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MKS1 mutations cause Joubert syndrome with agenesis of the corpus callosum

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ABSTRACT

Joubert syndrome (JS) is a clinically and genetically heterogeneous ciliopathy characterized by episodic hyperpnea and apnea, hypotonia, ataxia, cognitive impairment and ocular motor apraxia. The "molar tooth sign" is pathognomonic of this condition.

Mutations in the *MKS1* gene are a major cause of Meckel-Gruber syndrome (MKS), the most common form of syndromic neural tube defects, frequently resulting in perinatal lethality. We present the phenotype and genotype of a child with severe JS and agenesis of the corpus callosum (ACC). In our patient, a next generation sequencing (NGS) approach revealed the following two variants of the *MKS1* gene: first, a novel missense variant [c.240G > T (p.Trp80Cys)], which affects a residue that is evolutionarily highly conserved in mammals and ciliates; second, a 29 bp deletion in intron 15 [c.1408-35_1408-7del29], a founder mutation, which in a homozygous state constitutes the major cause of MKS in Finland.

We review the *MKS1*-variants in all of the eleven JS patients reported to date and compare these patients to our case. To our knowledge, this is the first patient with Joubert syndrome and agenesis of the corpus callosum where a potentially causal genotype is provided.

1. Introduction

Joubert syndrome [JS, MIM 213300] was first described by Marie Joubert in 1969 in four siblings (Joubert et al., 1968) and by Boltshauser and Isler in another three patients (Boltshauser and Isler, 1977) as a recognizable congenital phenotype with episodic hyperpnea, abnormal eye movements, ataxia and mental retardation, associated with agenesis of the cerebellar vermis. The "molar tooth sign" in magnetic resonance imaging (MRI) of the brain is pathognomonic of JS (Poretti et al., 2014); agenesis of the corpus callosum (ACC) has been infrequently reported in patients with JS (Zamponi et al., 2002).

The estimated birth prevalence of JS is 1:80,000 to 1:100,000 and inheritance is autosomal recessive with a single exception when the causal mutation is located in the X-chromosomal *OFD1*-gene. At least 30 genes are known to cause JS.

Meckel-Gruber syndrome [MKS, MIM 240999] is a severe developmental disorder, primarily diagnosed in foetuses, with a high frequency of perinatal lethality. Similarly to JS, MKS is caused by a dysfunction of primary cilia during early embryogenesis. Clinical hallmarks of MKS are cystic kidneys, encephalocele, other central nervous system anomalies, fibrotic/cystic changes of the liver and polydactyly (Barisic et al., 2015). The mean prevalence of

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MKS is 2.6 per 100,000 births with regional differences, and the inheritance is autosomal recessive. Mutations in 12 genes are known to cause MKS (Szymanska et al., 2014). The *MKS1* gene is mutated in approximately 7–14% of MKS patients, with increasing frequency in Northern Europe due to a founder mutation-the so-called *MKS1*-Fin(major) mutation (Kyttala et al., 2006).

Rare hypomorphic mutations in *MKS1* have been reported to cause Bardet-Biedl syndrome (BBS), a genetically heterogeneous ciliopathy characterized by retinitis pigmentosa, obesity, polydactyly, hypogenitalism, renal anomalies and learning difficulties (Xing et al., 2014; Leitch et al., 2008). Mutations in *MKS1* have not been reported to cause JS until recently (Kroes et al., 2015; Romani et al., 2014; Bachmann-Gagescu et al., 2015).

We report the phenotype and genotype of a child of Austrian descent with severe JS including complete ACC. A next-generation sequencing (NGS)approach revealed the following two variants of the *MKS1* gene: the *MKS1*-Fin(major) mutation and a novel missense variant at a position that is highly conserved in evolution and located outside of the conserved B9-C2 domain.

2. Clinical report

The boy is the first child born to healthy, non-consanguineous parents of Austrian descent. The mother was 24 years old, and the father was 30 years old. The family history was unremarkable. In the 27th week of gestation prenatal ultrasound investigation revealed enlarged ventricles and led to invasive prenatal diagnostics that gave a normal male karyotype as a result. The birth was normal and occurred in the 41st week of gestation. The growth parameters at birth were normal. The boy had episodes of apnea during the first 7 months of life. He had severe hypotonia, congenital rotatory nystagmus and a delay of developmental milestones. At 18 months of age, a brain MRI was performed showing the “molar tooth sign” (Fig. 1d) and ACC (Fig. 1e, f). At 21 months of age, there was no evidence of retinal involvement.

At 3 years and 5 months of age, the patient could sit independently. At 5 years and 2 months of age, the patient’s height and weight were between the 2nd and 9th percentile, and the occipitofrontal head circumference was at the 9th percentile.

At 6 years and 2 months of age, the patient could not stand or walk independently. Dysmorphic features at this age included a slightly broad forehead, ptosis of the left eye, epicanthus inversus, smooth philtrum, enlarged nares, and thin vermilion of the upper lip (Fig. 1a, b). Camptodactyly of digits III and V (Fig. 1c) was present symmetrically in both hands. The genitalia were small. The kidney and liver were of normal shape, location and function.

An atactic movement disorder and trunk hypotonia are obvious, but dysphagia is not present. He can grasp for objects and obey simple commands but has no active speech and is communicating with simple gestures. He can maintain good eye contact and has friendly and charming behaviour. He is seated in a wheelchair and can move the wheelchair by his own manual propulsion to a limited extent. He is not diaper-free.

3. Methods and results

A total of 258 known and potential ciliopathy genes were enriched, using the Roche/NimbleGen sequence capture approach, amplified and sequenced simultaneously by Illumina technology (NGS) using an Illumina MiSeq system, as described elsewhere

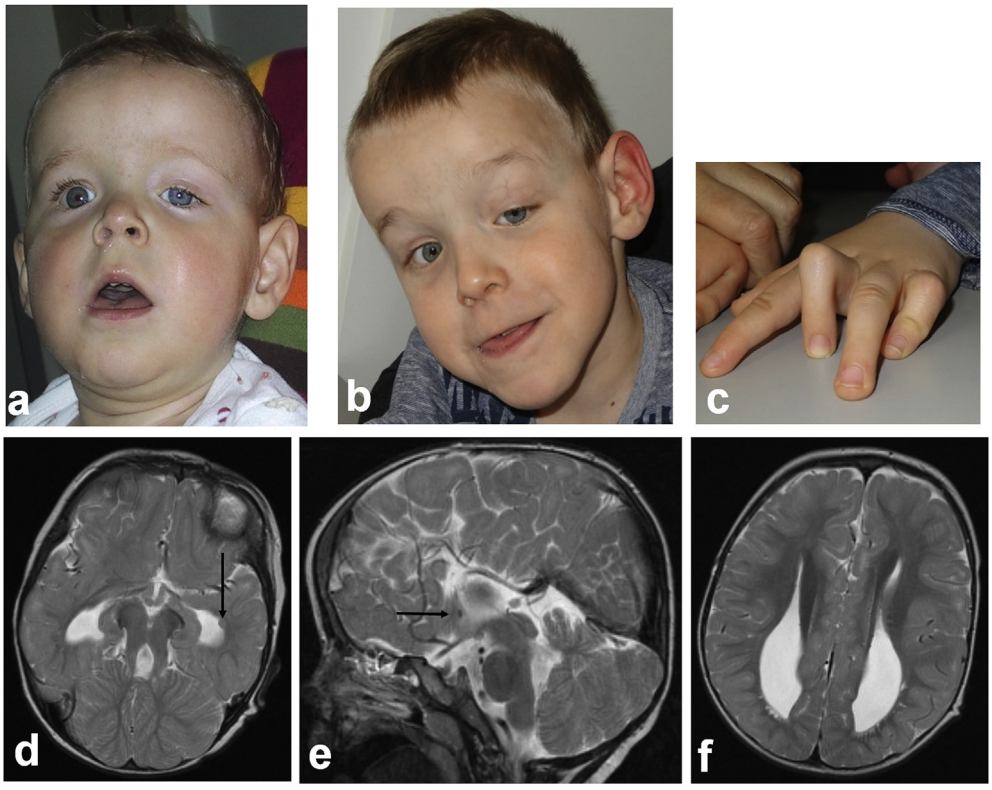

Fig. 1. **a)** Patient at the age of 21 months; **b)** at 6 years 2 months of age; **c)** camptodactyly of the 3rd and 5th fingers of the left hand (right hand is similar, not shown); **d-f)** T2 w MRI at 18 months: **d)** axial view through posterior fossa showing molar tooth sign, cerebellar dysplasia (irregular white matter arborisation), enlarged temporal horns, and periventricular heterotopia adjacent to left temporal horn (arrow); **e)** sagittal view demonstrating complete ACC, the anterior commissure is present (arrow); **f)** axial view at the level of the lateral ventricles showing their colpocephalic shape. Additional anomaly: hippocampal malrotation (not shown).