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Resources for Genetics Professionals — Genetic Disorders Associated with Founder Variants Common in the Cree and/or Ojibway 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 Cree and/or Ojibway 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 Cree and/or Ojibway Population

Gene	Disorder	MOI	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	% of Pathogenic Variants in Gene [2,3]	Carrier Frequency	Ethnicity (Specific Region of Canada)	Reference Sequences	Reference(s)
CRYAB	Fatal infantile myofibrillar myopathy (OMIM 613869)	AR	c.60delC	p.Ser21AlafsTer24	100%	Unknown	Cree (N Ontario & Alberta)	NM_001885.3 NP_001876.1	Del Bigio et al [2011]
DONSON	Microcephaly-micromelia syndrome (OMIM 251230)	AR	c.1047-9A>G (IVS6-9A>G)	--	100%	Unknown	Cree (N Saskatchewan)	NM_017613.4	Evrony et al [2017]
EIF2B5	Cree leukoencephalopathy (See Childhood Ataxia with Central Nervous System Hypomyelination / Vanishing White Matter.)	AR	c.584G>A	p.Arg195His	100%	1/10	Cree (N Quebec & Manitoba)	NM_003907.3 NP_003898.2	Fogli et al [2002]
FREM1	Manitoba oculotrichoanal syndrome (See *FREM1* Autosomal Recessive Disorders.)	AR	c.824+627_c.3840-1311del (IVS7+631_IVS23-1311 del; del8-23 exon)	p.385_1327del	100%	1/7 to 1/12	Ojibway-Cree (Island Lake, Manitoba)	NM_144966.5 NP_659403.4	Slavotinek et al [2011]
GCDH	Glutaric acidemia type 1	AR	c.91+5G>T (IVS2+5G>T)	--	100%	1/17	Ojibway-Cree (Island Lake, Manitoba, & NW Ontario)	NM_000159.4	Greenberg et al [2002]
GLIS2	Nephronophthisis-related ciliopathies	AR	c.775+1G>T (IVS5+1G>T)	--	100%	Unknown	Ojibway-Cree (Canada)	NM_032575.3	Attanasio et al [2007]
IKBKB	Immunodeficiency 15B (OMIM 615592)	AR	c.1292dupG	p.Gln432ProfsTer62	100%	1/13	Cree (Manitoba & Saskatchewan)	NM_001556.3 NP_001547.1	Pannicke et al [2013], Rubin et al [2018]
PC	Pyruvate carboxylase deficiency	AR	c.1828G>A	p.Ala610Thr	100%	Up to 1/10	Ojibway-Cree (White Dog, Ontario)	NM_000920.4 NP_000911.2	Carbone et al [1998]

Table. continued from previous page.

Gene	Disorder	MOI	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	% of Pathogenic Variants in Gene [2,3]	Carrier Frequency	Ethnicity (Specific Region of Canada)	Reference Sequences	Reference(s)
PRUNE1	Neurodevelopmental disorder with microcephaly, hypotonia, & variable brain anomalies (OMIM 617481)	AR	c.521-2A>G (IVS4-2A>G)	--	100%	Unknown	Cree (N Manitoba)	NM_021222.3	Hartley et al [2019]
SLC25A38	Sideroblastic anemia 2 (OMIM 205950)	AR	c.560G>A	p.Arg187Gln	100%	Unknown	Cree (Canada)	NM_017875.4 NP_060345.2	Uminski et al [2020]
TREX1	Cree encephalitis (See Aicardi-Goutières Syndrome.)	AR	c.490C>T	p.Arg164Ter	100%	1/10	Cree (Quebec)	NM_033629.6 NP_338599.1	Crow et al [2003], Crow et al [2006]

Included if ≤3 pathogenic variants account for ≥50% of variants identified in a specific ethnic group
AR = autosomal recessive; MOI = mode of inheritance; N = Northern; NW = Northwest
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 Cree and/or Ojibway descent (from region specified).

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- 16 May 2019 (sw) Initial posting

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