



U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Wallace SE, Bean LJH. Resources for Genetics Professionals — Genetic Disorders Associated with Founder Variants Common in the Inuit Population. 2018 Dec 27 [Updated 2023 Aug 24]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. **Bookshelf URL:** <https://www.ncbi.nlm.nih.gov/books/>



Resources for Genetics Professionals – Genetic Disorders Associated with Founder Variants Common in the Inuit Population

Stephanie E Wallace, MD^{1,2} and Lora JH Bean, PhD^{3,4}

Created: December 27, 2018; Revised: August 24, 2023.

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.

Author Affiliations: 1 Senior Editor, GeneReviews; Email: editor2@uw.edu. 2 Clinical Professor, Pediatrics, University of Washington, Seattle, Washington; Email: editor2@uw.edu. 3 Molecular Genetics Editor, GeneReviews. 4 Senior Director, Laboratory Quality Assurance, Perkin-Elmer Genomics, Inc, Pittsburgh, Pennsylvania.

Copyright © 1993-2024, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

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
<i>AGL</i>	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]
<i>ATP8B1</i>	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]
<i>BRCA1</i>	<i>BRCA1</i> - & <i>BRCA2</i> -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]
<i>BRIPI</i>	Fanconi anemia	AR	c.2392C>T	p.Arg798Ter	~100% ³	Unknown	Inuit	NM_032043.3 NP_114432.2	Levrant et al [2005]
<i>CLPB</i>	CLPB deficiency	AR	c.803C>T	p.Thr268Met	~100% ³	1/31	Inuit	NM_030813.6 NP_110440.1	Saunders et al [2015]
<i>PCCB</i>	Propionic acidemia	AR	c.1538_1540dupCCC	p.Ala513_Arg514insPro	~88%	1/20	Inuit	NM_000532.5 NP_000523.2	Ravn et al [2000]
<i>PMS2</i>	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]
<i>SI</i>	Congenital sucrose-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]
<i>SLC17A5</i>	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.

References

- Andersen S, Okkels H, Krarup H, Laurberg P. Geographical clustering and maintained health in individuals harbouring the mutation for Greenland familial cholestasis: a population-based study. *Scand J Gastroenterol*. 2006;41:445-50. PubMed PMID: 16635913.
- Hansen TV, Ejlertsen B, Albrechtsen A, Bergsten E, Bjerregaard P, Hansen T, Myrhøj T, Nielsen PB, Timmermans-Wielenga V, Andersen MK, Jønson L, Nielsen FC. A common Greenlandic Inuit BRCA1 RING domain founder mutation. *Breast Cancer Res Treat*. 2009;115:69-76. PubMed PMID: 18500671.
- Hansen TV, Jønson L, Albrechtsen A, Steffensen AY, Bergsten E, Myrhøj T, Ejlertsen B, Nielsen FC. Identification of a novel BRCA1 nucleotide 4803delCC/c.4684delCC mutation and a nucleotide 249T>A/c.130T>A (p.Cys44Ser) mutation in two Greenlandic Inuit families: implications for genetic screening of Greenlandic Inuit families with high risk for breast and/or ovarian cancer. *Breast Cancer Res Treat*. 2010;124:259-64. PubMed PMID: 20437199.
- Harboe TL, Eiberg H, Kern P, Ejlertsen B, Nedergaard L, Timmermans-Wielenga V, Nielsen IM, Bisgaard ML. A high frequent BRCA1 founder mutation identified in the Greenlandic population. *Fam Cancer*. 2009;8:413-9. PubMed PMID: 19504351.
- Levrano O, Attwooll C, Henry RT, Milton KL, Neveling K, Rio P, Batish SD, Kalb R, Velleuer E, Barral S, Ott J, Petrini J, Schindler D, Hanenberg H, Auerbach AD. The BRCA1-interacting helicase BRIP1 is deficient in Fanconi anemia. *Nat Genet*. 2005;37:931-3. PubMed PMID: 16116424.
- Li L, Hamel N, Baker K, McGuffin MJ, Couillard M, Gologan A, Marcus VA, Chodirker B, Chudley A, Stefanovici C, Durandy A, Hegele RA, Feng BJ, Goldgar DE, Zhu J, De Rosa M, Gruber SB, Wimmer K, Young B, Chong G, Tischkowitz MD, Foulkes WD. A homozygous PMS2 founder mutation with an attenuated constitutional mismatch repair deficiency phenotype. *J Med Genet*. 2015;52:348-52. PubMed PMID: 25691505.
- Lines MA, Rupar CA, Rip JW, Baskin B, Ray PN, Hegele RA, Grynspan D, Michaud J, Geraghty MT. Infantile sialic acid storage disease: two unrelated Inuit cases homozygous for a common novel SLC17A5 mutation. *JIMD Rep*. 2014;12:79-84. PubMed PMID: 23900835.
- Marcadier JL, Boland M, Scott CR, Issa K, Wu Z, McIntyre AD, Hegele RA, Geraghty MT, Lines MA. Congenital sucrase–isomaltase deficiency: identification of a common Inuit founder mutation. *CMAJ*. 2015;187:102-7. PubMed PMID: 25452324.
- Ravn K, Chloupkova M, Christensen E, Brandt NJ, Simonsen H, Kraus JP, Nielsen IM, Skovby F, Schwartz M. High incidence of propionic acidemia in Greenland is due to a prevalent mutation, 1540insCCC, in the gene for the β -subunit of propionyl CoA carboxylase. *Am J Hum Genet*. 2000;67:203-6. PubMed PMID: 10820128.
- Rousseau-Nepton I, Okubo M, Grabs R, the FORGE Canada Consortium, Mitchell J, Polychronakos C, Rodd C. A founder AGL mutation causing glycogen storage disease type IIIa in Inuit identified through whole-exome sequencing: a case series. *CMAJ*. 2015;187:E68-73. PubMed PMID: 25602008.
- Saunders C, Smith L, Wibrand F, Ravn K, Bross P, Thiffault I, Christensen M, Atherton A, Farrow E, Miller N, Kingsmore SF, Ostergaard E. CLPB variants associated with autosomal-recessive mitochondrial disorder with cataract, neutropenia, epilepsy, and methylglutaconic aciduria. *Am J Hum Genet*. 2015;96:258-65. PubMed PMID: 25597511.

Revision History

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

- 27 December 2018 (sw) Initial posting

License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (<http://www.genereviews.org/>) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the [GeneReviews® Copyright Notice and Usage Disclaimer](#). No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the [GeneReviews® Copyright Notice and Usage Disclaimer](#).

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.