A Novel Mutation in *VPS13B* Gene Causing Cohen Syndrome in Two Siblings

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Abstract

Cohen syndrome is a rare disorder with facial dysmorphism, microcephaly, truncal obesity and intellectual disability. Clinical diagnosis of this syndrome is challenging due to the variability in the phenotype observed in this syndrome. We present a family with two affected siblings with microcephaly and global developmental delay. We report a novel insertion variation in *VPS13B* gene identified by exome sequencing. This case report expands the mutation spectrum of Cohen syndrome and highlights the utility of next generation sequencing in definitive diagnosis and genetic counseling of such rare disorders.

Introduction

Cohen syndrome (MIM #216550) is a very rare genetic disorder associated with intellectual disability, microcephaly, hypotonia, variable truncal obesity and progressive retinopathy. It is inherited in an autosomal recessive pattern and is caused by pathogenic variations in the *VPS13B* (MIM #607817) gene.

Case report

A 16-year old girl (III.1; Figure 1A), born to a non-consanguineous couple was evaluated for developmental delay and microcephaly. She was born at term by normal vaginal delivery and weighed 1.7 kg (-3 SD) at birth. She sat without support at 4 years and walked independently after 5 years of age. Speech was also markedly delayed and she could speak few words at present. There was no history of any behavioural abnormalities in her. On examination, her height was 129 cm (-5 to -6 SD), head circumference was 44 cm (-8 to -9 SD), weight was 29 kg (-4 SD) and BMI was 17.4 kg/m^2. Low anterior hairline, strabismus, narrow and high arched palate, low hanging columella, hypoplastic nasal alae, dental crowding, prominent central incisors, small mouth, distal joint laxity, pes planus, long and slender fingers and short third, fourth and fifth toes in both feet were noted (Figure 1B). Magnetic resonance imaging (MRI) of the brain was normal.

Her younger sib (III.2), a 14-year old girl was born at term by normal vaginal delivery with birth weight of 1.5 kg. She presented with significant developmental delay. On examination her head circumference measured 46 cm (-6 to -7 SD) and height 120 cm (-5 SD). Low anterior hairline, prominent nose, hypoplastic alae nasi, small mouth, long slender fingers and pes planus similar to that of her elder sibling were observed in her (Figure 1B). Exome sequencing was done in both the siblings to identify the cause of their condition.

Methodology

A complete clinical history and an informed consent were taken from the family. Whole-exome sequencing (WES) was carried out to achieve an average coverage depth of 100–130x, such that ~95% of the bases are covered at >20x, with a sensitivity of >90% (Girisha et al., 2016) in both the siblings followed by validation and segregation analysis by Sanger sequencing.

Result

Analysis of the whole exome data showed a novel homozygous insertion, c.6010_6011dupTT [p.(Asp2005LeufsTer15)], in exon 35 of the *VPS13B* gene (NM_017890.4). This variant was not observed in homozygous state in population databases

like 1000 Genome project and ExAC population database. The variant is a frameshift mutation that is predicted to cause either non-sense mediated decay or premature truncation of the protein. The variation was confirmed by Sanger sequencing in both the sibs. Segregation analysis showed parents are carriers for the same insertion variation as observed in the siblings (Figure 1C).

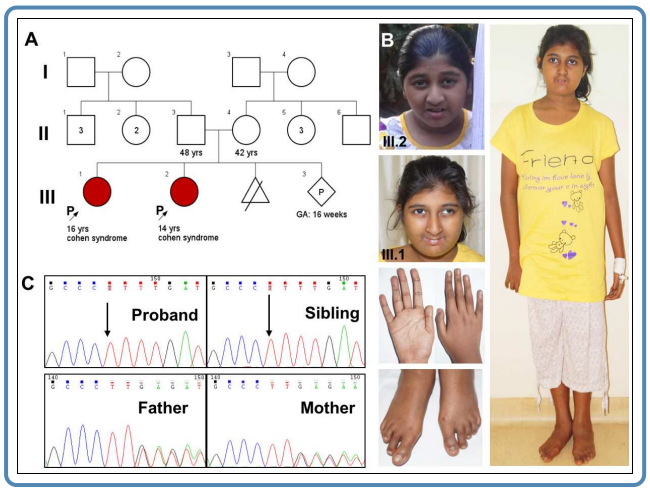

Figure 1 A) Family pedigree. B) Low anterior hairline, low hanging columella, hypoplastic nasal alae, small mouth, long and slender fingers, pes planus and short stature observed in both siblings. Strabismus, prominent central incisors and short third, fourth and fifth toes observed in proband III.1. C) Sanger validation of the variant, c.6010_6011dupTT in exon 35 of *VPS13B* gene in proband, her affected sibling and parents.

Discussion

Cohen syndrome was ascertained by whole exome sequencing in both siblings with a novel homozygous insertion variation in the *VPS13B* gene. It is a rare disorder characterized by intellectual disability, facial dysmorphism, microcephaly, truncal obesity, retinal dystrophy and high myopia, joint hypermobility, sociable behaviour and neutropenia. However, phenotypic variability is often noted in this syndrome and there are no diagnostic criteria till date (Seifert et al., 2006). Though the facial gestalt resembled Cohen syndrome in our subjects, truncal obesity was absent in both.

More than 200 patients of diverse populations have been diagnosed till date that have causative variants for this syndrome in *VPS13B* gene (Douzgou et al., 2011). Missense, nonsense, splicing and indel pathogenic variations have been reported. Founder mutations have been noted in Finnish, Amish, Greek and Mediterranean, and Irish populations (Bugiani et al., 2008; Falk et al., 2004; Kolehmainen et al., 2003; Murphy et al., 2007).

Cohen syndrome is an autosomal recessive disorder and hence the risk of recurrence is 25% in sibs. Prenatal diagnosis can be done if the causative mutation is identified in the families. Ophthalmological evaluation, physical, occupational and speech therapy along with monitoring of growth and weight are integral for the management of these individuals.

Here, we emphasize the utility of next generation sequencing for definite diagnosis of this rare disorder which helps to provide genetic counseling and aids in informed choices for the family. We also report a novel variant in *VPS13B* gene that expands the mutation spectrum of this syndrome.

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