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Homozygous Missense Mutation in *ABR* Causes Cerebellar Hypoplasia with Early Lethality – A New Condition Identified by Exome Sequencing?

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We performed whole exome sequencing (WES) in a consanguineous Pakistani family with a recurrent pattern of cerebellar hyposplasia, intra-uterine growth restriction, and various CNS/non-CNS malformations, resulting in early lethality (1 perinatal death and 1 intrauterine death). Karyotype (in the first pregnancy) and oligonucleotide array (in the 2nd affected pregnancy) were normal. Parents declined post-mortem examination. By WES, a novel homozygous missense mutation was identified in the *ABR* gene (*ABR*: NM_021962.4:c.G2455T: p.A819S) in both affected pregnancies. Both parents were identified to be heterozygous of the same mutation while the healthy child did not carry any mutation. The mutation is located in a highly conserved region and is predicted to be highly damaging by all the commonly used *in silico* mutation prediction tools. The protein encoded by *ABR* gene contains a GTPase-activating protein domain, a domain found in members of the Rho family of GTP-binding proteins. Previous reports showed that *OPHN1*, mutations in which cause X-linked mental retardation with cerebellar hypoplasia (OMIM300486), also encodes for a regulator of GTPase-activating protein. Both *OPHN1* and *ABR* are highly expressed in the human brain especially in the cerebellum, and both contain a GTPase-activating domain. Rho proteins are important mediators of intracellular signal transduction, which affects cell migration and cell morphogenesis. Other studies have demonstrated a regulatory role of Rho GTPase in differentiation of cerebellar neurons, and that ethanol-associated impairment of Rho GTPase might contribute to brain defects in fetal alcohol syndrome. Further functional studies, including zebrafish morpholino studies, are currently ongoing. WES can be helpful in individual families with undiagnosed lethal MCA syndromes to identify potentially responsible autosomal recessive mutations and may lead to a better understanding of the role of various developmental pathways in human embryogenesis.