Bristol Genetics Laboratory is a UKAS accredited medical laboratory No.9307.

# Galactosaemia / *GALT* Pathogenic Variant Analysis

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## Sample Required

**See Sample requirements page at www.nbt.nhs.uk/genetics for full details**

- Paediatric: at least 1ml EDTA (preferably >2ml)
- Guthrie card or other tissue sample be may relevant in some cases (contact lab).

**Prenatal testing MUST be discussed with the laboratory, prior to the taking of any samples.**

Samples should be accompanied by a FULLY completed request form (available as download at www.nbt.nhs.uk/genetics or from the laboratory).

Please include details of the test required, family history, address and POSTCODE, NHS number, referring clinician and centre.

## Consent and Storage:

All genetic testing requires consent. **It is the responsibility of the referring clinician to ensure that appropriate consent has been obtained.**

DNA is stored from **ALL** patients undergoing DNA testing, unless consent for this is specifically denied.

Stored material from all referrals may be retained for quality assurance purposes and may be used anonymously for the development of new tests for the disorder in question.

## Clinical Background and Genetics

- The autosomal recessive disorder classical Galactosaemia is caused by the deficiency in activity of the enzyme galactose-1-phosphate uridyl transferase (GAL-1-PUT), which catalyses the conversion of galactose-1-phosphate to uridyl diphosphate (UDP)-galactose.
- Galactosaemia often presents in the neonatal period with failure to thrive, vomiting, jaundice, hepatomegaly and bacterial sepsis. It can result in life-threatening complications. Dietary restriction of lactose/galactose produces a rapid clinical improvement in the neonate, however the neurological and cognitive prognosis may be poor as long-term problems may still arise including speech abnormalities, bone deterioration, ovarian failure and problems with social interaction.
- Diagnosis of galactosaemia in neonates is carried out biochemically with the following GALT levels: classical galactosaemia: <5% GALT activity; carriers ~50%, Duarte 2 galactosaemia: ~25%.
- The incidence of galactosaemia in the local UK population is ~1/44,000 with a carrier frequency of ~1/110, however there is wide population variation throughout the world. The incidence of galactosaemia in the Irish traveller population is the highest, at 1/550, and in the general Irish population the incidence is ~1/30,000.
- Galactosaemia is caused by pathogenic variants in the *GALT* gene which is located at 9p13 and has 11 coding exons. To date over 220 pathogenic variants have been reported in the *GALT* gene. The most common pathogenic variant c.563A>G p.(Gln188Arg) is in exon 6. This accounts for between 63-75% of all *GALT* pathogenic variants in the local population. This varies in other populations. There are a number of population-specific pathogenic variants.
- Sequencing of the 11 coding exons would be expected to detect ~98% of *GALT* pathogenic variants**.** MLPA and long-range PCR are available to detect large deletions or duplications of the *GALT* gene. To date two different large deletions have been reported both of which have been detected in this laboratory. These deletions have been found in specific populations including Spanish, Ashkenazi Jewish and Cypriot populations.

## Service Offered

- **Diagnostic Testing:** A full *GALT* gene screen in Bristol is generally offered as confirmation of or clarification of a biochemical diagnosis. An initial screen is carried out on all patients for the common pathogenic variant, c.563A>G p.(Gln188Arg). Following this test, if affected individuals are not homozygous for p.(Gln188Arg), a full screen of the complete coding region of the *GALT* gene is undertaken.
- **Carrier Testing:** Testing of parental samples is offered once the familial variants have been identified in the affected offspring.
- **Cascade testing** can be undertaken on close adult relatives for the identified familial pathogenic variants.
- **Prenatal diagnosis** *may* be carried out **if there are adequate clinical grounds,** after discussion on a case-by-case basis. Please contact the laboratory to discuss

## Referrals

Referrals for *GALT* gene analysis are accepted in the following scenarios:

- A biochemical/suspected diagnosis of Galactosaemia
- Parents / siblings of a child with Galactosaemia
- Adult relatives of a child with Galactosaemia or *GALT* variant carrier.
- Population risk partner of a known *GALT* carrier

**Clinical Advice:** If clinical discussion is required we would recommend contact with Dr Germaine Pierre, Paediatric Metabolic Consultant, Bristol Children's Hospital, (Tel: 0117 342 8513)

**Biochemistry Lab contact:** Dr H. Kemp, Biochemical Genetics, Southmead Hospital, Bristol (Tel: 0117 414 8425)

## Target reporting Times

| | Standard / Urgent |
|---|---|
| Level 1: c.563A>G, p.(Gln188Arg) pathogenic variant analysis | 42 days / 14 days |
| Level 2: Full *GALT* gene sequencing screen | 42 days / 21 days |
| MLPA (please contact laboratory) | 42 days / 21 days |
| Level 3: Known familial variant analysis | 42 days / 21 days |
| Prenatal Diagnosis (Please contact laboratory) | 3 days |

## Quality

This laboratory participates in the following external quality assurance schemes which cover the technique and strategies used for this service: EMQN Sanger DNA sequencing scheme (since the pilot scheme was introduced in 2002) and GENQA Pathogenicity of sequence variants interpretation only scheme (pilot scheme introduced in 2012).

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