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CORRESPONDENCE

TSEN54 mutation in a child with pontocerebellar hypoplasia type 1

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Pontocerebellar hypoplasias (PCHs) are genetically determined conditions characterized by disturbances of maturation of the ventral pontine nuclei and hemispheric cerebellar cortex. Characteristic clinical findings (such as progressive microcephaly, the presence of spasticity, the occurrence of dyskinesia), the possible involvement of anterior horn cells (AHCs) of the spinal cord, and the peculiar neuropathological features led to the identification of two major forms, PCH1 and PCH2. In the past few years, mutations in genes encoding subunits of the tRNA-splicing endonuclease (TSEN) complex—*TSEN54* in most of the cases—were detected in patients who displayed classical PCH2 features, or its allelic, more severe PCH4. The genetics of the phenotypically heterogeneous PCH1 is less clear, and, only recently, two genes were identified [2, 3, 5].

In this work, a review of the archival clinical records of three sibs with early onset, complicated AHC disease, and neuropathological features of PCH in one, prompted us to analyze the known genetic causes of PCH, after DNA retrieval from paraffin blocks [3].

Phenotypic heterogeneity was present in this family (Fig. 1). The eldest child (II,2) had died at age 10 months and received a clinical diagnosis of Werdnig–Hoffmann-like disease (*SMN1* gene was normal). His two sisters showed microcephaly and hypotonia at birth, weak tendon reflexes and muscle retraction, multiple cranial nerve involvement, and optic nerve atrophy. Case II,4 died at age 11 years, whereas the more severely affected child II,6 (the proband) died at 20 months because of respiratory failure. Electromyography (EMG) showed a denervation pattern in both girls. The common *TSEN54* mutation (i.e., c.919G > T/p.A307S) was found to be homozygous in case II,6, whereas it was not searched for in her relatives because of the lack of stored biological material. Neuropathological findings in case II,6 (Fig. 2) showed normal size and gyration of both cerebral hemispheres. Both the ventral pons and the olivary profiles were shrunken. The cerebellum was remarkably small, with shallow hemispheric sulci; the left hemisphere was softened; only the anterior portion of the vermis was present. There was severe cell loss of the ventral pontine nuclei and, to a less extent, of the raphe neurons. Transverse pontine fibers were also reduced, whereas long fiber tracts were preserved and properly myelinated. Inferior olivary nuclei (ION) showed a normal, convoluted profile, with evidence, however, of neuronal cell loss. Arcuate nucleus was hypoplasic. Intense gliosis of both pontine and medullary structures was present. A large cystic lesion filled the *centrum semiovale* of the left cerebellar hemisphere. The cerebellar folia were reduced in number and size, and they were missing on the basal cerebellum. There was a dramatic loss of both internal granule neurons and Purkinje cells, and some folia were completely devoid of neurons. Thin axonal bundles could be detected in the lamellae axis. Dentate nuclei remnants were detected. Intense gliosis was spread over the cerebellar tissue. There was neuronal cell loss of the anterior horns of the cervical cord and moderate gliosis. Some neuronal cell loss was detected of the telencephalic cortex and thalamic nuclei. Myelination occurred properly throughout the neural structures.

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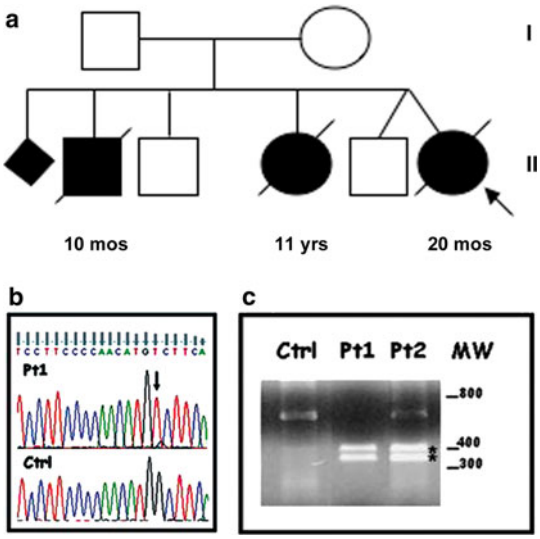

Fig. 1 Genealogic tree of the reported family (**a**). The age of death of the affected children is outlined. The proband is indicated with an *arrow*. Identification of the common *TSEN54* mutation in the proband (**b**). Electropherogram of the sequence flanking the c.919G > T/p.A307S mutation (*arrow*) detected in the proband (*Pt1*) as compared to a normal control (*Ctrl*). Rapid determination by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis of the c.919G > T/p.A307S mutation (**c**), homozygous in the proband (*Pt1*) and heterozygous in an unrelated patient (*Pt2*). The mutation introduces a single site of cleavage for *Nsp*I, resulting in fragments sized 402 and 349 bp (*asterisks*). The wild-type sequence remains uncleaved, whereas the heterozygote shows fragments sized 751, 402, and 349 bp. *Ctrl* control DNA, *MW* 100-bp DNA molecular marker size

The case herein described stands among the most severe descriptions of PCH1 [4]. The pathological features show regressive patterns, such as the features of the cortical lesions and the cystic cavitation, and are consistent with a progressive process of early onset, as guessed by the hypodense lesion of the left cerebellar hemisphere observed in the proband by brain computed tomography scanning.

The topography of the pontocerebellar lesions is shared between PCH1 and PCH2 [1]. Differences are related to the pattern of the ION, which may show a fetal morphology, and the cerebellar changes, which can be much more severe in PCH1. From this perspective, a "continuum" pattern of lesions between PCH1, PCH2, or PCH4 would justify the involvement of a single gene. The common *TSEN54* mutation accounts for >90% of described alleles associated with early (PCH4) or late (PCH2) fatal outcome, and PCH1 can be added to the spectrum of possible phenotypes.

TSEN54 expression is strictly restricted to the structures affected in PCH during human development by the 20–28th week of gestation. It can be assumed that impaired gene function can account for the developmental pathology observed in PCH. Interestingly, however, *TSEN54* is not expressed in anterior horns, whose neuronal loss is thought to anatomically distinguish between PCH1 and PCH2. The heterogeneous neuropathological features seen in PCH call for further understanding of the role of TSEN complex in AHC neurons.

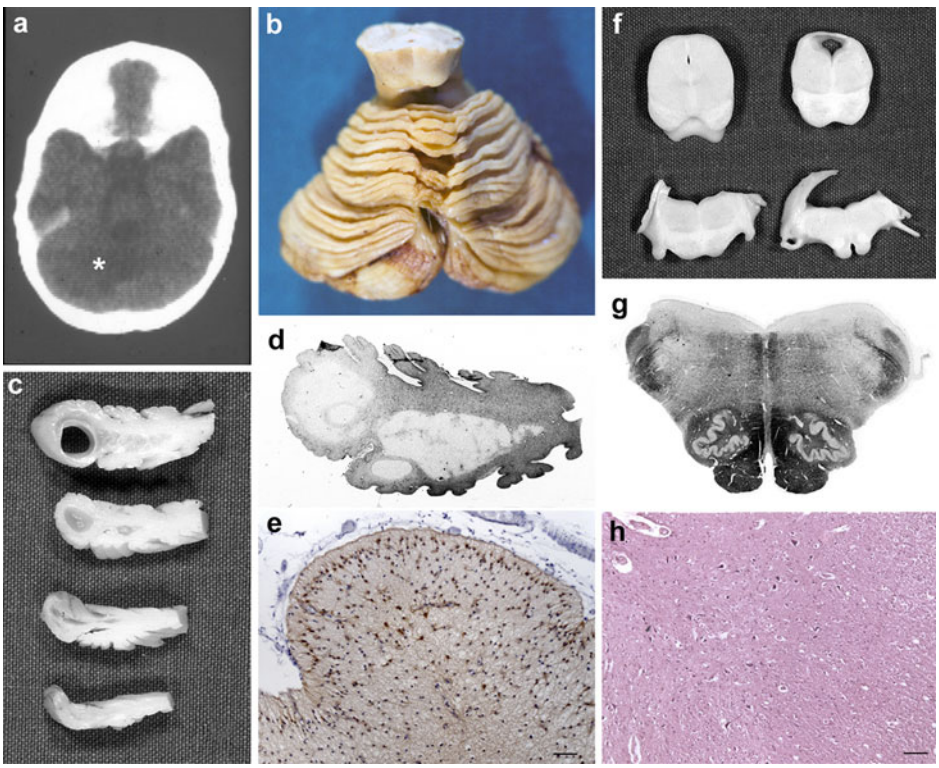

Fig. 2 Large hypodense area (*asterisk*) of the left cerebellar hemisphere. Computed tomography (CT) scan at age 9 months (**a**). Marked cerebellar atrophy as depicted by the deep sulcation of the hemispheres (**b**), the reduced number of folia, and the extremely thin cortical ribbon; note the cystic cavitation of the *centrum semiovale* (**c**, **d**: Nissl stain). Intense gliosis of a markedly hypoplasic folium, with cortical neurons replaced by reactive astrocytes (**e**; glial fibrillary acidic protein (GFAP) immunohistochemistry, *bar* 50 μm). Severe atrophy of the ventral pons, well-preserved cerebral peduncles and pyramids. Normal pattern of the inferior olivary nuclei and proper myelination of the pyramids (**f**, **g**: Woelcke stain modified for myelin). Remarkable cell loss of the anterior horn cell (AHC) (**h**; cervical spinal cord, HE stain, *bar* 100 μm)

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Conflict of interest The authors declare that they have no conflict of interest.

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