CASE REPORT

A prenatal case of lissencephaly with cerebellar hypoplasia: New mutation in RELN gene

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Abstract

Reelinopathies cause a distinctive lissencephaly type associated with cerebellar hypoplasia. To help further management, we wanted to report here the first prenatal diagnosis due to a homozygous inherited reelinopathy.

KEYWORDS

cerebellar hypoplasia, lissencephaly, reelinopathy, RELN

1 | INTRODUCTION

Lissencephaly is a set of rare brain disorders where the surface of the brain appears smooth, resulting from an impaired neuronal migration during organogenesis. Reelin (RELN) gene mutations cause a distinctive lissencephaly type associated with cerebellar hypoplasia. We report here the first prenatal diagnosis due to a homozygous inherited reelinopathy.

We define Lissencephaly as a rare congenital brain malformation in which cortex appears smooth, from Ancient Greek λισσός (lissós, "smooth"), due to reduced cerebral convolutions, consequence of a disorganization of the six cortical layers.[1] This is caused by an impaired

neuronal migration during the embryonic development. Patients usually suffer from severe neurological disorders and epilepsy. The lissencephaly phenotype embeds several pathologies which are commonly classified in type 1 and type 2, the latter often associated with systemic malformations.[1] However, their classification remains complex as the number of causative genes and the understanding of pathophysiological mechanisms of the proteins involved constantly increase.[2]

Mutations in reelin gene, RELN, have an autosomic recessive or dominant inheritance. In the latter, the phenotype includes focal epilepsy associated with auditory symptoms (auras) and aphasia (MIM 616436), while mutations of RELN with a recessive inheritance (MIM 257320)

are known to cause a distinctive lissencephaly where the cerebellum presents severe abnormalities, called lissencephaly with cerebellar hypoplasia (LCH).[2,3] Reelin is an extracellular matrix-associated glycoprotein produced by Cajal-Retzius cells during brain development.[4] It plays an important role in post-mitotic neuronal migration.[5]

We report here the first prenatal diagnosis of lissencephaly due to a homozygous inherited reelin gene mutation.

2 | CASE REPORT

Our patient, a healthy 33-year-old Iranian woman, gravida 6, para 4, was followed by our genetic department since the couple had already two boys with, respectively, intellectual disability and epilepsy for the first child, impaired neurological development and severe epilepsy for the second one and two daughters with behavioral disorders. Our patient and her husband are related. Genetic analysis, through next-generation sequencing (NGS), showed that parents are heterozygous for c.2972G>A (p. Trp991*) mutation (chromosome 7, exon 22) of the RELN gene with a recessive inheritance. The first boy was found homozygous for this mutation and the second heterozygous for the RELN gene mutation and carrier of a de novo 17q12 deletion.

For this fifth pregnancy, the fetus presented a 3-mm nuchal translucency (NT) at 12 weeks of gestational age (GA). The non-invasive prenatal test (NIPT) did not detect fetal aneuploidy for a female fetus. Due to follow up in different hospitals, the physician was not aware of the exact genetic diagnosis at the first trimester ultrasound so an early second trimester scan was organized and meanwhile gather the family genetic analysis. At 15 weeks of GA, ultrasound (US) findings were given as: persistent nuchal edema, retrognathia, abnormal posterior fossa with suspicion of cerebellar herniation, femoral bones inferior

to percentile five and echogenic bowels and kidneys. An amniocentesis (AC) was accepted by the parents. At 21 weeks of GA we observed additional findings: partial agenesis of cerebellar vermis, abnormal Sylvian sulcus, hypertelorism, prefrontal edema, sloping forehead, and clenched hands. Furthermore, the 31-week US showed lissencephaly (Figure 1A,B), an abnormal facial profile with a long philtrum and ascites with a consequent estimated fetal weight above the 99th percentile. Amniotic fluid and fetal dopplers were normal, but fetal movements were reduced. A fetal Magnetic Resonance Imaging (fMRI) confirmed the lissencephaly, the cerebellar hypoplasia and the opercular dysplasia and showed a bilateral mild ventriculomegaly at 11 mm (Figure 2A,C). The array-based comparative genomic hybridization (CGH) was normal but the targeted polymerase chain reaction (PCR) for the RELN gene was positive for the known mutation in a homozygous state. A termination of the pregnancy (TOP) was offered after the positive AC and accepted at 32 weeks of GA. A 2500 g stillborn girl was delivered. Post-mortem analyzes were refused.

3 | DISCUSSION

Lissencephaly includes different types of brain malformations characterized by a smooth appearing cortex due to an impaired neuronal migration. Its incidence is rare and estimated at 1/100.000 births.[1] Lissencephaly is part of a heterogenous group of malformations of cortical development (MCD). The classification of MCD has changed and evolved through the last decades since there have been a lot of improvements in the field of the cerebral embryology as well as in the discovery of the causative genes and the underlying altered cellular signalization. The latest update of their classification is based on the involved impaired mechanism.[6] Lissencephaly is included in group II, englobing
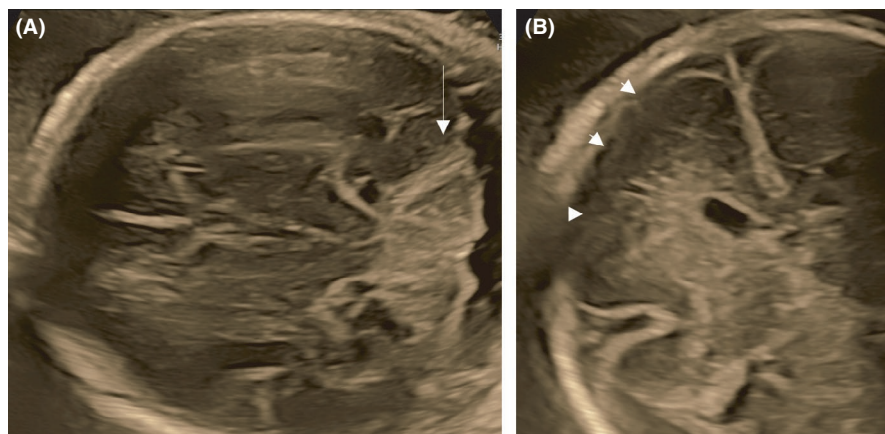
FIGURE 1 Axial (A) and coronal (B) US scans of the fetal brain at 30W of GA showing the cerebellar hypoplasia (arrow) and the suspected lissencephaly (arrow heads)

FIGURE 2 Sagittal and coronal MR images on the fetus (A,C) and a normal one for comparison (B,D) at 31 weeks. The fetus presents cerebellar and vermis hypoplasia (arrow) with poor gyration and abnormal Sylvian operculation (arrow heads)
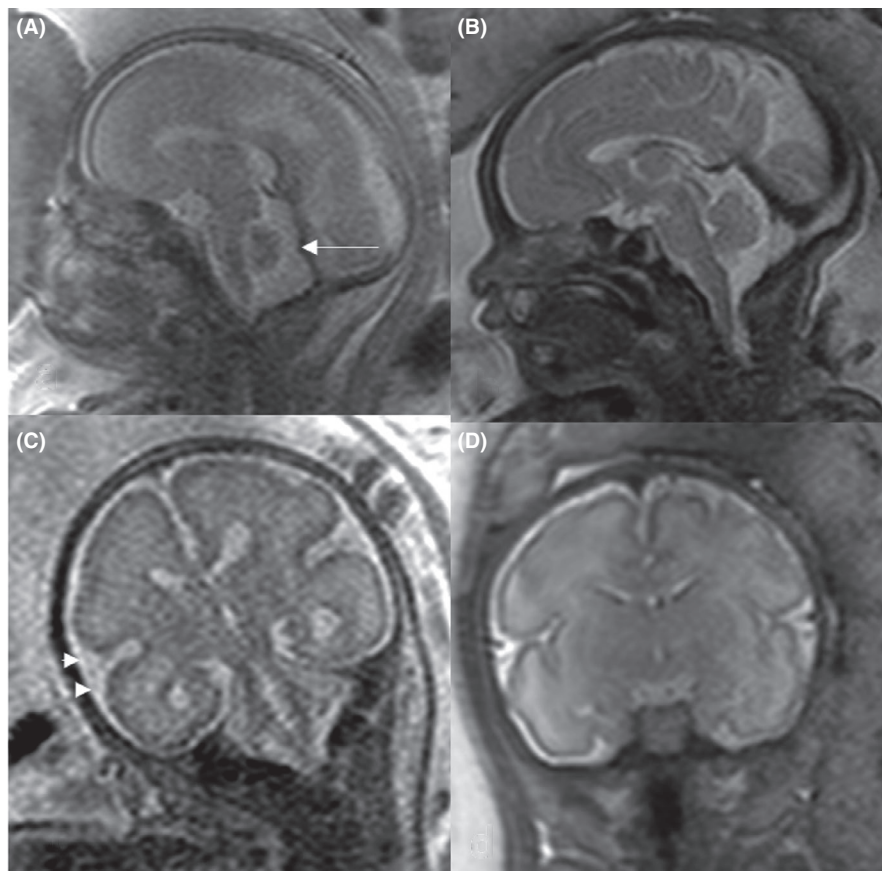
malformations due to an abnormal neuronal migration, whether it occurs in the neuroependyma, through the mantle or in the terminal migration.[6]

Neuronal migration starts in the early fetal life, from 12 weeks of GA and continues until 24 weeks of GA.[7] If this migration is disrupted, it can result either in lissencephaly, heterotopia, agyria, or pachygyria. Thus, US findings of lissencephaly can be theoretically observed in experts' hands from the early second trimester.[8] However, if no indirect signs are observed, such as microcephaly and/or ventriculomegaly, lissencephaly is then often not suspected until the routine scan of the third trimester (30–32 weeks of GA) as this is the best period to study the cortical gyration.[9] Once a lissencephaly is suspected, proposing a fMRI is mandatory if available. Fetal cerebral MRI gives the final prenatal diagnosis, since it provides further details about the cerebral parenchyma as it has a better contrast resolution than US.[8]

In our case, second trimester US showed partial agenesis of cerebellar vermis and an abnormal Sylvian sulcus, but true lissencephaly was only suspected at the third trimester. The fMRI confirmed both the lissencephaly and the cerebellar hypoplasia and it also showed an opercular dysplasia (abnormal Sylvian sulcus). Familial history and US abnormalities prompted us to look for the RELN gene mutation after amniocentesis. A prenatal diagnosis of lissencephaly with cerebellar hypoplasia, secondary to

the known mutation of the RELN gene in a homozygous state, was then possible.

Point mutations, intragenic deletions, reciprocal translocations, and pericentric inversions of the RELN gene in a homozygous or compound heterozygous state, have been described as causing a particular type of lissencephaly associated with cerebellar hypoplasia (LCH).[3,4,10,11] Other genes are involved in this particular type of lissencephaly, such as mutations in tubulin genes (TUBA1A, TUBB2B) and in the very low density lipoprotein receptor (VLDLR) gene.[2,3] However, if reelin pathway is impaired, the LCH presents with particular phenotypic features: an anterior predominant lissencephaly, severe cerebellar hypoplasia, and hippocampal malformations.[3]

Identifying the causative gene mutation of a rare disease is one of the key points in order to provide the best counseling to the patients and their families, to assess the recurrence risk, to give prognosis information to the multidisciplinary team following the patients, and to allow future prenatal diagnosis.[2] Our patient's clinical presentation, the presence of a proband and the family segregation analysis (Figures 3 and 4) guided the targeted gene identification and allowed a prenatal diagnosis. We could thus give a counseling for the ongoing pregnancy.

Additionally, the second child has a de novo 17q12 deletion. The syndrome related to this de novo deletion combines neurodevelopmental and psychiatric disorders,
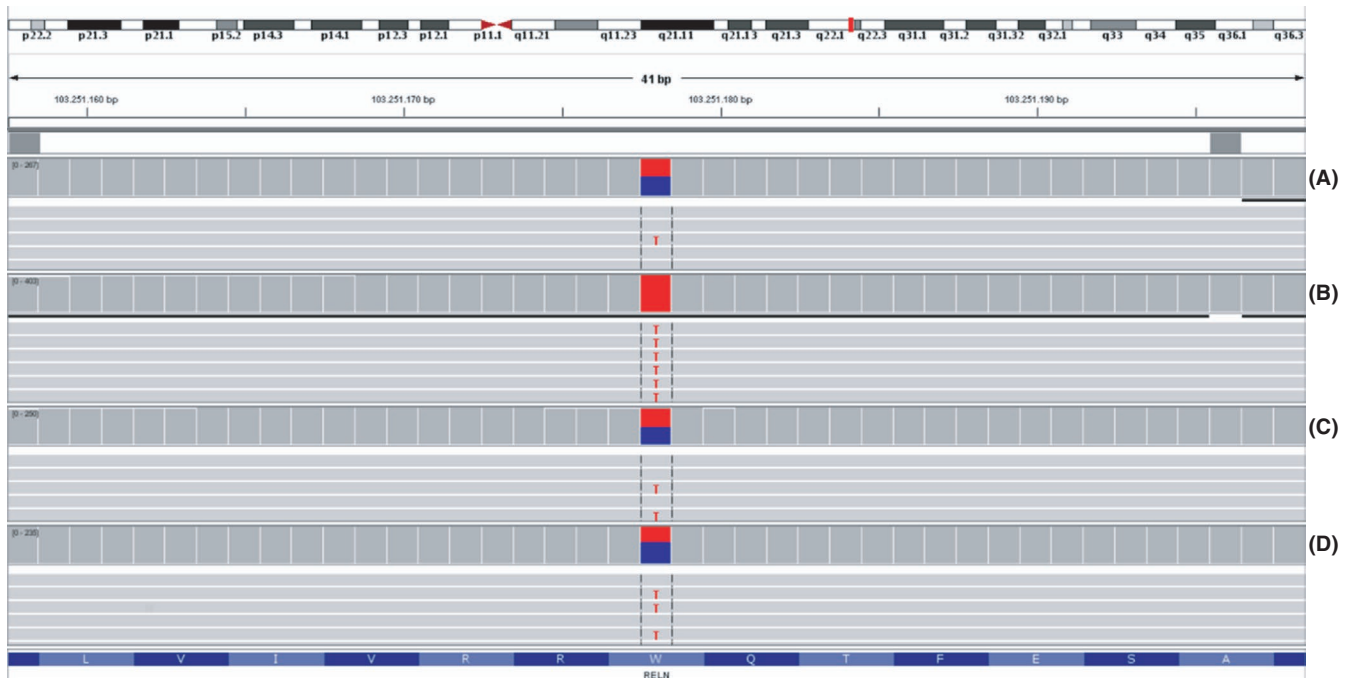
FIGURE 3 Illustration highlighting the family genic situation through the result of the targeted PCR. In blue, non-altered gene and in red c.2972G>A mutation. A, First born child (heterozygous). B, Affected child (homozygous). C, Father (heterozygous). D, Mother (heterozygous)
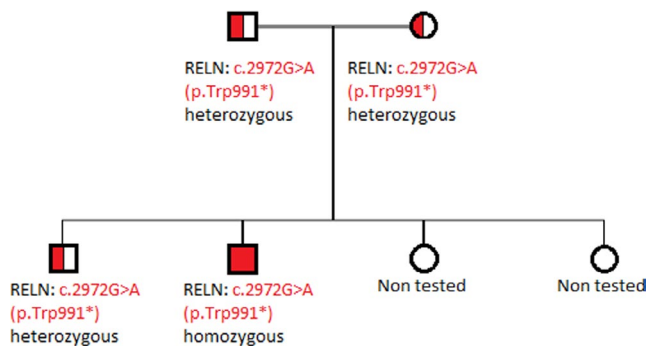
FIGURE 4 Genealogic scheme of the family's situation

renal and urinary tract abnormalities and diabetes which could explain his clinical phenotype. However as said before, he is also carrier of a heterozygous mutation of RELN. The role of this latter mutation in the final phenotype of the child is still unclear as the parents are asymptomatic even if they are also carrier of the RELN mutation at heterozygous state. Functional studies would be useful. To this day, we are still awaiting the genetic results of the girls and as the couple wants another pregnancy, a new appointment with the geneticists is scheduled.

To our knowledge, this is the first report of the c.2972G>A (p. Trp991*) in the literature, and the first case of RELN prenatal diagnosis reported. This case report adds further information on the field of MCD and contributes to their improving knowledge.

CONFLICTS OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
CB and GG: wrote the article. CV, JD, JS, KVB, and KK analyzed the genetics data. MC, TC, WBA, and XK served as the author of the antenatal ultrasound examinations. GG, JD, and MC: coordinated the final version of the manuscript.

CONSENT
The patient and her husband signed an informed consent for genetic analysis and case publication.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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