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Original article

DNA analysis of *AHI1*, *NPHP1* and *CYCLIN D1* in Joubert syndrome patients from the Netherlands

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Abstract

Joubert syndrome (JBS) is a clinically variable and genetically heterogeneous developmental brain disorder with autosomal recessive inheritance. Five genes, *AHI1*, *NPHP1*, *CEP290*, *MKS3*, and *RPGRIP1L*, and two additional loci on chromosome 9 and 11 have been identified so far. The relative contributions of *AHI1* mutations and *NPHP1* deletions have not yet been determined in a population-based JBS patient cohort. We therefore undertook a nationwide survey of JBS in the Netherlands and performed DNA analysis of the *AHI1* and *NPHP1* genes, as well as a new candidate gene *CYCLIN D1*. We obtained clinical

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data and DNA samples of 25 Dutch JBS patients. DNA analysis of *AHI1* revealed pathogenic homozygous or compound heterozygous *AHI1* mutations in four patients (16%). Based on the birth prevalence of about 1 in 100,000 for JBS in the Netherlands, we estimated a carrier frequency of *AHI1* mutations of approximately 1 in 400. In another two patients, the *AHI1* mutation Arg830Trp was identified (homozygously and heterozygously), a possible low penetrance allele. No deletions of *NPHP1* or *CYCLIN D1* mutations were detected in these 25 patients. In the four patients with *AHI1* mutations, retinal disease (Leber congenital amaurosis or retinal dystrophy) was present in two, whereas none had renal disease. Pooling our data and data from the literature, retinal disease seems to occur in 75% of *AHI1*-associated JBS patients. Renal disease is present in 10% at most.

We conclude that *AHI1* mutations are an important cause of JBS in Dutch patients, and should always be looked for in patients suspected of JBS, especially when retinal dystrophy is present. Patients with *AHI1* mutations should be regularly checked for retinal and renal disease up until adolescence.

Keywords: Joubert syndrome; Molar tooth sign; *AHI1*; *NPHP1*; *CYCLIN D1*; Carrier frequency; Digenic inheritance

1. Introduction

Joubert syndrome (JBS) is a developmental brain disorder with diverse associated symptoms in several organs. Its key symptoms are developmental delay, hypotonia, ataxia, breathing abnormalities (predominantly in the neonatal period), and oculomotor abnormalities [25]. The most consistent feature of JBS is hypoplasia of the cerebellar vermis and a midbrain–hindbrain malformation called the 'molar tooth sign' (MTS) on MRI. The MTS is caused by three radiological features occurring together: a deep interpeduncular fossa at the pontomesencephalic junction, thickened and elongated superior cerebellar peduncles, and cerebellar vermis hypoplasia [18,19].

Various associated anomalies are reported, especially retinal dystrophy, choroidoretinal and optic nerve colobomas, renal cystic disease and hepatic fibrosis, and occasionally polydactyly and meningoencephalocele. This makes the disorder difficult to delineate, since the phenotype shows considerable overlap with some other syndromes, e.g. COACH syndrome, Senior-Løken syndrome, Meckel–Gruber syndrome, and OFD type VI. The MTS has also been reported in patients with these syndromes. Therefore, the term 'Joubert syndrome-related disorders' (JSRD) has been introduced for this group of overlapping, poorly delineated syndromes (see review by Gleeson et al. [9]). Some authors feel the term Joubert syndrome should be restricted to patients with the classical neurological phenotype, without any of the associated anomalies mentioned above [9].

The clinical variability of JSRD is partly explained by the extensive genetic heterogeneity. Five genes and two loci associated with JSRD have been identified so far: JBTS1 on chromosome 9q34.3 [24], JBTS2 on chromosome 11p12–11q13.3 [13], JBTS3 (the *AHI1* gene) on chromosome 6q23.3 [7,8,15], JBTS4 (the *NPHP1* gene) on chromosome 2q13 [20], JBTS5 (the *CEP290* gene or *NPHP6* gene) on chromosome 12q21.3 [26,33], JBTS6 (the *MKS3* gene) on chromosome 8q21.13–q22.1 [2] and recently JBTS7 (the *RPGRIP1L* gene) on chromosome 16q12.2 [1,5]. Inheritance is autosomal recessive. JBTS1 seems to be associated with a phenotype consisting primarily of the neurological features of JBS, and retinopathy in some patients [24,32]. The JBTS2 locus is seen in JBS families with retinal disease (retinal dysplasia or colobomas) and/or renal cystic disease [13]. JBTS4-associated JSRD is caused by homozygous