Dynacare®

POLG c.2243G>C Fact Sheet

What is the *POLG* gene?

The *POLG* gene is an important gene that controls the health of the mitochondria in the human body. Mitochondria are present in every cell of our body and provide the energy needed for our cells to function and communicate with other cells.

We all have variants/changes in our DNA; most of them don't cause any health-related problems, however, some affect the way our bodies metabolize drugs/supplements, and some are related to the development of certain health conditions.

We have 2 copies of the *POLG* gene. We inherit one copy from each parent. If the *POLG c.2243G>C* variant is present in one copy of the *POLG* gene, this can cause an adverse reaction to a certain type of medication called Sodium valproate (VPA) also known as Valproic acid (Depakene®) or sodium divalproate (divalproex) (Depakote®). Valproic acid (VPA) is A widely used anti-epileptic drug and prescribed to treat seizures, migraine, chronic headache and bipolar disorder.

The variation c.*2243G*>C present in one copy of the *POLG* gene reduces the ability for the body to metabolize VPA and results in a toxic effect on the liver called VPA-induced liver toxicity.[i]

What does having the c.2243G>C *POLG* variant mean for me and my family?

Individuals who have the *POLG c.2243G>C* variant (approx. 0.6%-2% of the population)[ii] have adverse reactions to VPA that can result in hepatotoxicity (liver damage). VPA-induced hepatotoxicity can cause symptoms such as jaundice (yellow skin), abdominal pain, fever, rash and fatigue.

In addition to adverse reactions to medications, people with a *POLG c.2243G>C* variant are at risk for a condition called autosomal dominant Progressive External Ophthalmoplegia (adPEO). adPEO can be associated with several health conditions including ophthalmoplegia (eye muscle paralysis), ataxia (loss of balance), dysphagia (swallowing difficulty), hearing loss, and various types of neuromuscular symptoms. Not all carriers of a *POLG* variant will experience symptoms and if they do the age of onset is quite variable.

Two individuals who both have a *POLG* variant have a 25% chance of having a child who inherits both copies of the *POLG* variant.

An individual who inherits two copies of a *POLG* gene variant can present with several serious medical conditions including: Alpers–Huttenlocher syndrome (AHS), childhood myocerebrohepatopathy spectrum (MCHS), Myoclonic epilepsy myopathy sensory ataxia (MEMSA), Ataxia neuropathy spectrum (ANS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO).[iii, iv]

Important facts:

- Individuals with the *POLG c.2243G>C* variant should not take any form of Sodium Valproate.
- Carriers should be assessed by their primary health care professional to assess for any symptoms associated with autosomal dominant PEO (adPEO).
- A person with a *POLG c.2243G>C* variant who is considering pregnancy should consider having their partner tested for *POLG* variants.
- Prenatal Diagnosis options are available to couples who both carry a *POLG* variant to determine the POLG genetic status of the fetus.
- Newborn infants from a parent who has the *POLG c.2243G>C* variant should be flagged to avoid any administration of sodium valproate (VPA).

How can I get more information?

A referral to a genetic counsellor can help clarify individual risks and determine other at-risk family members who could benefit from predictive testing for the *POLG c.2243G>C* variant.

In Canada, genetic counselling is available at provincial genetic clinics by referral. Your healthcare provider can send a referral to Dynacare Genetics Specialty team at 450.901.3076. Our online referral form can be completed here. Alternatively, to locate a genetic clinic near you, visit the Canadian Association of Genetic Counsellors at www.cagc-accg.org

Genetic Counselling Referral forms:

- Dynacare Pharmacogenomic Genetic Counselling Referral

[i] Stewart JD, Horvath R, Baruffini E, Ferrero I, Bulst S, Watkins PB, Fontana RJ, Day CP, Chinnery PF. Polymerase γ gene POLG determines the risk of sodium valproate-induced liver toxicity. Hepatology. 2010 Nov;52(5):1791-6. doi: 10.1002/hep.23891. PMID: 21038416; PMCID: PMC3841971.

[ii] Van Goethem G, Löfgren A, Dermaut B, Ceuterick C, Martin JJ, Van Broeckhoven C. Digenic progressive external ophthalmoplegia in a sporadic patient: recessive mutations in POLG and C10orf2/Twinkle. Human mutation. 2003 Aug 1;22(2):175.

[iii] Rahman S, Copeland WC. POLG-related disorders and their neurological manifestations. Nat Rev Neurol. 2019 Jan;15(1):40-52. doi: 10.1038/s41582-018-0101-0. PMID: 30451971; PMCID: PMC8796686.

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