Dynacare®

c.211G>A *UGT1A1* Fact Sheet

What is the *UGT1A1* Gene?

The *UGT1A1* gene provides instructions for making enzymes called UPD-Glucuronosyltransferases. The UPD-Glucuronosyltransferase enzymes are important for metabolizing (breaking down) certain types of drugs and supplements. Metabolization is required to avoid accumulation of drugs/supplements which can result in toxicity in our body.

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.

The c.211G>A *UGT1A1* variant (also known as *UGT1A1**6) can be inherited from a male OR female parent and can be passed on to both biological female and biological male children. A working copy of the *UGT1A1* gene is known as *UGT1A1**1. The *UGT1A1**6 gene variation can post health risks to that individual when one copy of the gene contains this variant while the other copy of the gene does not carry the variant (*UGT1A1* *1/*6) and/or when both copies of the gene contain this variant (*UGTA1A1* *6/*6).

What does having a c.211G>A *UGT1A1* variant mean for me and my family?

Individuals who have the c.211G>A *UGT1A1**6 variant (as high as 15-30% in Asian populations)[i], can have adverse reactions to a class of medications called Irinotecan (IRI). The brand name of Irinotecan is called "Camptosar" or "Campto". Irinotecan is a type of chemotherapy used for treatment of cancer that started in the bowel (bowel cancer).

Individuals with one copy of the c.211G>A *UGT1A1**6 variant (*UGT1A1**6) and one copy without the *UGT1A1* variant (*UGT1A1**1) who are treated with Irinotecan can experience adverse affects such as severe diarrhea, myelosuppression (bone marrow suppression), and neutropenia (low level of white blood cells). Individuals with **two** copies of the c.211G>A *UGT1A1* variants (*UGT1A1* *6/*6) have risk for these same symptoms but are at risk for more severe presentations. This is referred to as "IRI-induced toxicity".[ii]

Literature has demonstrated that newborn infants who carry the c.211G>A *UGT1A1*6* variant (*UGT1A*1*6/*1) can be more susceptible to develop early-onset neonatal breastfeeding jaundice[iii], and hyperbilirubinemia. [iv],[v],[vi],[vii] Adults with two copies of the c.211G>A *UGT1A1* variant (*UGT1A1**6/*6) have been shown to be significantly associated with the risk of adult hyperbilirubinemia. [viii]

Bilirubin is yellow liquid waste that occurs naturally as the body breaks down old red blood cells. Excess bilirubin is known as hyperbilirubinemia and can result in skin and whites of the eyes to look yellow (referred to as Jaundice).

Individuals who have two copes of the c.211G>A *UGT1A1* variant (*UGT1A1**6/*6) have a genetic condition called Gilbert's syndrome. Gilbert's syndrome is an inherited (genetic) liver disorder that affects the body's ability to process bilirubin resulting in excess accumulation of bilirubin (hyperbilirubinemia). Gilbert syndrome is considered "benign" and patients typically have excellent prognosis. Patients with this condition are not at significant risk for progressive liver disease. It has been shown however that Gilbert syndrome patients are at an increased risk of developing gallstones,[ix] and avoidance of certain environmental "triggers" may be advantageous to reduce anxiety about abnormal bilirubin values.[x]

Important Facts:

- Individuals with two *UGT1A1* c.211G>A variants (*6/*6) should receive a reduced dose of irinotecan. [xi]
- Neonates with one copy of the *UGT1A1* c.211G>A variant (*6/*1) are more susceptible to develop early-onset neonatal breastfeeding jaundice.
- Individuals with two *UGT1A1* c.211G>A variants (*6/*6) will have Gilbert's syndrome.
- Variants in the *UGT1A1* gene are inherited in a recessive manner. A person who carries one variant in *UGT1A1* is called a carrier. When two individuals who are both carriers of an *UGT1A1* variant have children, there is a 1 in 4 (25%) chance with each pregnancy of passing on two *UGT1A1* variants to a child, who will have Gilbert's syndrome.
- While Gilbert's syndrome and carriers of a single *UGT1A1* c.211G>A variant are not at risk for serious health concerns it is recommended that patients with Gilbert syndrome and carriers should be informed about potential triggers such as fasting, intercurrent illness, menstruation, overexertion, hemolytic reactions, and dehydration that may cause a rise in unconjugated bilirubin.
- Experts recommend that you share this information with your healthcare provider who can refer you to the nearest genetic clinic for a genetic counselling appointment.

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 *UGT1A1* c.211G>A 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 Zhang X, Yin JF, Zhang J, Kong SJ, Zhang HY, Chen XM. UGT1A1*6 polymorphisms are correlated with irinotecan-induced neutropenia: a systematic review and meta-analysis. Cancer Chemother Pharmacol. 2017 Jul;80(1):135-149. doi: 10.1007/s00280-017-3344-3. Epub 2017 Jun 5. PMID: 28585035.

ii Zhang X, Yin JF, Zhang J, Kong SJ, Zhang HY, Chen XM. UGT1A1*6 polymorphisms are correlated with irinotecan-induced neutropenia: a systematic review and meta-analysis. Cancer Chemother Pharmacol. 2017 Jul;80(1):135-149. doi: 10.1007/s00280-017-3344-3. Epub 2017 Jun 5. PMID: 28585035.

iii Chou HC, Chen MH, Yang HI, Su YN, Hsieh WS, Chen CY, Chen HL, Chang MH, Tsao PN. 211 G to a variation of UDP-glucuronosyl transferase 1A1 gene and neonatal breastfeeding jaundice. Pediatr Res. 2011 Feb;69(2):170-4. doi: 10.1203/PDR.0b013e31820263d2. PMID: 20975617.

iv Prachukthum S, Nunnarumit P, Pienvichit P, Chuansumrit A, Songdej D, Kajanachumpol S, Pakakasama S, Hongeng S. Genetic polymorphisms in Thai neonates with hyperbilirubinemia. Acta Paediatr. 2009 Jul;98(7):1106-10. doi: 10.1111/j.1651-2227.2009.01275.x. Epub 2009 Apr 21. PMID: 19397531.

v Long J, Zhang S, Fang X, Luo Y, Liu J. Neonatal hyperbilirubinemia and Gly71Arg mutation of UGT1A1 gene: a Chinese case-control study followed by systematic review of existing evidence. Acta Paediatr. 2011 Jul;100(7):966-71. doi: 10.1111/j.1651-2227.2011.02176.x. Epub 2011 Feb 25. Erratum in: Acta Paediatr. 2012 Nov;101(11):1184. PMID: 21272068.

vi Long J, Zhang S, Fang X, Luo Y, Liu J. Association of neonatal hyperbilirubinemia with uridine diphosphate-glucuronosyltransferase 1A1 gene polymorphisms: meta-analysis. Pediatr Int. 2011 Aug;53(4):530-40. doi: 10.1111/j.1442-200X.2011.03337.x. PMID: 21342357.

vii Maruo Y, Nishizawa K, Sato H, Sawa H, Shimada M. Prolonged unconjugated hyperbilirubinemia associated with breast milk and mutations of the bilirubin uridine diphosphate- glucuronosyltransferase gene. Pediatrics. 2000 Nov;106(5):E59. doi: 10.1542/peds.106.5.e59. PMID: 11061796.

viii Chen Z, Su D, Ai L, Jiang X, Wu C, Xu Q, Wang X, Fan Z. UGT1A1 sequence variants associated with risk of adult hyperbilirubinemia: a quantitative analysis. Gene. 2014 Nov 15;552(1):32-8. doi: 10.1016/j.gene.2014.09.009. Epub 2014 Sep 6. PMID: 25200497.

ix Bale G, Avanthi US, Padaki NR, Sharma M, Duvvur NR, Vishnubhotla VRK. Incidence and Risk of Gallstone Disease in Gilbert's Syndrome Patients in Indian Population. J Clin Exp Hepatol. 2018 Dec;8(4):362-366

x Thoguluva Chandrasekar V, Faust TW, John S. Gilbert Syndrome. [Updated 2023 Feb 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470200/

xi Fujita K., Kubota Y., Ishida H., Sasaki Y. Irinotecan, a key chemotherapeutic drug for metastatic colorectal cancer. World J Gastroenterol. 2015 Nov 21;21(43):12234–48