Rare maternal inheritance of ARFGEF1-variant associated developmental disability: A case report

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Introduction

Developmental delay, impaired speech, and behavioral abnormalities, with or without seizures (DEDISB) (OMIM #619964) is a neurodevelopmental condition associated with heterozygous pathogenic variants in *ARFGEF1* (OMIM #604141). Previously reported cases have occurred both *de novo* and via autosomal dominant inheritance. Of the inherited cases, most have been passed down from the father. Here we report a novel case of DEDISB inherited from a symptomatic but undiagnosed mother.

Case Presentation

Neonatal History

- Male was born to a 22-year-old G2P1>2 mother via a classic C-section
- Prenatal ultrasound: hydrocephalus, Dandy-Walker malformation, macrocephaly, and reduced fetal activity
- Age 2 days: Ventriculoperitoneal and cystoperitoneal shunts placed

Additional Medical History

- Age 2 months: Diagnosis of focal epilepsy following multiple seizures
- Age 16 months: Presented to the genetics clinic with motor and speech delays, strabismus, frontal bossing, low-set ears, hypertelorism, down-slanting palpebral fissures, high arched palate, and inguinal hernia
- Age 2 years: Family reports tantrums and head banging; now also receiving physical therapy

Maternal History

- Maternal grandmother was taking coumadin during her pregnancy with the patient's mother
- Childhood: Diagnosed with epilepsy, hydrocephalus, and brain cyst
- Adulthood: Diagnosed with pulmonary stenosis and psychiatric conditions (aggression, bipolar disorder, oppositional defiant disorder, post-traumatic stress disorder)
- Phenotype allegedly attributed to Warfarin embryopathy, although this diagnosis does not appear in the medical chart
- Warfarin embryopathy can be characterized by central nervous system changes, like hydrocephalus, but also typically includes skeletal abnormalities and respiratory difficulties[1]

Exome Sequencing

- Pathogenic heterozygous variant of maternal origin in *ARFGEF1* (c.4208+2T>C, p.?)

Discussion

- The variant detected in *ARFGEF1* is diagnostic for DEDISB, also known as autosomal dominant *ARFGEF1*-related neurodevelopmental spectrum disorder
- 21 cases of DEDISB have been reported in the literature[2-5]
- Fine and gross motor impairment, dysmorphic features, strabismus, abnormal brain findings, and epilepsy are features associated with DEDISB seen in this patient
- Intellectual disability, speech delay, and behavioral challenges are features associated with DEDISB that are emerging in this patient
- 52% of cases are *de novo* and 24% are paternally inherited variants[2-5]
- This case is only the second known report of a maternally inherited variant in DEDISB
- While the mother presented with some features of Warfarin embryopathy, it is likely that her clinical presentation is better explained by DEDISB

Conclusion

We report a case of DEDISB in a patient with a maternally inherited variant in *ARFGEF1*. This is the second known case of maternal inheritance of an *ARFGEF1* variant. The novel findings suggest the need to follow both the patient and mother for a better assessment of genotype-phenotype correlation in a heritable case of DEDISB.

References

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	Case Patient	A1	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	C1	C2	C3	C4	C5	D1	D2
Age on referral or follow-up	16 mo.	6 mo.	6 yrs.	10 yrs.	14 yrs.	11 yrs.	5 yrs.	3 mo.	9 yrs.	11 yrs.	10 yrs.	13 yrs.	11 yrs.	32 yrs.	10 yrs.	7 mo.	2 yrs.	2 yrs.	3 yrs.	2 yrs.	Prenatal	UN
Sex	M	M	M	M	M	M	M	M	M	M	F	M	M	M	M	M	M	M	M	F	F	M
Speech Delay	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	N/A	+
Motor Delay	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	N/A	UN
ID	+	UN	+	+	-	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	N/A	+
Epilepsy	+	+	-	-	+	+	+	+	+	-	-	-	-	-	+	+	+	+	+	+	N/A	UN
Autism	UN	UN	-	+	-	-	-	-	-	+	-	+	-	-	-	-	-	+	-	-	N/A	+
ADHD, attention issues, hyperactivity	UN	UN	-	-	-	-	+	+	+	-	+	+	+	-	+	-	-	-	-	-	N/A	-
Aggression, Tantrums	+	UN	-	-	-	+	+	-	+	+	-	-	-	+	+	-	-	-	-	-	N/A	-
Hydrocephalus	+	UN	-	-	-	-	-	-	-	-	-	UN	UN	UN	-	-	-	-	-	-	+	UN
Myelination Delay	-	UN	-	+	-	-	-	-	-	+	+	UN	UN	UN	-	-	-	-	-	-	-	UN
Other Brain MRI Findings	+	UN	+	-	+	-	-	-	+	-	-	UN	UN	UN	+	-	-	-	-	+	+	UN
cDNA variants	c.4208+2 T>C	c.4365 C>A	c.2392 G>A	c.5320 C>T	c.3592–2 A>G	c.2158 del	c.C2524 T	c.2923_ 2924dup	c.1006 delA	c.1942 C>T	c.1942 C>T	c.3697 C>T	c.3697 C>T	c.4033 C>T	c.2395 C>T	c.2850+ 2T>A	c.4951 delG	c.917-1 G>T	c.3539 T>G	c.2923_c .2924del CT	c.3814 C>T	c.3814 C>T
Amino acid variants	p.?	p.Cys14 55Ter	p.(Asp7 98Asn)	p.(Arg17 74*)	p.?	p.(Leu72 0Serfs *24)	p.(Gln 842*)	p.(Cys 976 Phefs*6)	p.(Met 336Trp fs*2)	p.(Gln 648*)	p.(Gln 648*)	p.(Gln 1233*)	p.(Gln 1233*)	p.(Arg 1345*)	p.(Arg 799*)	p.?	p.Ala 1651Gln fs*24	p.?	p.Ile 1180Arg	p.Leu 975Pro fs*41	p.R 1272*	p.R 1272*
Familial segregation	Maternal	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	Paternal	Paternal	Paternal	Paternal	Paternal	UN	Not mat., pat. UN	*De novo*	*De novo*	Maternal	*De novo*	*De novo*	Not mat., pat. UN	Not mat., pat. UN

Table 1 – Features and molecular findings observed in the 21 additional cases reported in the literature. Like our patient, the majority of cases are in males and present with speech delay, motor delay, and intellectual disability (ID). Over half of reported cases presented with epilepsy. Only one other patient has been reported to have had hydrocephalus, but nine other cases in general had some abnormal brain MRI findings. Of note, the genetic change in our patient has not been reported before. The one other known case of maternal inheritance exhibited a similar phenotype to this patient but did not have abnormal brain MRI findings. Case A1 from Teoh et al., cases B1-B13 from Thomas et al., cases C1-C5 from Xu et al., and D1-D2 from Coltri et al. M – Male. F – Female. UN – Unknown. ADHD – Attention-Deficit/Hyperactivity Disorder.