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Prenatal diagnosis of familial corpus callosum dysgenesis (Raynaud–Claes Syndrome) associated with CLCN4 variant: a case report

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Introduction

Raynaud–Claes syndrome is an extremely rare X-linked dominant disorder caused by pathogenic variants in CLCN4 (Xp22), which encodes the CIC-4 channel, a voltage-dependent 2Cl⁻/H⁺ exchanger prominently expressed in the hippocampus and cerebellum. The clinical spectrum ranges from mild to severe intellectual disability, with impaired language development, structural brain anomalies, facial dysmorphism, hypotonia, and drug-resistant epilepsy. Female carriers may exhibit milder clinical manifestations.

Case Presentation

A 29-year-old woman, gravida 2 para 1, was referred at 22+2 weeks' gestation for non-visualization of the cavum septum pellucidum on a detailed obstetric ultrasound. Perinatology evaluation confirmed agenesis of the cavum septum pellucidum and dysgenesis of the corpus callosum. Her son, born in 2020, has drug-resistant epilepsy, psychomotor developmental delay, strabismus, and cryptorchidism; brain magnetic resonance imaging at one year of age demonstrated hypoplasia of the caudal corpus callosum.

Family History & Genetic Testing

Whole-exome sequencing in the affected son revealed a hemizygous CLCN4 variant, and subsequent family screening showed that the mother was heterozygous for the same variant. In the current pregnancy, amniocentesis was performed, and karyotype analysis along with targeted genetic testing based on the family history was carried out. Targeted genetic testing revealed a heterozygous NM_001256944.2 c.509T>G (p.Val170Gly) variant in the CLCN4 gene. To our knowledge, this missense variant has not been previously reported in the literature, and this family represents the first described case of this CLCN4 variant.

Discussion

Absence of the cavum septum pellucidum on routine ultrasound should prompt detailed neurosonographic evaluation. A detailed family history, in this case, the presence of a son with drug-resistant epilepsy and developmental delay, played a key role in reaching the diagnosis. X-linked inheritance should be considered when male family members present with neurodevelopmental abnormalities. Identification of the causative variant enables informed genetic counselling and reproductive planning, including the option of prenatal diagnosis or preimplantation genetic testing in future pregnancies.

Conclusion

A detailed family history and targeted molecular testing were essential for prenatal diagnosis of this rare X-linked syndrome. To our knowledge, the NM_001256944.2 c.509T>G (p.Val170Gly) missense variant has not been previously reported in the literature. Therefore, this family represents the first reported case of this variant in the CLCN4 gene.



Figure 1. Axial neurosonographic view at 24 weeks demonstrating absence of the cavum septi pellucidi.

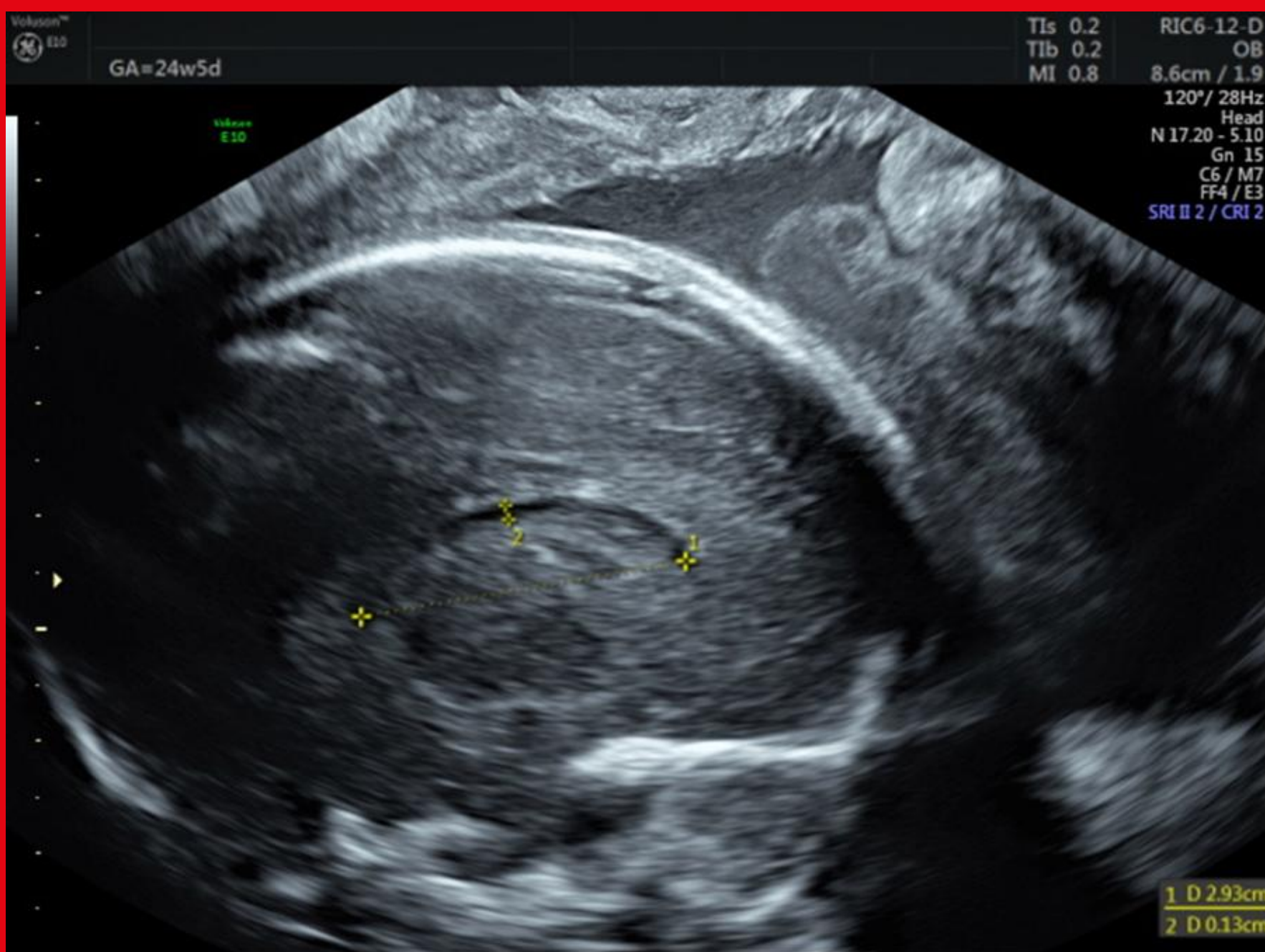


Figure 2. Midsagittal view demonstrating dysgenesis of the corpus callosum.

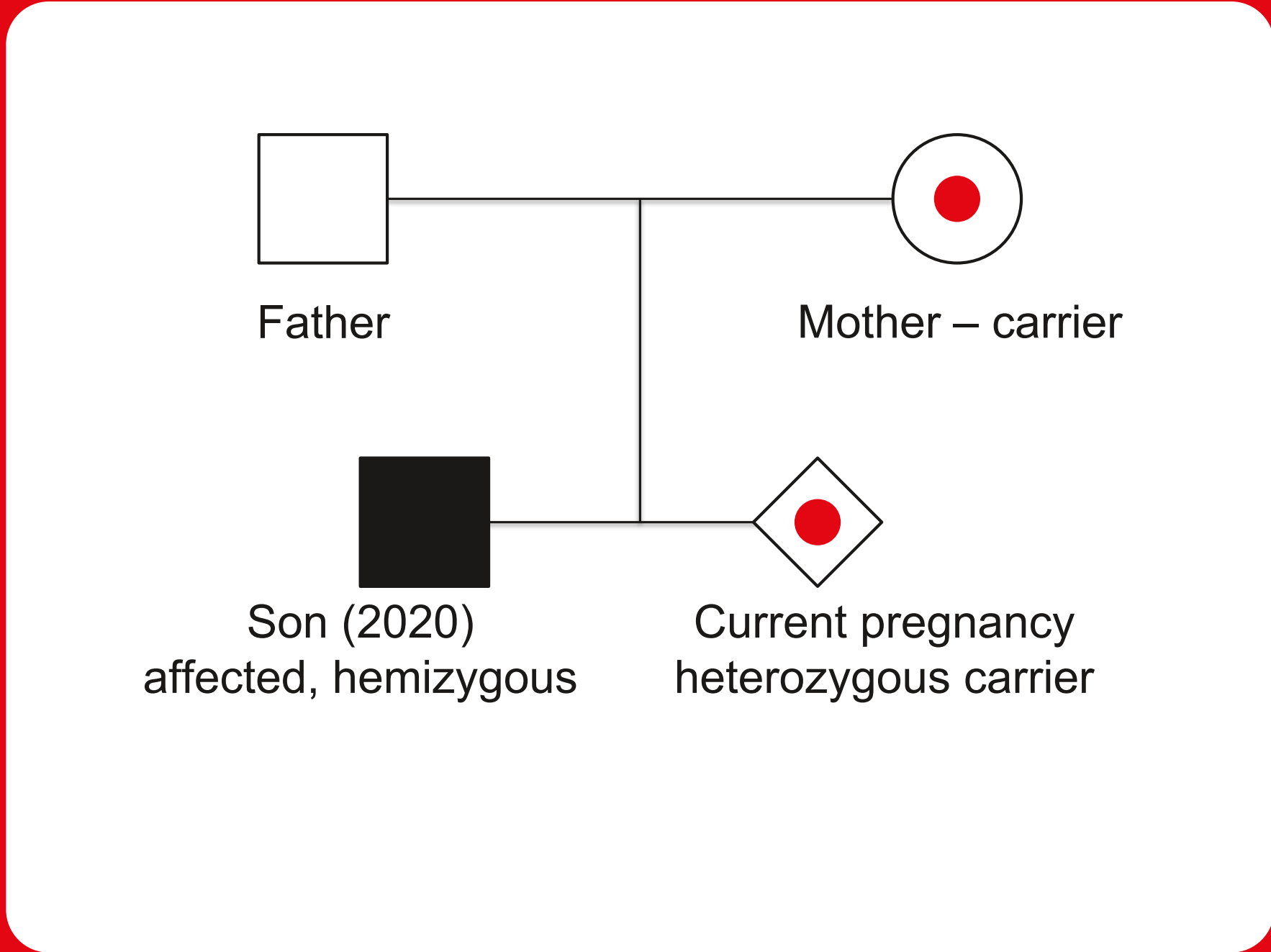


Figure 3. Family pedigree illustrating CLCN4 inheritance: unaffected father, heterozygous-carrier mother, affected hemizygous son (b. 2020), and a heterozygous-carrier fetus in the current pregnancy.