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Resources for Genetics Professionals — Genetic Disorders Associated with Founder Variants Common in the Inuit 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 Inuit 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 Inuit 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
AGL	Glycogen storage disease type III	AR	c.4456delT	p.Ser1486ProfsTer18	~100% [3]	1/25 [4]	Inuit (Nunavik)	NM_000642.3 NP_000633.2	Rousseau-Nepton et al [2015]
ATP8B1	ATP8B1 deficiency	AR	c.1660G>A	p.Asp554Asn	~100% [3]	1/4 to 1/20	Inuit	NM_005603.6 NP_005594.2	Andersen et al [2006]
BRCA1	*BRCA1*- & *BRCA2*-Associated Hereditary Breast & Ovarian Cancer	AD	c.115T>G	p.Cys39Gly	>95%	NA	Inuit (Ammassalik)	NM_007294.4 NP_009225.1	Hansen et al [2009], Harboe et al [2009], Hansen et al [2010]
BRIP1	Fanconi anemia	AR	c.2392C>T	p.Arg798Ter	~100% [3]	Unknown	Inuit	NM_032043.3 NP_114432.2	Levran et al [2005]
CLPB	CLPB deficiency	AR	c.803C>T	p.Thr268Met	~100% [3]	1/31	Inuit	NM_030813.6 NP_110440.1	Saunders et al [2015]
PCCB	Propionic acidemia	AR	c.1538_1540dupCCC	p.Ala513_Arg514insPro	~88%	1/20	Inuit	NM_000532.5 NP_000523.2	Ravn et al [2000]
PMS2	Lynch syndrome & constitutional mismatch repair deficiency	AD AR	c.2002A>G [5]	--	~100% [3]	1/16 [4]	Inuit (Nunavik)	NM_000535.7	Li et al [2015]
SI	Congenital sucrase–isomaltase deficiency (OMIM 222900)	AR	c.273_274delAG	p.Gly92LeufsTer8	~100% [3]	1/4	Inuit (Nunavut)	NM_001041.4 NP_001032.2	Marcadier et al [2015]
SLC17A5	Infantile sialic acid storage disease (See Free Sialic Acid Storage Disorders.)	AR	c.526-2A>G (IVS3-2A>G)	--	~100% [3]	1/129	Inuit	NM_012434.5	Lines et al [2014]

Included if ≤3 pathogenic variants account for ≥50% of variants identified in a specific ethnic group
AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; NA = not applicable
1. Does not conform to standard HGVS nomenclature
2. This percentage does not account for the possibility of rare *de novo* pathogenic variants occurring in this population.
3. Additional pathogenic variants in this gene have not been reported to date in individuals of Inuit descent.
4. Calculated carrier frequency is based on the incidence of the disorder in individuals of Inuit ancestry; estimated carrier frequency is not based on molecular testing of the population.
5. DNA nucleotide change introduces new splice site and does not result in predicted protein change.

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Revision History

- 24 August 2023 (sw) Revision: updated reference sequences
- 24 November 2021 (sw) Revision: added Fanconi anemia

- 27 December 2018 (sw) Initial posting

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