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Resources for Genetics Professionals — Genetic Disorders Associated with Founder Variants Common in the Navajo Population

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A founder variant is a pathogenic variant observed at high frequency in a specific population due to the presence of the variant in a single ancestor or small number of ancestors. The presence of a founder variant can affect the approach to molecular genetic testing. When one or more founder variants account for a large percentage of all pathogenic variants found in a population, testing for the founder variant(s) may be performed first. The table below includes common founder variants – here defined as **three or fewer variants that account for >50% of the pathogenic variants identified in a single gene in individuals of a specific ancestry** – in individuals of Navajo ancestry. Note: Pathogenic variants that are common worldwide due to a DNA sequence hot spot are not considered founder variants and thus are not included.

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Table. Genetic Disorders Associated with Founder Variants Common in the Navajo Population

Gene	Disorder	MOI	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Proportion of Pathogenic Variants in Gene [2]	Carrier Frequency	Ethnicity (Specific Region)	Reference Sequences	References
ARSA	Arylsulfatase A deficiency	AR	c.854+1G>A	--	~100% [3]	1/25 to 1/50	Navajo (Western Navajo Nation)	NM_000487.6	Pastor-Soler et al [1994], Holve et al [2001]
DCLRE1C	Severe combined immunodeficiency (SCID-A) (OMIM 602450)	AR	c.597C>A	p.Tyr199Ter	~100% [3]	~1/20 to 1/25	Navajo	NM_001033855.3 NP_001029027.1	Kwan et al [2015]
HOXA1	Navajo brain stem syndrome (OMIM 601536)	AR	c.76C>T	p.Arg26Ter	~100% [3]	1/28 [4]	Navajo	NM_005522.5 NP_005513.2	Holve et al [2003], Tischfield et al [2005]
MPV17	Navajo neurohepatopathy (*MPV17*-related mitochondrial DNA maintenance defect)	AR	c.149G>A	p.Arg50Gln	~100% [3]	1/26 [4]	Navajo (Western Navajo Nation)	NM_002437.5 NP_002428.1	Karadimas et al [2006], Bitting & Hanson [2016]
						1/60 [4]	Navajo (Eastern)		
MYO5B	Microvillus inclusion disease (OMIM 251850)	AR	c.1979C>T	p.Pro660Leu	~100% [3]	1/55 [4]	Navajo	NM_001080467.3 NP_001073936.1	Schlegel et al [2018]
OCA2	Oculocutaneous albinism type 2 (OMIM 203200)	AR	g.103171_225796del (c.1044+1363_2080-6952; 122.5-kb del, incl exons 10-20)	--	~100% [3]	~1/22	Navajo	NG_009846.1	Yi et al [2003]
TNFRSF11B	Paget's disease (OMIM 239000)	AR	g.119932595_120030098del97504 (~100 kb del, incl entire gene)	--	~100% [3]	Unknown	Navajo	NG_012202.1	Whyte et al [2002]

Table. continued from previous page.

Gene	Disorder	MOI	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Proportion of Pathogenic Variants in Gene [2]	Carrier Frequency	Ethnicity (Specific Region)	Reference Sequences	References
USB1	Poikiloderma with neutropenia	AR	c.499delA	p.Thr160ProfsTer98	~100% [3]	Unknown	Navajo	NM_024598.4 NP_078874.2	Clericuzio et al [2011]

Included if ≤3 pathogenic variants account for ≥50% of variants identified in a specific ethnic group
AR = autosomal recessive; MOI = mode of inheritance
1. Does not conform to standard HGVS nomenclature
2. Percentage does not account for the possibility of rare *de novo* pathogenic variants occurring in this population.
3. To date, additional pathogenic variants in this gene have not been reported in individuals of Navajo descent.
4. Calculated carrier frequency based on the incidence of the disorder in individuals of Navajo ancestry; estimated carrier frequency is not based on molecular testing of the population.

Revision History

- 3 November 2022 (sw) Revision: updated carrier frequencies, added Holve et al [2003], Bitting & Hanson [2016], Schlegel et al [2018]
- 27 June 2019 (sw) Initial posting

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