Disease NIPD for *FGFR2*-related craniosynostosis

Contact details

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Samples required

- **Pregnant Women**
  2x 10mls venous blood in plastic EDTA bottles or glass Streck tubes, this should ideally reach the laboratory within 24-48 hours of sampling
- The minimum gestation (by scan) is 9wks for accepting a sample. If earlier than 18wks then 2 blood samples a week apart may be required
- **Testing must be arranged in advance**, through your Local Clinical Genetics Department or Fetal Medicine Unit
- A completed DNA request card and ultrasound report should accompany all samples **with an appropriate telephone number and a secure fax number.**
- **Pregnancy outcome**
  Details of pregnancy outcome will be required for confirmation of laboratory results as part of the ongoing validation of new tests

Patient details

To facilitate accurate testing and reporting please provide patient demographic details (full name, date of birth, address and ethnic origin), details of any relevant family history and full contact details for the referring clinician

Introduction

The *FGFR2*-related craniosynostosis syndromes are characterised by skull deformity such as cloverleaf skull, distinctive facial features, and variable hand and foot findings. A wide range of presentations have been described among individuals with identical mutations in *FGFR2* who have Crouzon (MIM 123500), Pfeiffer (101600) or Jackson-Weiss (123150) syndromes. This suggests that other factors play a role in determining symptoms. Within a family the same mutation is usually reported to result in the same clinical syndrome. These conditions are autosomal dominant or *de novo* with complete penetrance and variable expression. Antley-Bixler syndrome (ABS) (MIM 207410) is an exceptionally rare craniosynostosis syndrome characterised by radiohumeral synostosis present from the perinatal period. *FGFR2*-related isolated coronal synostosis is characterised by uni- or bicoronal craniosynostosis only. Non-invasive prenatal genetic diagnosis (NIPD) by next generation sequencing (NGS) is possible using cell free fetal DNA (cffDNA) in pregnancies at risk of *FGFR2*-related craniosynostosis syndromes.

Referrals

All referrals should be made via a Clinical Genetics Department or Fetal Medicine Unit and will be accepted in either of the categories given below. If you wish to refer a case which does not fulfil these criteria please contact Professor Lyn Chitty (l.chitty@ucl.ac.uk) (Clinical) or Fiona McKay (Fiona.McKay@gosh.nhs.uk) (Laboratory)

- Paternal *FGFR2*-related craniosynostosis syndrome due to one of the mutations listed below **OR**
- a previous pregnancy has been confirmed to have *FGFR2*-related craniosynostosis syndrome due to one of the mutations listed below, thus there is a very small risk of recurrence due to germline mosaicism

c.755C>T, p.(Ser252Leu)
c.760C>T, p.His254Tyr)
c.863T>G, p.(Ile288Ser)
c.868T>C, p.(Trp290Arg)
c.869G>C, p.(Trp290Ser)
c.870G>T, p.(Trp290Cys)
c.1018T>C, p.(Tyr340His)
c.1019A>C, p.(Tyr340Ser)
c.1023_1025del, p.(Cys342del)
c.1024T>A, p.(Cys342Ser)
c.1025G>C, p.(Cys342Ser)
c.1025G>T, p.(Cys342Phe)
c.1030C>G, p.(Ala344Pro)
c.1032G>A p.(=)
c.758C>T, p.(Pro253Leu)
c.863T>A, p.(Ile288Asn)
c.866A>C, p.(Gln289Pro)
c.868T>G, p.(Trp290Gly)
c.870G>C, p.(Trp290Cys)
c.1018T>A, p.(Tyr340His)
c.1019A>G, p.(Tyr340Cys)
c.1021A>C, p.(Thr341Pro))
c.1024T>C, p.(Cys342Arg)
c.1024T>G, p.(Cys342Gly)
c.1025G>A, p.(Cys342Tyr)
c.1026C>G, p.(Cys342Trp)
c.1031C>G, p.(Ala344Gly)
c.1040C>G, p.(Ser347Cys)

Service offered

NGS for 28 *FGFR2*-related craniosynostosis syndrome mutations

Technical

Maternal EDTA blood spun as soon as possible after collection, cffDNA extracted from plasma. Molecular analysis by PCR followed by NGS (Illumina MiSeq). Amplification of fetal DNA is confirmed using HLA markers, or *ZFY*-specific sequences.

Target reporting time

Results are normally available within 5 days of sample receipt