NIPD for FGFR3-related skeletal dysplasias

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. Hypochondroplasia (HCH) (MIM 146000) has very similar skeletal features to those seen in ACH but tends to be milder. About 70% of affected individuals are heterozygous for a mutation in FGFR3. Non-invasive prenatal genetic diagnosis (NIPD) by next generation sequencing (NGS) is possible using cell free fetal DNA (cffDNA) in pregnancies at risk of FGFR3-related skeletal dysplasias.

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 the laboratory (Genetics.Labs@gosh.nhs.uk).

1. At risk pregnancy
   - Paternal FGFR3-related skeletal dysplasia OR
   - a previous pregnancy has been confirmed to have FGFR3-related skeletal dysplasia, thus there is a very small risk of recurrence due to germline mosaicism

2. Abnormal ultrasound findings

Thanatophoric dysplasia

- 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

- 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 FGFR3 mutations associated with skeletal dysplasia.

Technical

Maternal EDTA blood is spun as soon as possible after collection, cffDNA is extracted from plasma. Molecular analysis is performed by PCR, followed by NGS (Illumina MiSeq). Amplification of fetal DNA will be confirmed using gender analysis in males or by the presence of paternal HLA sequences. When this is uninformative a separate NGS assay is used containing 50 heterogeneous SNPs to identify paternally inherited alleles.

Target reporting time

Results are normally available within 5 days of sample receipt.