Joubert syndrome: congenital cerebellar ataxia with the molar tooth

Marta Romani, Alessia Micalizzi, Enza Maria Valente

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Neurogenetics Unit, Mendel Laboratory, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy (M Romani PhD, A Micalizzi BSc, Prof E M Valente MD); **and Department of Medicine and Surgery, University of Salerno, Salerno, Italy** (E M Valente)

Correspondence to: Prof Enza Maria Valente, Neurogenetics Unit, CSS-Mendel Institute, Viale Regina Margherita 261, 00198 Rome, Italy **e.valente@css-mendel.it**

Joubert syndrome is a congenital cerebellar ataxia with autosomal recessive or X-linked inheritance, the diagnostic hallmark of which is a unique cerebellar and brainstem malformation recognisable on brain imaging—the so-called molar tooth sign. Neurological signs are present from the neonatal period and include hypotonia progressing to ataxia, global developmental delay, ocular motor apraxia, and breathing dysregulation. These signs are variably associated with multiorgan involvement, mainly of the retina, kidneys, skeleton, and liver. 21 causative genes have been identified so far, all of which encode for proteins of the primary cilium or its apparatus. The primary cilium is a subcellular organelle that has key roles in development and in many cellular functions, making Joubert syndrome part of the expanding family of ciliopathies. Notable clinical and genetic overlap exists between distinct ciliopathies, which can co-occur even within families. Such variability is probably explained by an oligogenic model of inheritance, in which the interplay of mutations, rare variants, and polymorphisms at distinct loci modulate the expressivity of the ciliary phenotype.

Introduction

Joubert syndrome is an inherited congenital cerebellar ataxia that is characterised by an unusual midbrain–hindbrain malformation, the molar tooth sign (figure 1), and variable organ involvement. The pathogenic basis of this clinically and genetically heterogeneous disorder relates to the dysfunction of a subcellular organelle, the primary cilium, which makes Joubert syndrome part of an expanding group of disorders collectively called ciliopathies.

The recent advent of next-generation sequencing strategies has enabled impressive progress in our knowledge of Joubert syndrome, with several genes being identified and characterised at the pathophysiological level. In turn, this progress has led to a dissection of the complexity of the primary cilium, to explain how the malfunction of this ubiquitous organelle could result in such a variety of phenotypes, ranging from developmental malformations to progressive defects.

In this Review, we discuss the clinical range and genetic basis of Joubert syndrome, the overlap with other ciliopathies, and the evidence supporting oligogenic inheritance. Finally, we review the multifaceted roles of primary cilia in CNS development and in the function of neuronal cells.

Primary cilium

The primary cilium is an immotile organelle that protrudes from the surface of nearly all cell types. Although long thought to be a vestigial remnant without a relevant function, this organelle has recently become the focus of intensive research that has drawn attention to its many key roles in embryonic development, inherited human diseases, and even tumorigenesis.

Primary cilia emerge from the basal body, a modified centriolar structure anchored to the plasma membrane. Their structural core is the axoneme, composed of nine doublets of microtubules, which is surrounded by a membrane contiguous with the cell plasma membrane but expresses specific signalling molecules. The basal body is joined to the axoneme by the y-shaped fibres of the transition zone, a recently described region that works as a functional ciliary gate, which regulates and restricts the flux of specific proteins to the cilium, to maintain it as a compartmentalised organelle (figure 2).[1–3]

In many adult tissues, primary cilia work as sensors for extracellular signals, and transduce them within cells to regulate tissue maintenance, polarity, or proliferation. The disruption of these sensory functions in specialised cells such as the kidney and bile duct epithelium or the retinal photoreceptors explains many of the organ defects seen in ciliopathies. Moreover, studies have shown that most neuronal cell types possess a primary cilium, which draws attention to its many roles in brain development and function.[4–6]

Clinical range of Joubert syndrome

Epidemiology

Reliable epidemiological data for Joubert syndrome are scarce. A prevalence of between 1 per 80 000 and 1 per 100 000 livebirths is reported by many investigators, but this is probably an underestimate that is indicative of the low awareness of the molar tooth sign in historical texts.[7,8] In the Askhenazi Jewish population, the predicted prevalence of Joubert syndrome is as high as one per 34 000 people because of the presence of the founder mutation Arg73Lys in *TMEM216*, which has a carrier frequency of 1 per 90 to 1 per 100 of the population.[9,10] Similarly, in the Hutterite population, about one in 17 healthy people carry the founder mutation Arg18X in *TMEM237*, leading to a predicted disease prevalence of about one per 150 of the population.[11]

Neurological features and multiorgan involvement

Joubert syndrome can be clinically suspected from as early as the first few months of life, upon the observance of hypotonia, abnormal ocular movements (mainly ocular motor apraxia, nystagmus, and strabismus), and occasionally changes in respiratory pattern, characterised