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Uncommon runs of homozygosity disclose homozygous missense mutations in two ciliopathy-related genes (*SPAG17* and *WDR35*) in a patient with multiple brain and skeletal anomalies

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ABSTRACT

We describe a patient severely affected with multiple congenital anomalies, including brain malformations and skeletal dysplasia suggestive of cranioectodermal dysplasia (CED) ciliopathy, who unusually carries several homozygosity tracts involving homozygous missense mutations in *SPAG17* (exon 8; c.1069G > C; p.Asp357His) and *WDR35* (exon 13; c.1415G > A; p.Arg472Gln) as revealed by homozygosity mapping and next generation sequencing. *SPAG17* is essential for the function and structure of motile cilia, while *WDR35* belongs to the same intraflagellar transport (IFT) gene family whose protein products are part of functional IFT A and B complexes. Formerly, *SPAG17* was related – through polymorphic variants – to an influence on individuals' height; more recently, *Spag17−/−* mice models were reported to present skeletal and bone defects, reduced mucociliary clearance, respiratory distress, and cerebral ventricular enlargement. Homozygous or compound heterozygous mutations in *WDR35* have mainly been related to CED2 or short-rib thoracic dysplasia 7, with only three cases showing some brain anomalies. Given that our patient presents these clinical features and the close functional relationship between *SPAG17* and *WDR35*, it is feasible that the combined effects from both mutations contribute to his phenotype. To our knowledge, this patient is the first to harbor a likely pathogenic homozygous mutation in both genes at the same time. Thus, the resulting complex phenotype of this patient illustrates the heterogeneity associated with ciliopathies and further expands the clinical and mutational spectrum of these diseases. Finally, we highlight the combined use of high-throughput tools to diagnose and support the proper handling of this and other patients.

1. Introduction

Ciliopathies are a clinically and genetically heterogeneous group of diseases resulting from defective ciliary genes or proteins and the subsequent impairment of cilia machinery and intraflagellar transport (IFT) (Huber and Cormier-Daire, 2012; Halbritter et al., 2013). Since cilia dysfunction can affect multiple tissues, a wide range of clinical features, such as renal cystic disease, polydactyly, intellectual disability, skeletal abnormalities, short ribs and limbs, hepatic disease, and ectodermal defects, have been described in ciliopathy patients (Schock and Brugmann, 2017; Oud et al., 2017). Ciliopathies encompass multiple recessive entities, including Joubert syndrome (JBTS), Meckel-Gruber syndrome (MKS), short-rib thoracic dysplasia (SRTD), Ellis-van Creveld syndrome (EVC), oral-facial-digital syndrome (OFDS), and cranioectodermal dysplasia (CED, also known as Sensenbrenner syndrome) (Oud et al., 2017).

Several ciliopathies are increasingly being associated with long continuous stretches of homozygosity (LCSHs) or runs/regions of homozygosity (ROHs) (e.g., Hildebrandt et al., 2009; Thevenon et al., 2016; Khan et al., 2016; Smith et al., 2016). These regions are long segments of homozygous SNP markers occurring in an uninterrupted sequence (typically > 1 Mb) that often enable the unmasking of

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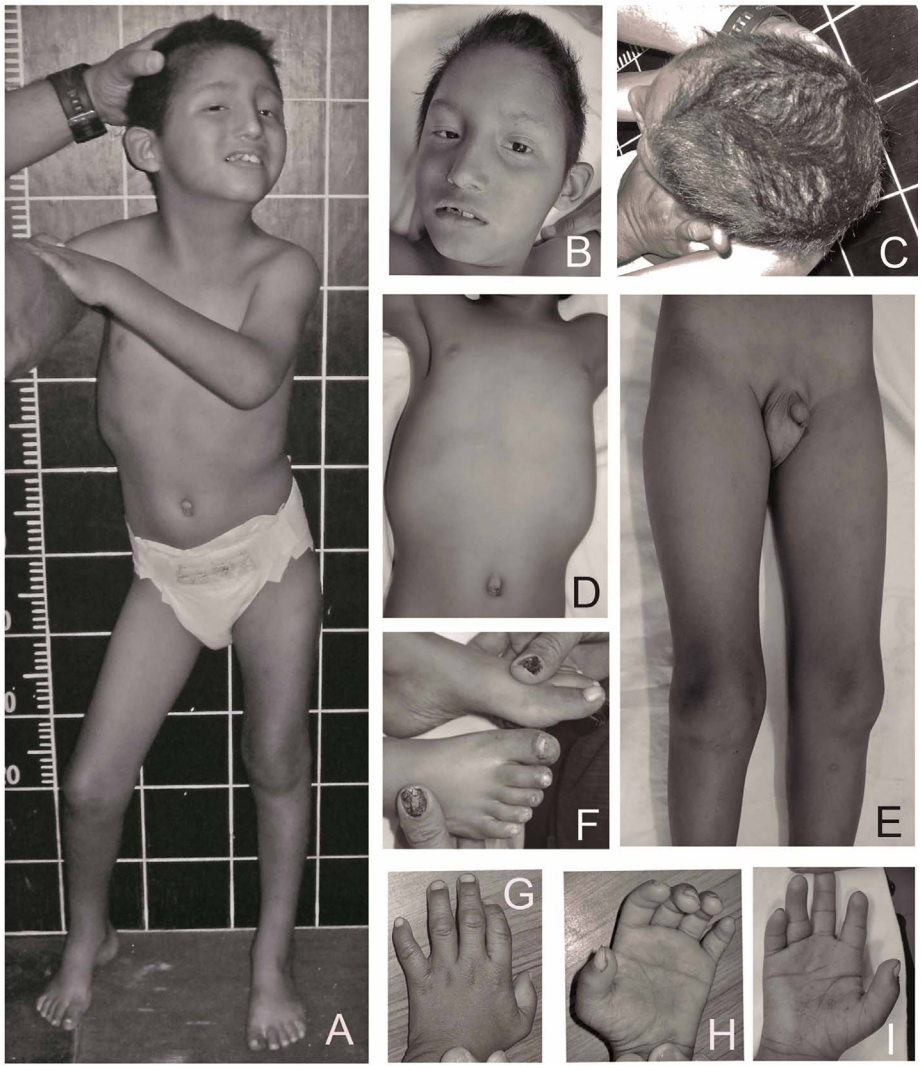

Fig. 1. Clinical features of the patient. (A) Complete view showing hypertonic and generalized hyperreflexia; legs with symmetrically vent; short neck with acanthosis nigricans; (B, C) dolichocephaly, sparse hair, narrow forehead with hypertrichosis; hypotrichotic eyebrows, down-slant palpebral fissures, curly and short eyelashes, long nose with high nasal bridge and broad nasal tip, hypoplastic and anteverted nares, broad and short columella and smooth philtrum; downturned corners of the mouth; microthia, anteverted helix with hypoplastic and attached earlobes, and hypoplastic tragus; (D) thorax was asymmetric with upper narrowing (bell-shaped chest), with nipples widely spaced; abdomen without organomegaly; (E) genitalia with micropenis, phimosis, cryptorchidism, and shawl scrotum; (F-H) his upper extremities with short hands, bilateral multiple and deep palmar creases, bilateral brachysyndactyly and symphalangism with absence of distal crease over the 2nd, 4th, and 5th fingers, a single palmar crease on the left hand, and medial arch deviation of the right foot.

recessive diseases. Several factors, such as mutation rate, ancestry, population structure, uniparental disomy, natural selection, recombination, and linkage disequilibrium, can influence the length, abundance, and location of homozygosity stretches (Gibson et al., 2006). Whether or not an LCSH is pathogenic likely depends on the location, gene content, size, epigenetics, and recessiveness of the related traits (Gibson et al., 2006; Papenhausen et al., 2011; Lapunzina and Monk, 2011). Herein, we describe an inbred patient severely affected with multiple congenital brain anomalies and skeletal dysplasia associated with novel homozygous missense mutations in the ciliopathy-related genes *SPAG17* and *WDR35* (also named *IFT121*) as revealed by homozygosity mapping and whole-exome sequencing (WES).

1.1. Clinical description

A 7.9-year-old male patient (Fig. 1) was evaluated for severe intellectual disability (ID), short stature, microcephaly, and pulmonary valve stenosis. This patient was the product of the first pregnancy of an 18-year-old mother; during pregnancy, oligohydramnios was suspected. The patient was born at 30 weeks of gestation by vaginal delivery due to premature rupture of membranes. His growth and development parameters at birth were weight 2.5 kg (−1.5 SD), length 47 cm (−1 SD), occipitofrontal circumference 33 cm (+1 SD), and an Apgar score of 5–8. Soon after birth, kyphoscoliosis and pulmonary valve stenosis were observed. TORCH and ophthalmological evaluation were performed with negative and mild pallor of optical nerve (1+) results, respectively. At 2 months, cardiac catheterization confirmed pulmonary valve stenosis. The patient received rehabilitation at the age of 6 months, with modest improvement of fine motor skills. This patient has also suffered from pneumonia, seizures, esophageal reflux disease, chronic constipation, and gastritis. In addition, he presented attention deficit disorder, hyperactivity, and aggressive behavior at 2 years of age. Anterior fontanel closure occurred at 2.3 years of age.

On physical examination at 7.9 years of age, the weight, height, and occipitofrontal circumference of the patient were 14.5 kg (Z - 5.119), 104 cm (Z −4.131), and 45 cm (Z – 3), respectively. He was hypertonic and showed generalized hyperreflexia (Fig. 1A); dolichocephaly, sparse hair on the scalp, a narrow forehead with hypertrichosis (Fig. 1B–C); hypotrichotic eyebrows, short palpebral fissure (2.4 cm; −2 SD), an inner canthal distance of 3 cm (+1 SD), an outer canthal distance of 8.5 cm (50 percentile), down-slant palpebral fissures, curly and short eyelashes, a long nose with high nasal bridge and broad nasal tip, hypoplastic and anteverted nares, broad and short columella and smooth philtrum (Fig. 1B); downturned corners of the mouth, a high and narrow palate, microdontia and oligodontia with dental malocclusion, gingival overgrowth; microthia, anteverted helix with hypoplastic and attached earlobes, and hypoplastic tragus; a short neck with acanthosis nigricans; an asymmetric thorax with upper narrowing (bell-shaped chest), widely spaced nipples, and dorsal-lumbar kyphoscoliosis (convexity to the left); an abdomen without organomegaly (Fig. 1D); and genitalia with micropenis, phimosis, cryptorchidism, and shawl scrotum (Fig. 1E). His hands were short: total length 11.2 cm (< 3rd