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Supplemental Information

DVL3 Alleles Resulting in a −1 Frameshift of the Last Exon Mediate Autosomal-Dominant Robinow Syndrome

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Table S1. Phenotypic features of *DVL1*-mediated Robinow syndrome

	Citation	**Current**	**White et al (2015) *Am J Hum Genet 96*:612-622**								TOTAL
	Individual ID	BAB8062	BAB4073	BAB4878	BAB5264	016462	016516	016517	017604	030526	
	Current age	1yr	11 yr	22 yr	6 yr	20 yr	21 yr	21 yr	15yr 6 ms	42	
	Genotype	c.1522delC	c.1570_1571delinsC	c.1505_1517del ACCCGGCTGCCC	c.1519delT	c.1505_1517del ACCCGGCTGCCC	c.1508delC	c.1508delC	c.1615del	c.1529delA	
	De novo	+	+	+	NA	+	+	+	+	NA	
	Gender	M	F	F	M	F	M	M	M	F	
Growth	Height percentile	<3%	10%	17%	<3%	70%	90%	75%	80%	<3%	
	OFC SD	ND	+4 SD	+2.5 SD	>+2 SD	>+4 SD	>+4 SD	>+4 SD	>+4SD	> +6 SD	
Facial features	Macrocephaly	+	+	+	+	+	+	+	+	+	9/9
	Frontal bossing	+	+	+	+	+	+	+	+	+	9/9
	Hypertelorism	+	+	+	+	+	+	+	+	+	12/12
	Upslanting palpebral fissures	+	+	+	-	ND	-	-	-	-	3/9
	Prominent eyes	+	+	-	+	ND	+	+	-	+	6/8
	Anteverted nares	+	+	+	+	+	+	+	-	ND	7/8
	Depressed nasal bridge	+	+	+	+	ND	+	+	+	+	10/10
	Short nose	+	+	+	+	+	+	+	+	+	11/11
	Gingival hyperplasia	+	+	+	+	+	+	+	+	-	10/12
	Cleft soft palate	+	+	-	-	ND	-	-	-	-	4/11
	Dental anomalies	+	+	+	+	+	+	+	+	+	12/12
	Micrognathia	+	+	-	+	+	-	-	-	-	4/9
Skeletal	Mesomelia	+	+	+	+	+	+	+	+	+	9/9
	Brachydactyly	+	+	+	+	+	+	+	-	+	10/12
	Clinodactyly	+	+	+	+	+	-	-	+	+	7/9
	Bifid phalanges	-	-	-	-	ND	+	+	ND	-	4/9
	Scoliosis or kyphosis	+	-	-	-	+	-	-	+	+	4/10
	Pectus anomaly	+	+	+	-	ND	+	+	+	-	7/9
	Increased bone density (skull)	+	ND	+	ND	+	-	-	+	ND	7/9
Other features	Hearing loss	-	-	-	+	+	-	-	-	+	3/9
	Sacral dimple	+ (+dimple between scrotum and anus)	+	-	ND	ND	-	-	-	-	3/9
	Absent anterior nasal spine	+	-	-	-	+	-	-	-	+	3/9

Abbreviations are as follows: +, Present; -, Absent; F, Female; M, Male; ND, No data; NA, Not available; OFC, Occipitofrontal Circumference.

Supplemental Note: Case reports

BAB7990

BAB 7990 is a female patient born from a healthy mother and an affected father. She was born with omphalocele, short gut, multiple congenital heart defects (hypoplastic right heart, ventricular septum defect (VSD), pulmonary atresia), chronic lung disease with tracheomalacia and cleft palate, requiring multiple surgeries and a tracheostomy. She was developmentally delayed presumed to be due to multiple medical interventions. She walked at age 3y and spoke at age 5y. She is intellectually normal and attends regular school at the age appropriate grade. Clinical examination at age 10y noted short stature, midface hypoplasia, short neck, prominent eyes, upslanted palpebral fissures, long eyelashes, hypertelorism, bushy eyebrows, short nose with anteverted nares, long philtrum, downslanted mouth corners, bifid short tongue, gingival hyperplasia, dental malalignment, anteriorized anus, single palmar crease on the left hand, large duplicated thumb, camptodactyly, syndactyly. Upon physical evaluation she displayed mesomelia with both upper and middle arm segments below 5th centile, more pronounced in the middle segment. She has pectus excavatum and urinary reflux. Sanger sequencing did not show *DVL1* mutations.

Father of BAB7990

BAB 7990 (Father) is a male patient born from a non-consanguineous healthy couple. He was examined by us at age 33. Clinical examination noted short stature (3rd centile), midface hypoplasia, epicanthal folds, long eyelashes, upslanted palpebral fissures, hypertelorism, wide nasal bridge, short and wide nose, anteverted nares, long philtrum, downturned mouth corners, cleft lip and palate, bifid tongue, microretrognathia and dental malocclusion. His arms have mildly mesomelic shortening. He has brachydactyly, large thumbs, clinodactyly, large halluces, pectus excavatum. He was born with omphalocele.

He was diagnosed with Robinow syndrome just after his daughter's birth. He has yet to be tested for *DVL3* mutations.

BAB4569

She was born by C-section at 40 weeks of gestation from non-consanguineous parents and had no major problems during the neonatal period. She has a fraternal female twin. Though her development was normal she had physical and speech therapy. She walked at 15 months and spoke at 18 months. She graduated college as a nurse. Clinical examination at age 25 years old revealed that she weighed 62kg (<75^{th} centile), height 144 cm (<3^{rd} centile). She displayed mesomelia based on physical evaluation with forearm <5^{th} centile and arm $5^{th-10th}$ centile. She has only 22 permanent teeth and had a submucous cleft palate. She was born with a VSD. She has bilateral cataracts and 50% unilateral hearing loss. She underwent breast reduction surgery, and had cystic ovaries and had premature menopause. Her genitalia were referred to as normal. She was screened for mutations in *WNT5*A and no mutations were found. Whole exome sequencing did not show variants in *WNT5A* or *ROR2*.

015902

015902 is a female patient born from a non-consanguineous couple. At clinical examination at age 27y she is obese, has short stature, macrocephaly (>98^{th} centile), midface hypoplasia, upslanted palpebral fissures, hypertelorism, downturned mouth corners, bifid tongue, gingival hyperplasia, retrognathia, webbed neck. She has several missing teeth. Examination was performed after facial esthetical surgeries. She has mesomelic limb shortening, short hands, brachydactyly, large halluces and a sandal gap by physical evaluation. The mother is reported to have a similar phenotype but she was not examined or tested. Screening of *WNT5A* and *DVL1* identified no pathogenic variants.

BAB7982

BAB 7982 is a 12 year old male patient born from non-consanguineous healthy parents. At birth he presented with cleft lip and palate, undescended testicles, persistent ductus arteriosus (PDA), patent foramen ovale (PFO) and tricuspid regurgitation. On physical examination at age 13 months he had short stature (length 3rd centile), frontal bossing, broad nasal root, hypertelorism, short nose with anteverted nares, low placed ears, gingival hyperplasia, micrognathia, widely spaced nipples, rhizomelic limb shortening, broad and wide fingers, 5th finger clinodactyly. Radiographic evaluation revealed mesomelia. His penis was buried but of normal size and he had left cryptorchidism (previous orchidopexy of the right testicle).

BAB8062

The proband is a 13-month-old Turkish male patient who was born to a 27 years old G4P2 healthy mother after an uncomplicated pregnancy and delivery with a birth weight of 3020g (10^{th} centile) and birth length of 42 cm ($<3^{rd}$ centile) (occipitofrontal circumference not available). The mother`s first and second pregnancies were terminated at 8 weeks of gestation due to undetected fetal cardiac activity. The patient was admitted to the neonatal intensive care unit after delivery for 11 days because of antenatally detected cleft lip and palate and ambiguous genitalia. Because of the ambiguous genitalia the levels of 17-OH progesterone, 4-androstenedione, cortisol, and testosterone were tested and found to be normal. Chromosome analysis also revealed a normal 46,XY karyotype. He underwent right unilateral inguinal hernia and orchidopexy at 4 months of age and cleft lip and palate surgery at 7 months of age. He was able to hold his head at 4.5 months of age and sit unsupported at 11 months of age.

He was referred to the genetics clinic at age 13 months because of short stature and dysmorphic features. The anthropometric measures at that age were 9000 g (10-25 centile) body weight, 73.5 cm (3-10^{th} centile) height, and 49 cm (90^{th} centile)

occipitofrontal circumference. On head and neck examination relative macrocephaly, large anterior fontanelle (2x2 cm), frontal bossing, wide and high forehead, mid-face hypoplasia, prominent eyes, hypertelorism, blue sclerae, epicanthal folds, telecanthus, broad nasal root, short nose, aplasia of the uvula, dental anomalies secondary to cleft lip and palate, gingival hyperplasia, micrognathia, low-set and question mark shaped ears, and short neck were detected. On skeletal system examination, mesomelic shortening of limbs, brachydactyly, clinodactyly of 5^{th} fingers, broad thumbs, nail hypoplasia, and prominent left 12^{th} costovertebral region. Genitourinary system examination revealed non-palpable testes, micropenis, hypospadias, sacral dimple, and dimple on pelvic floor (between scrotum and anus). On neurologic examination he was not able to walk unsupported and there was no speech. X-ray survey showed hyperostosis of the skull base (especially at the sella turcica), flattened vertebral bodies (platyspondyly), kyphoscoliosis, and bilateral developmental dysplasia of the hip. On scrotal ultrasound right testis (16x7 mm) was viewed in inguinal canal and left testis (11x8 mm) was viewed in lower left abdomen. A clinical diagnosis of Robinow syndrome was rendered.