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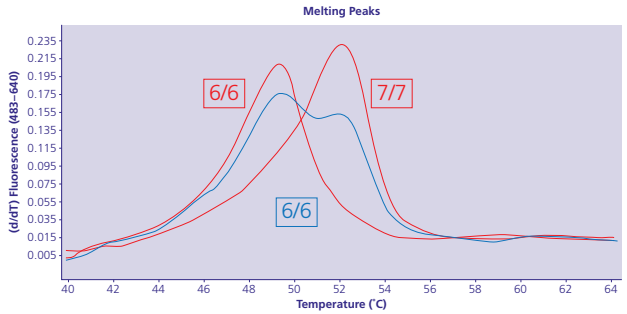
Detection of UGT1A1*28 Mutation & Genetic Screening for Gilbert Syndrome



Clinical Biochemistry

BCPS
NHS Pathology Serving the Black Country

Provided by Sandwell and West Birmingham NHS Trust, The Dudley Group NHS Foundation Trust, The Royal Wolverhampton NHS Trust and Walsall Healthcare NHS Trust.

Role of UGT1A1

UGT1A1 is an enzyme of the glucuronidation pathway, which transforms exogenous and endogenous lipophilic molecules into water-soluble and excretable molecules.

UGT1A1 polymorphism

Numerous mutations of UGT1A1 have been identified with frequencies showing extensive variability across ethnic groups. UGT1A1*28 is the most common mutation within White and African-American populations. This mutation is cause by the insertion of extra nucleotides within the TATA box of the UGT1A1 gene promoter. An elongated TA repeat A[TA]7TAA results in decreased transcription of the UGT1A1 gene and enzyme deficiency (1).

Clinical use of UGT1A1*28 genotyping

Gilbert syndrome

UGT1A1*28 mutation is associated with Gilbert syndrome, an inherited form of unconjugated hyperbilirubinaemia. Typically serum bilirubin concentration does not exceed 68-85 µmol/L, with normal standard liver function tests (2). A key reason to establish the diagnosis is to prevent further unnecessary investigations/procedures, which could include highly invasive liver biopsy.

Pharmacogenetics

UGT1A1 is involved in the metabolism of multiple drugs.

- Irinotecan is a chemotherapeutic agent used for the treatment of metastatic colorectal cancer. Its active metabolite SN-38 is principally metabolised via UGT1A1. Published trials have reported an association between UGT1A1*28 mutation, severe neutropenia and diarrhoea. In 2004 the US FDA advisory committee on pharmaceutical sciences advised Pfizer Pharmaceuticals to amend the product information for Irinotecan (Camptosar) to include recommendations to reduce dosage for patients homozygous for UGT1A1*28 (7/7 genotype) (3).
- Raloxifene is used in the prevention and treatment of osteoporosis in postmenopausal women. This drug shows strong interindividual pharmacokinetic variability. Patients homozygous for UGT1A1*28 show a higher serum concentration of Raloxifene and a greater increase in hip bone mineral density (4).
- The published guidelines from Clinical Pharmacogenetics Implementation Consortium (CPIC, 2015) on the use of Atazanavir in patients with UGT1A1 mutations indicate that alternative treatment should be considered due to a significant risk of developing hyperbilirubinaemia.
- Homozygous mutant patients should be started on a reduced dose of Belinostat.
- Studies have showed that the UGT1A1 mutation is associated with hyperbilirubinaemia in patients taking drugs such as Nilotinib and Pazopanib.

UGT1A1 genotyping

Mutation analysis in the promoter of the UGT1A1 is performed by real-time Polymerase Chain Reaction (LightCycler 480, Roche) using FastStart DNA master hybprobe with LightSNiP.

Results are expressed as follow:

- 6/6 genotype: no mutation detected
- 6/7 genotype: UGT1A1*28 heterozygote
- 7/7 genotype: UGT1A1*28 homozygote

Patient consent

Patient must give consent for genetic testing prior to taking the sample.

Sample requirement

- EDTA whole blood sample only (1 mL minimum volume)
- Send sample by first class post at room temperature to the address on the back of this leaflet
- Do not freeze sample
- Store sample at room temperature or 4°C prior to dispatch