INFO BROCHURE NIPD

FOR ACHONDROPLASIA
OR THANATOPHORIC DYSPLASIA

Non - Invasive Prenatal Diagnosis (NIPD) for Achondroplasia or Thanatophoric Dysplasia

Achondroplasia : Achondroplasia is the most frequent form of short-limb dwarfism. Affected individuals exhibit short stature caused by rhizomelic shortening of the limbs with an average adult height of 131 centimeters for males and 123 centimeters for females. Additional features are a characteristic facies with frontal bossing and midface hypoplasia, large skull and trident hand. The disorder has autosomal dominant inheritance. The c.1138G>A mutation in the FGFR3 gene accounts for 98 % of cases.
Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) is due to a single autosomal dominant mutation in the FGFR3 gene : c.1949A>T (p.Lys650Met).

Hypochondroplasia : Hypochondroplasia is a mild form of achondroplasia that can be caused by various autosomal dominant mutations in the FGFR3 gene.
Hypochondroplasia plus acanthosis nigricans is due to a single mutation in the FGFR3 gene : c.1949A>C (p.Lys650Thr).

Thanatophoric Dysplasia : Thanatophoric Dysplasia (TD) is a lethal skeletal dysplasia divided into two types based upon radiological findings. TD type I is associated with curved femora and variable but milder craniosynostosis and TD type II 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 : the c.742C>T (p.Arg248Cys) accounts for approximately 55% of cases. The FGFR3 mutation of the affected patient is not present in the unaffected parents as all cases of Thanatophoric Dysplasia are sporadic cases. Thanatophoric dysplasia is sporadic with the patient mutation not detected in parental lymphocyte DNA. There is a small risk of recurrence due to germline mosaicism in one parent.

Methods : 27 FGFR3 mutations causing Achondroplasia or Thanatophoric Dysplasia are analysed in DNA isolated from maternal blood (cell free DNA - cfDNA) which also contains fetal DNA. Such **N**on - **I**nvasive **P**renatal **D**iagnosis is referred to as NIPD. In contrast to invasive procedures such as amniocentesis (AC) or chorionic biopsy (CVS) that have an overall risk of miscarriage of 1 %, NIPD is non-invasive and has no risk for the fetus.

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The 27 FGFR3 mutations analysed in this test include :

1. Achondroplasia: c.1138G>A (p.Gly380Arg), c.1138G>C (p.Gly380Arg), c.1123G>T (p.Gly375Cys), c.1130T>G (p.Leu377Arg) and c.835A>T (p.Ser279Cys).

2. Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN): c.1949A>T (p.Lys650Met)

3. Hypochondroplasia: c.1142T>A (p.Val381Glu), c.1619A>C (p.Asn540Thr), c.1619A>G (p.Asn540Ser), c.1620C>G (p.Asn540Lys), c.1620C>A (p.Asn540Lys), c.1948A>C (p.Lys650Gln), c.1950G>C (p.Lys650Asn), c.1950G>T (p.Lys650Asn)

4. Hypochondroplasia plus acanthosis nigricans: c.1949A>C (p.Lys650Thr)

5. Thanatophoric dysplasia: c.742C>T(p.Arg248Cys), c.1118A>G (p.Tyr373Cys), c.746C>G (p.Ser249Cys) , c.1108G>T (p.Gly370Cys), c.1111A>T (p.Ser371Cys), c.2419T>G (p.*807Glyext*102), c.2419T>A (p.*807Argext*102), c.2420G>T (p.*807Leuext*102), c.2420G>C (p.*807Serext*102), c.2421A>T (p.*807Cysext*102), c.2421A>C (p.*807Cysext*102), c.2421A>G (p.*807Trpext*102), c.1948A>G (p.Lys650Glu)

Samples : At least 20 ml blood in specific blood tubes provided by GENDIA is required from the mother. The maternal blood can be taken from week 10 of the pregnancy. The sample has to be sent by Express mail to GENDIA's lab in Antwerp, Belgium, and arrive there within 2 days of withdrawal.
All testing must be arranged in advance by emailing to NIPT@GENDIA.net.
It is essential that the laboratory is advised of the pregnancy gestation and that this has been confirmed by ultrasound scan.

Turnaround time : NIPD takes approximately 2 weeks to complete from arrival of the sample in the GENDIA lab.

Indications : NIPD for FGFR3-related Skeletal Dysplasia can be performed when :

1. The father has FGFR3-related Skeletal Dysplasia with a documented FGFR3 mutation.

2. 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.

3. Neither of the parents is affected, but FGFR3-related Skeletal Dysplasia in the fetus is suspected based upon fetal ultrasound findings.

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Contraindications : NIPD for FGFR3-related Skeletal Dysplasia can NOT be performed when :

1. When the mother is affected no NIPD can be performed as the maternal FGFR3 mutation cannot be differentiated from the fetal mutation in maternal blood.

2. Samples from twin / multiple pregnancies or missed abortion / vanishing twin cannot be accepted for NIPD.

Limitations of NIPD : Samples are analyzed for 29 FGFR3 mutations only.

Reliability of NIPD results : The reliability of NIPD is very high (99 %).

Results : NIPD results will be sent to the physician / genetic counseler who ordered the test and who will explain the test results and recommended follow-up steps if necessary.

Follow up steps :

1. In case of a normal NIPD result : when the FGFR3 mutations are absent from the maternal blood no specific follow up is necessary, unless ultrasound examination of the fetus reveals anomalies and further genetic studies might be indicated.

2. In case of an abnormal NIPD result : when a FGFR3 mutation is found in the maternal blood, the fetus is affected. The physician / genetic counseler will discuss the implications of this finding with the parents.

Price : 1400 Euro.

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