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NLM Citation: Wallace SE, Bean LJH. Resources for Genetics Professionals — Genetic Disorders Associated with Founder Variants Common in the Newfoundland and Labrador Populations. 2020 Apr 30 [Updated 2023 Aug 17]. 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 Newfoundland and Labrador Populations

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Created: April 30, 2020; Revised: August 17, 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 Newfoundlander and/or Labradorian 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 Newfoundland and/or Labrador 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
APC	Familial adenomatous polyposis, attenuated	AD	c.221-1G>A (IVS2-1G>A)	--	~80%	NA	Newfoundland	NM_00038.6	Spirio et al [1999], Woods et al [2010]
BBS1	Bardet-Biedl syndrome	AR	c.1169T>G	p.Met390Arg	~100% [3]	1/67	Newfoundland (southwest)	NM_024649.5 NP_078925.3	Fan et al [2004]
CDH1	Hereditary diffuse gastric cancer	AD	c.2398delC	p.Arg800AlafsTer16	Most families	NA	Newfoundland	NM_004360.5 NP_004351.1	Kaurah et al [2007]
CLDN14	Deafness, AR 29 (OMIM 614035)	AR	c.488C>T	p.Ala163Val	~100% [3]	1/44	Newfoundland	NM_144492.3 NP_652763.1	Pater et al [2017]
CLN6	Neuronal ceroid lipofuscinosis 6 (OMIM 601780)	AR	c.268_271dupAACG	p.Val91GlufsTer42	~100% [3]	Unknown	Newfoundland (southern coast)	NM_017882.3 NP_060352.1	Moore et al [2008]
F13A1	Factor XIIIA deficiency (OMIM 613225)	AR	c.691-1G>A (IVS5-1G>A)	--	86%	Unknown	Newfoundland & Labrador	NM_000129.4	Scully et al [2018]
F8	Hemophilia A	XL	c.6104T>C	p.Val2035Ala	74%	Unknown	Newfoundland & Labrador (Twillingate)	NM_000132.4 NP_000123.1	Scully et al [2018]
MEN1	Multiple endocrine neoplasia type 1	AD	c.1378C>T	p.Arg460Ter	~100%	NA	Newfoundland (Burin Peninsula)	NM_130799.2 NP_570711.1	Olufemi et al [1998]
MSH2	Lynch syndrome	AD	Deletion of exon 8	--	<30%	NA	Newfoundland	NG_007110.2	Stuckless et al [2007], Woods et al [2010]
			c.942+3A>T (IVS5+3A>T)	--	~30%-60%		Newfoundland (northeast coast)	NM_000251.3	
RLBP1	Newfoundland rod cone dystrophy (OMIM 607476)	AR	c.141+2T>C (IVS3+2T>C)	--	~20%	Unknown	Newfoundland	NM_000326.5	Eichers et al [2002]
			c.141G>A [4] (IVS3-1G>A)	--	~80%	1/106			
STAR	Lipoid congenital adrenal hyperplasia (OMIM 201710)	AR	c.562C>T	p.Arg188Cys	~100% [3]	Unknown	Newfoundland & Labrador	NM_000349.3 NP_000340.2	Tsai et al [2016]

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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
TMEM43	Arrhythmogenic right ventricular cardiomyopathy	AD	c.1073C>T	p.Ser358Leu	~100% [3]	NA	Newfoundland	NM_024334.3 NP_077310.1	Merner et al [2008], Milting et al [2015]
TPP1	Neuronal ceroid lipofuscinosis 2 (OMIM 204500)	AR	c.509-1G>C (IVS5-1G>C)	--	33%	Unknown	Newfoundland (southern coast)	NM_000391.4	Moore et al [2008]
			c.851G>T	p.Gly284Val	42%		Newfoundland (east coast)	NM_000391.4 NP_000382.3	
			c.1424delC	p.Ser475TrpfsTer13	11%		Newfoundland (northern coast)		
VAMP1	Spastic ataxia 1 (See Hereditary Ataxia Overview.)	AD	c.340+2T>G (IVS4+2T>G)	--	~100% [3]	NA	Newfoundland	NM_014231.5	Bourassa et al [2012]

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. To date, additional pathogenic variants in this gene have not been reported in individuals of Newfoundlander and/or Labradorian descent.

4. DNA nucleotide change introduces new splice site and does not result in predicted protein change.

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Revision History

- 17 August 2023 (sw) Revision: added *BBS1* and updated reference sequences
- 30 April 2020 (sw) Initial posting

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