Joubert syndrome: report of 11 cases

Faruk İncecik[1], M. Özlem Hergüner[1], Şakir Altunbaşak[1], Joseph G. Gleeson[2]

[1]Department of Pediatric Neurology, Çukurova University Faculty of Medicine, Adana, Turkey, and [2]Department of Neuroscience and Pediatrics, Neurogenetics Laboratory, Howard Hughes Medical Institute, University of California, San Diego, CA, USA. E-mail: fincecik@yahoo.com

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Joubert syndrome (JS) is an autosomal recessive condition characterized by hypotonia, ataxia, psychomotor delay, and variable occurrence of oculomotor apraxia and neonatal breathing abnormalities. The 11 cases were searched according to their clinic, radiologic, and mutation analysis findings, according to which they were diagnosed as JS. Physical, neurological and fundus examinations were performed in all patients. Cerebral magnetic resonance imaging scan, abdominal ultrasonography, and if necessary, echocardiography were performed. CC2D2A and ARL13B mutations were analyzed in our 11 JS patients. The mean age was 31.09±37.49 months (range: 1 month - 10 years). Two of the cases were siblings. Nine of the cases had a history of episodic hyperpnea. The other findings were hypotonia, ataxia, psychomotor retardation, and nystagmus. In all patients, the "molar tooth sign" was observed with scanning methods. In addition, cerebellar cortical dysplasia was established in one of the cases. Macrocephaly (1 patient), multiple renal cysts (1 patient), ocular coloboma (2 patients), ptosis (1 patient), congenital heart disease (1 patient), polydactyly (2 patients), and congenital hip dislocation (2 patients) were also determined. We identified mutation (c.C4452T → p.R1518W) in CC2D2A in two patients. JS can show heterogeneity clinically, neuroradiologically and genetically. Determination of the symptoms, early diagnosis and genetic consultation are the goals for decision-making to begin treatment and rehabilitation programs.

Key words: Joubert syndrome, clinical and radiological findings, mutation analysis.

Joubert syndrome (JS) is characterized by congenital cerebellar ataxia, hypotonia, oculomotor apraxia, intellectual disability, and specific mid-hindbrain malformation ("molar tooth sign", MTS). JS is associated with the MTS, a radiologic finding that includes cerebellar vermis hypoplasia or dysplasia, thick and horizontally oriented superior cerebellar peduncles, and an abnormally deep interpeduncular fossa[1]. Other clinical features define subtypes of JS, termed JS and related disorders (JSRD). These include occipital encephalocele, polymicrogyria, polydactyly, ocular coloboma, retinal dystrophy, cystic kidney disease, nephronophthisis, and hepatic fibrosis[2].

Joubert syndrome (JS) is a clinically, genetically and radiologically heterogeneous disorder. JSRD are genetically heterogeneous with mutations in 13 genes known to date. Most demonstrate autosomal recessive inheritance, although cases of X-linked inheritance and autosomal dominant inheritance have been described[3].

The purpose of this study was to evaluate the clinical and neuroradiologic findings and mutation analysis in 11 patients with JS.

Material and Methods

Eleven patients matching the JS diagnostic criteria as revised by Maria et al.[4] were included in the study. Diagnostic criteria of classic JS include: 1. Cranial magnetic resonance imaging (MRI) findings demonstrating the MTS on axial imaging with these three components: midline cerebellar vermis hypoplasia, deepened interpeduncular fossa, and thick, elongated superior cerebellar peduncles, 2. Hypotonia in infancy, 3. Developmental delay/intellectual

disability, of variable severity, and 4. One or both of the following (not absolutely required but supportive of the diagnosis): a. Irregular breathing pattern in infancy (episodic tachypnea and/or apnea), b. Abnormal eye movements (including nystagmus, jerky eye movements, and oculomotor apraxia or difficulty with smooth visual pursuits) [4].

The medical histories of all patients had been taken, and additionally, physical, neurological and fundus examinations of all patients were performed. In all patients, laboratory examination, including complete blood count, blood biochemistry, serum lactate, ammonia, and plasma and urine amino acids, and metabolic screening of blood were performed.

Cerebral MRI scans were done in all patients using a 1.5 Tesla MR scanner. Special attention was paid to some characteristic appearances for JS defined by different authors, such as the MTS, "bat wing" appearance, apposition of cerebellar hemispheres, and vermian cleft.

Ultrasonography (USG) of the abdomen was done in all patients. We also analyzed the CC2D2A and ARL13B mutations in our 11 JS patients. We performed direct bidirectional sequencing of the 10 coding exons and splice junction sites of ARL13B and CC2D2A.

Results

There were 11 patients aged between 1 month-10 years (median: 31.09±37.49 months); 4 were female and 7 were male. Two of the patients were sisters (patients 2 and 3). Parental consanguinity was present in 7 patients, and 1 patient had a brother who died with possible JS (unexplained death). Table I shows clinical findings and results of MRI and abdominal USG of all patients.

Episodic hyperpnea attacks were present in 4 of the patients. Additionally, 5 of the patients had episodic hyperpnea in early childhood. Hypotonia, ataxia, psychomotor retardation, and nystagmus were demonstrated in all of the patients. One of the patients had macrocephaly; one, multiple renal cysts; two, ocular coloboma; one, ptosis; one, congenital heart disease; two, polydactyly; and two, congenital hip dislocation. Axial MR scanning demonstrated deepening of intra-peduncular cisternae, thinning of the pontomesencephalic junction, thickening at the superior cerebellar peduncles, and MTS due to horizontal position and vermis hypoplasia (Fig. 1). In addition, on axial and coronal MRI, "bat wing" appearance was established due to vermian cleft by incomplete fusion, vermis hypoplasia or aplasia (Figs. 2, 3). Cortical dysplasia of the cerebellar hemisphere was established in one of the patients. Among all patients, mutation (c.C4452T → p.R1518W) in CC2D2A was identified in only 2 patients.

We found this mutation in patient 1 and patient 10. Patient 1 was a 2-month-old boy who presented with complaints of hypotonia, episodic hyperpnea and abnormal eye movements. He was born at term from non-consanguineous parents and suffered no significant perinatal asphyxia. He was the only child of his parents. There was no history of similar neurological illness in the family. On examination, he had abnormal ocular movement, episodic hyperpnea, and polydactyly. Motor examination revealed hypotonia with normal tendon reflexes. He had no social smile or head control. Head circumference was normal for age. Coloboma was detected on ocular examination.

The second patient (patient 10, a 54-month-old boy) is a sporadic case who presented with developmental delay and abnormal eye movements. He was born of a consanguineous marriage. He had two healthy siblings. On examination, he had intellectual disability. External ocular movements were normal

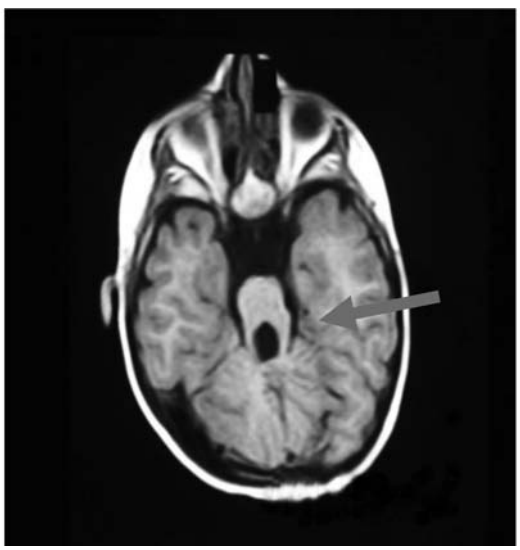

Figure 1. Axial T1-weighted cerebral MR image shows "molar tooth sign" (red arrow).

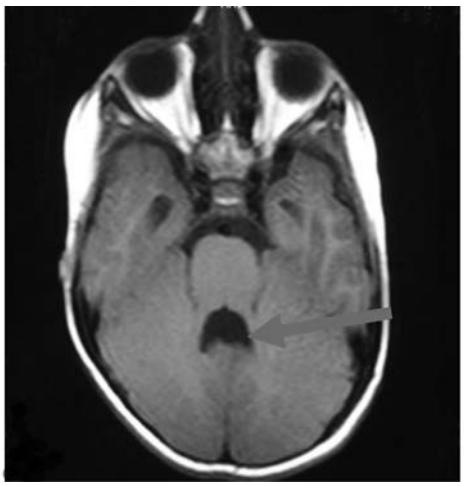

Figure 2. Axial T1-weighted cerebral MR image shows "bat wing appearance" (red arrow).

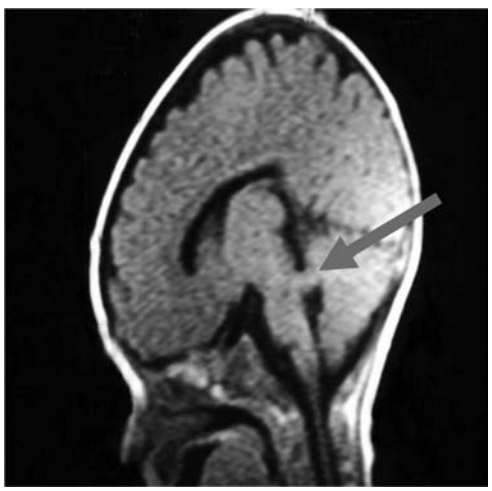

Figure 3. Coronal T1-weighted cerebral MR image shows vermian cleft (red arrow).

and mild horizontal nystagmus was present. He had mild truncal ataxia and hypotonia. Ocular examination and other neurological examinations were normal.

Discussion

Joubert syndrome (JS) was originally described in 1968 in four siblings with agenesis of the cerebellar vermis presenting episodic hyperpnea, abnormal eye movements, ataxia, and intellectual disability[1]. The incidence of JS has been estimated as between 1/80,000 and 1/100,000 live births[5].

Diagnostic criteria in JS include hypotonia, ataxia, global developmental delay, and the neuroradiological finding of MTS. The term 'JS and related disorders' (JSRD) was introduced to refer to a group of pleiotropic conditions presenting the pathognomonic features of JS associated with variable involvement of other organs and systems. These disorders have been classified as ciliopathies.

Cilia are classically divided into motile and non-motile based on the organization of the microtubules in the ciliary axonemes. The axoneme is the microtubule backbone along which microtubule-mediated intra-flagellar transport of various ciliary proteins occurs. The axoneme is anchored by the basal body in coordination with the action of centrosomal proteins and guanosine triphosphatases.

Ciliogenesis refers to the process of the docking of the basal body at the plasma membrane, followed by recruitment of ciliary proteins and protrusion of the newly emerging axoneme into the plasma membrane. Subsequently, proteins are transported into and out of the cilia, further utilizing intra-flagellar transport, which functions bidirectionally. A defect in the transport or arrangement of these cilia-centrosomal proteins adversely affects a variety of the critical developmental signalling pathways that are essential to cellular development, such as Sonic hedgehog, Wnt signalling, planar cell polarity, and directional movement[6]. Ciliary dysfunction can affect a single tissue or manifest as multi-organ involvement.

Although JS was first defined based upon the presence of neurological features alone, JSRD are characterized by extra-central nervous system involvement, such as retinopathy, cystic dysplastic kidneys or nephronophthisis, hepatic fibrosis, and polydactyly and midline facial defects, each named for a particular constellation of signs and symptoms. JSRD are now known to include cerebellar-ocular-renal syndrome, cerebellar vermis hypo-aplasia, oligophrenia, congenital ataxia, ocular coloboma, and hepatic fibrosis (COACH) syndrome, and Varadi-Papp syndrome based upon the presence of the unifying MTS.

Joubert syndrome-related disorders (JSRD), like many of the disorders considered ciliopathies, show considerable heterogeneity in their clinical features and molecular basis. The clinical features of JSRD are shared by many ciliary disorders, and typically involve the renal

Table I. Characteristic Clinical and Magnetic Resonance Imaging Findings of the Patients

Patient no	Age (months)/ sex	Abdominal US findings	Clinical/Ocular finding	MRI findings
Patient 1	2/boy	Normal	Hypotonia, motor/intellectual disability, abnormal ocular movement, episodic hyperpnea, polydactyly, coloboma	Cerebellar vermis aplasia, vermian cleft, MTS, BWA
Patient 2	36/girl	Normal	Hypotonia, ataxia, motor/ intellectual disability, congenital hip dislocation, abnormal ocular movement	Cerebellar vermis aplasia, vermian cleft, MTS, BWA
Patient 3	3/girl	Normal	Hypotonia, motor/intellectual disability, congenital hip dislocation, abnormal ocular movement, episodic hyperpnea	Cerebellar vermis aplasia, vermian cleft, MTS
Patient 4	12/girl	Multicystic kidney	Hypotonia, ataxia, motor/ intellectual disability, abnormal ocular movement, episodic hyperpnea, ptosis, optic atrophy	Cerebellar vermis aplasia, MTS, BWA
Patient 5	10/boy	Normal	Hypotonia, ataxia, motor/ intellectual disability, abnormal ocular movement, episodic hyperpnea	Cerebellar vermis aplasia, vermian cleft, MTS, BWA
Patient 6	24/boy	Normal	Hypotonia, ataxia, motor/ intellectual disability, abnormal ocular movement, coloboma	Cerebellar vermis aplasia, vermian cleft, MTS, BWA, cortical dysplasia
Patient 7	8/boy	Normal	Hypotonia, ataxia, motor/ intellectual disability, abnormal ocular movement, episodic hyperpnea	Cerebellar vermis aplasia, MTS, BWA
Patient 8	1/boy	Normal	Hypotonia, ataxia, motor/ intellectual disability, microcephaly, abnormal ocular movement, episodic hyperpnea	Cerebellar vermis aplasia, vermian cleft, MTS, BWA
Patient 9	120/girl	Normal	Hypotonia, ataxia, motor/ intellectual disability, abnormal ocular movement, episodic hyperpnea	Cerebellar vermis aplasia, vermian cleft, MTS, BWA
Patient 10	54/boy	Normal	Hypotonia, ataxia, motor/ intellectual disability, abnormal ocular movement, episodic hyperpnea	Cerebellar vermis aplasia, vermian cleft, MTS, BWA
Patient 11	72/boy	Normal	Hypotonia, ataxia, motor/ intellectual disability, polydactyly, abnormal ocular movement, episodic hyperpnea	Cerebellar vermis aplasia, vermian cleft, MTS, BWA

BWA: "Bat wing" appearance. MRI: Magnetic resonance imaging. MTS: Molar tooth sign. US: Ultrasonography.

epithelium, retinal photoreceptor cells, central nervous system, body axis, sensory organs, and others[3]. The first gene for this condition was identified in 2004, and 13 causative genes have been identified to date: AHI1, ARL13B, CC2D2A, CEP290, INPP5E, KIF7, NPHP1, OFD1, RPGRIP1L, TCTN1, TCTN2, TMEM67 (MKS3), and TMEM216[7].

The main clinical signs of JS are hypotonia, ataxia, intellectual disability, abnormal eye movements, and a respiratory pattern of alternating tachypnea-apnea during the first months of life. Hypotonia and intellectual disability are the constant features of JS. Infants have moderate to severe hypotonia. Most studies list hypotonia as one of major findings of the disease. Maria et al.[8] reported that neonatal hypotonia was present in all 59 of their cases. We also established hypotonia in all of our patients.

Developmental impairment and intellectual disability are usually severe and present across a variety of domains, including behavior and motor, language and general development[9]. It is difficult to state the mental deficit in patients with JS as the cerebrum seems to be spared; mainly, the cerebellar vermis and the pontomesencephalic junction are affected by the malformation. Studies have demonstrated the role of the vermis in cognitive functions and the relationship between developmental impairment and intellectual disability of both the vermis and brainstem. However, clinical studies have provided growing evidence on the role of the cerebellum in different cognitive domains that might be impaired in cases of injury or congenital absence of cerebellar cerebral connections[10].

The breathing pattern in JS is effortless hyperventilation, which is more conspicuous in the awake state and intensifies when the patient is stimulated, interspersed with central apnea. This abnormal breathing pattern is typically in the neonatal period and usually wanes with age[11]. It was reported as 71% in the study of Maria et al.[8], 68% in the study of Pellegrino et al.[12], and 44% in the study of Kendall et al.[13]. We detected episodic hyperpnea and/or apnea in nine patients (81.8%).

There is a broad spectrum of ocular findings

Table II. Features of Joubert and Cerebello-Oculo-Renal Syndromes

	Joubert	Dekaban-Arima	Senior-Loken	Vermian hypoplasia-retinopathy	Varadi-Papp	COACH
Cerebral and neurologic findings						
Intellectual disability	+	+	+	+	+	+
Vermis hypoplasia	+	+	+	+	+	+
Dandy-Walker malformation/ occipital encephalocele	+/-	+/-	+/-	-	+/-	+/-
Molar tooth sign	+	+/-	+/-	+	+	+/-
Cerebellar findings	+	+	+	-	+	+
Eye						
Leber congenital amaurosis	-	+	+	+	-	-
Coloboma	+	-	-	-	+/-	+
Kidney						
Multicystic dysplastic kidney	-	+	-	-	-	-
Nephronophthisis	-	-	+	-	-	+/-
Renal hypoplasia/ agenesia	-	-	-	+	-	-
Renal abnormalities	-	+/-	+/-	-	-	+/-
Other systems						
Cone-shaped epiphyses	-	-	+/-	-		-
Hepatic fibrosis	-	+/-	+/-	-	-	+/-
Visceral abnormalities	-	+	-	-		+/-
Other						
Early death	+/-	+	-	-		-

COACH: Cerebellar vermian hypoplasia, oligophrenia, congenital ataxia, coloboma, and hepatic fibrosis syndrome. +: Present. (+/-): Present in some patients. −: Absent.

in JS. Abnormalities of ocular motility are very common, particularly nystagmus, which can be horizontal, vertical and/or torsional, and typically has a pendular or sometimes see-saw pattern, and oculomotor apraxia. Nystagmus and oculomotor apraxia are often present at birth and may improve with age. Other common ocular anomalies may include strabismus, ocular coloboma, severe visual loss, ptosis, pigmentary changes in the fundus, and decreased vestibulo-ocular reflexes[14,15]. All of our patients had nystagmus. Two of the children had ocular coloboma. In one patient, unilateral ptosis and optic atrophy were also detected.

The hallmark imaging features of JS are: 1-dysgenesis of the isthmus (part of the brainstem between the pons and inferior colliculus), which is seen as elongation and thinning of the pontomesencephalic junction, and deep interpeduncular fossa; 2-thickening of the superior cerebellar peduncles; 3-hypoplasia of the vermis characterized by incomplete lobulation and enlarged fourth ventricles; and 4-incomplete fusion of the halves of the vermis, creating a sagittal vermis cleft seen on axial or coronal MRI planes. Combination of the first three features produce the characteristic MTS on axial MRI[4,16,17]. Hypogenesis of the vermis results in a triangular- shaped mid-fourth ventricle and a bat-wing-shaped superior fourth ventricle[1].

Generally, the cerebellar and cerebral hemispheres are not affected, but a few patients may reveal mild enlargement of lateral ventricles and cerebrospinal fluid spaces. The corpus callosum may be dysgenetic[13]. None of our patients had a cerebral pathology. In all our patients, vermian cleft, MTS and "bat wing" sign were established radiologically. Dekaban-Arima, Senior-Loken, COACH, and Varadi-Papp syndromes have to be considered in the differential diagnosis (Table II).

All of our patients had a clinical and radiological pattern of JS. Evaluation of a child with suspected JS should include MR scan, retinal examination, renal USG, electroretinogram, and karyotyping. It should be noted that computerized tomography or MRI finding of vermis hypoplasia in the absence of other typical clinical features, even with intellectual disability, does not lead to the diagnosis of JS.

A number of genes have been identified as contributing to JS. Mutations in the 13 ciliary/basal body genes have been identified in subjects with JSRD[18]. These genes account for an estimated 50% of causative mutations in JSRD[3]. Mutation screening was performed only for CC2D2A and ARL13B in our patients. Homozygous CC2D2A mutation could be identified in only two patients. Therefore, we think that other mutations may be seen in our other patients.

The CC2D2A gene was first identified in an extended consanguineous Pakistani family with autosomal recessive cognitive impairment with retinitis pigmentosa[19]. CC2D2A has been shown to interact with CEP290 and to localize to the basal body. It is estimated to cause almost 10% of JSRD[20]. Bachmann-Gagescu et al.[21] identified CC2D2A mutations in 20 subjects of 209 families with JS. They were reported as more likely to have ventriculomegaly and seizures than subjects without CC2D2A mutations. We found this mutation in two patients.

There is a varying degree of intellectual impairment that ranges from mild to severe, but prognosis is largely dependent on the severity of involvement of the organ systems, in particular the retina, liver and kidney. Unfortunately, there are currently no curative therapies for these genetic ciliopathic syndromes. Early diagnosis of JSRD is important for prognostic outcome and genetic consultation. Close follow-up is also necessary to identify potential complications of the disease.

REFERENCES

1. Joubert M, Eisenring JJ, Robb JP, Andermann F. Familial agenesis of the cerebellar vermis. A syndrome of episodic hyperpnea, abnormal eye movements, ataxia, and retardation. Neurology 1969; 19: 813-825.
2. Valente EM, Brancati F, Dallapiccola B. Genotypes and phenotypes of Joubert syndrome and related disorders. Eur J Med Genet 2008; 51: 1-23.
3. Parisi MA. Clinical and molecular features of Joubert syndrome and related disorders. Am J Med Genet C Semin Med Genet 2009; 151: 326–340.
4. Maria BL, Hoang KB, Tusa RJ, et al. "Joubert syndrome" revisited: key ocular motor signs with magnetic resonance imaging correlation. J Child Neurol 1997; 12: 423-430.
5. Brancati F, Dallapiccola B, Valente EM. Joubert syndrome and related disorders. Orphanet J Rare Dis 2010; 5: 20.
6. Sattar S, Gleeson JG. The ciliopathies in neuronal development: a clinical approach to investigation of Joubert syndrome and Joubert syndrome-related disorders. Dev Med Child Neurol 2011; 53: 793-798.

7. Sang L, Miller JJ, Corbit KC, et al. Mapping the NPHP-JBTS-MKS protein network reveals ciliopathy disease genes and pathways. Cell 2011; 145: 513-528.
8. Maria BL, Quisling RG, Rosainz LC, et al. Molar tooth sign in Joubert syndrome: clinical, radiologic, and pathologic significance. J Child Neurol 1999; 14: 368-376.
9. Hodgkins PR, Harris CM, Shawkat FS, et al. Joubert syndrome: long-term follow-up. Dev Med Child Neurol 2004; 46: 694-699.
10. Sztriha L, Al-Gazali LI, Aithala GR, Nork M. Joubert's syndrome: new cases and review of clinicopathologic correlation. Pediatr Neurol 1999; 20: 274-281.
11. Fabbri M, Vetrugno R, Provini F, Bosi M, Santucci M. Breathing instability in Joubert syndrome. Mov Disord 2012; 27: 64.
12. Pellegrino JE, Lensch MW, Muenke M, Chance PF. Clinical and molecular analysis in Joubert syndrome. Am J Med Genet 1997; 72: 59-62.
13. Kendall B, Kingsley D, Lambert SR, Taylor D, Finn P. Joubert syndrome: a clinico-radiological study. Neuroradiology 1990; 31: 502-506.
14. Sturm V, Leiba H, Menke MN, et al. Ophthalmological findings in Joubert syndrome. Eye (Lond) 2010; 24: 222-225.
15. Weiss AH, Doherty D, Parisi M, Shaw D, Glass I, Phillips JO. Eye movement abnormalities in Joubert syndrome. Invest Ophthalmol Vis Sci 2009; 50: 4669-4677.
16. Quisling RG, Barkovich AJ, Maria BL. Magnetic resonance imaging features and classification of central nervous system malformations in Joubert syndrome. J Child Neurol 1999; 14: 628-635.
17. Poretti A, Huisman TA, Scheer I, Boltshauser E. Joubert syndrome and related disorders: spectrum of neuroimaging findings in 75 patients. AJNR Am J Neuroradiol 2011; 32: 1459-1463.
18. Parisi MA. Clinical and molecular features of Joubert syndrome and related disorders. Am J Med Genet C Semin Med Genet 2009; 151: 326-340.
19. Noor A, Windpassinger C, Patel M, et al. CC2D2A, encoding a coiled-coil and C2 domain protein, causes autosomal-recessive mental retardation with retinitis pigmentosa. Am J Hum Genet 2008; 82: 1011-1018.
20. Gorden NT, Arts HH, Parisi MA, et al. CC2D2A is mutated in Joubert syndrome and interacts with the ciliopathy-associated basal body protein CEP290. Am J Hum Genet 2008; 83: 559-571.
21. Bachmann-Gagescu R, Ishak GE, Dempsey JC, et al. Genotype-phenotype correlation in CC2D2A-related Joubert syndrome reveals an association with ventriculomegaly and seizures. J Med Genet 2012; 49: 126-137.