Disease NIPD for FGFR3-related skeletal dysplasias

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

Achondroplasia (ACH) (MIM 100800) is an autosomal dominant skeletal disorder due to mutations in the *FGFR3* gene on chromosome 4p16.3. Around 80-90% of cases are sporadic. Thanatophoric Dysplasia (TD), a sporadic neonatal lethal skeletal dysplasia, is divided into two subsets based upon radiological findings. TD type I (MIM 187600) is associated with curved femora and variable but milder craniosynostosis and TD type II (MIM 187601) with straight femora and often cloverleaf skull. Mutations in the *FGFR3* gene have been identified in almost 100% of confirmed cases of TD. A single mutation, p.Lys650Glu, accounts for all TD type II patients reported to date. Several recurrent mutations have been identified in TD type I. Non-invasive prenatal genetic diagnosis (NIPD) by next generation sequencing (NGS) is possible using cell free fetal DNA (cffDNA) in pregnancies at risk of ACH or TD.

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)

1. At risk pregnancy
   - Paternal Achondroplasia **OR**
   - a previous pregnancy has been confirmed to have ACH or TD, thus there is a very small risk of recurrence due to germline mosaicism
2. Abnormal ultrasound findings

Achondroplasia

- Femoral length on or above the 3rd percentile (i.e. within normal range) at routine 18-20 week scan **AND** femur length and all long bones below 3rd percentile after 25 weeks gestation **AND** head circumference and abdominal circumference within or above the normal range for gestation at diagnosis. Fetal and maternal dopplers should be normal

Thanatophoric dysplasia

- The following features must be present: All long bones below the 3rd percentile **AND** small chest with short ribs
- Additional features include polyhydramnios, bowed femora, relative macrocephaly, cloverleaf skull, short fingers

Service offered

NGS for 29 *FGFR3* mutations associated with skeletal dysplasia.

Technical

Maternal EDTA blood spun as soon as possible after collection, cffDNA extracted from plasma. Molecular analysis by PCR to amplify 5 amplicons of *FGFR3*, 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