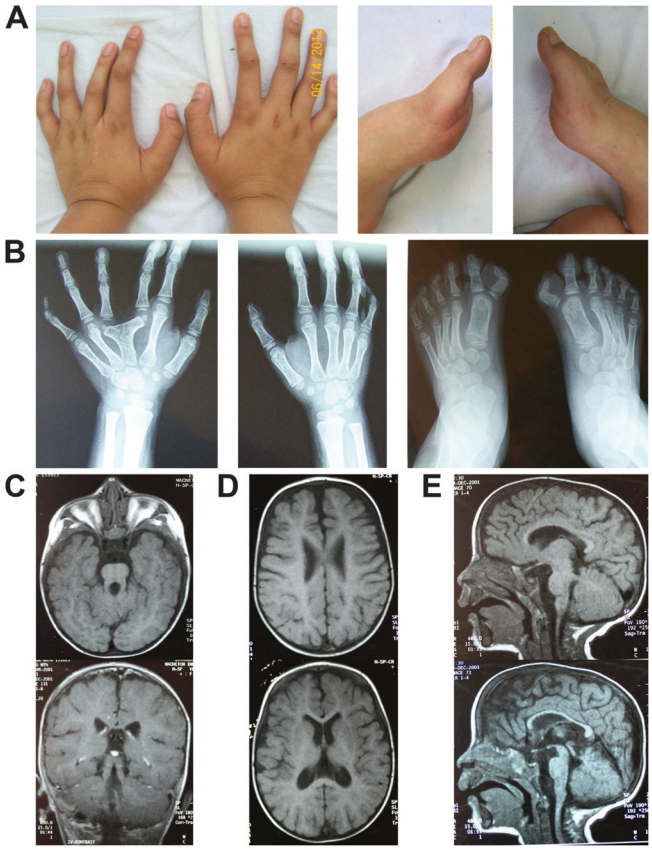

FIG. 1.

Photographs, X-ray, and MRI images of the index patient. (A) Hands and feet of the index patient. Note postoperative scars on the left hand and both feet. (B) X-ray photographs of the index patient before the surgical repair. Note the T-shape metacarpal on left hand and preaxial polydactyly on both feet. (C) Axial and coronal views of the cranial MRI. Note the molar tooth sign on axial cut and large superior cerebellar pedincules on coronal cut. (D) Axial views of the cranial MRI showing the mild cortical atrophy. Note the prominence of the cerebral sulci. (E) Midsagittal and parasagittal images of the cranial MRI. Note the thin corpus callosum.

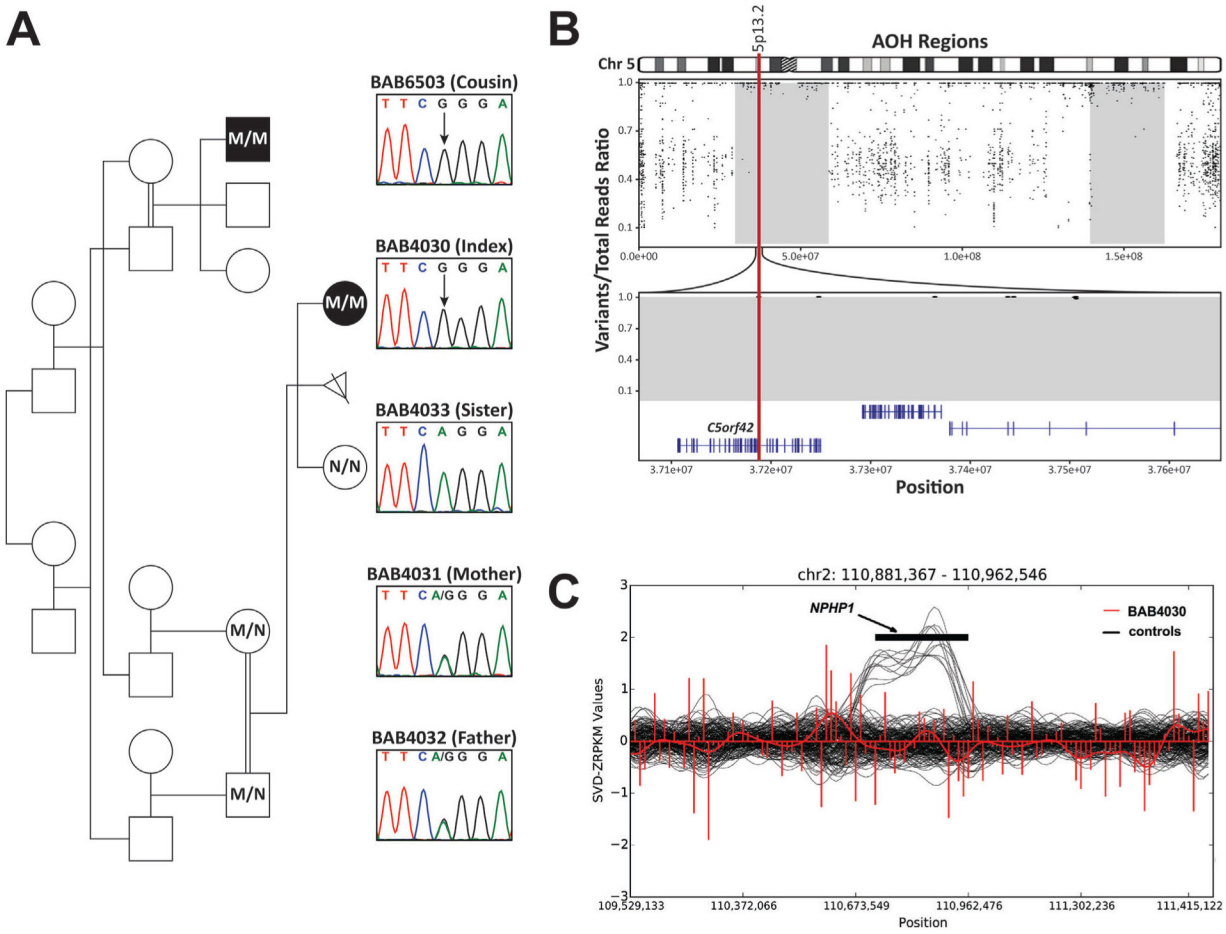

FIG. 2.

Segregation study, AOH regions, and CNV analysis of WES data around *NPHP1* region. (A) Pedigree and the Sanger sequence results of the family. Black filled boxes indicate affected individuals and the locations of the homozygous mutations are indicated with arrows. The index patient (BAB4030) and cousin (BAB6503) have the homozygous (M/M) c.4034A >G variant while the parents (BAB4031 and BAB4032) are heterozygous carriers (M/N) and the unaffected sister (BAB4033) is wild type (N/N). (B) AOH study of index patient based on calculated B-allele frequency data culled from WES analysis. Gray shaded areas indicate AOH regions. Note that the *C5orf42* mutation is located in ~29.05 Mb block of AOH region. (C) The duplication call made by Conifer CNV calling algorithm including *NPHP1* in a subset of controls (black lines) but not in BAB4030 (red line). The normalized reads per kilobase per million reads (rpkm) values are shown on the y axis. The x axis displays the indicated position on chromosome 2.

TABLE I

Comparison of the Clinical Findings in Our Patients With Those of Recently Reported OFDVI Patients [Lopez et al., 2014; Romani et al., 2015]

Clinical features	*C5orf42* mutation (+)	*C5orf42* mutation (−)	Index patient	Affected Cousin
Tongue hamartoma or lingual frenunla	50%	100%	−	−
Mesoaxial polydactyly	100%	76%	+	+
Preaxial polydactyly	100%	29%	+	+
CNS anomaly apart from MTS	57%	24%	+[a]	NA
Retinal/renal/hepatic involvement	0	24%	−	NA
Other congenital abnormalities outside the CNS	57%	6%	+[b]	NA
Intellectual disability	NA	NA	+	+

CNS, central nervous system; MTS, molar tooth sign; NA, data is not available.

[a] Mild cortical atrophy and thin corpus callosum.

[b] Hypoplasia of external genitalia and a surgically repaired inguinal hernia.