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## **Non - Invasive Prenatal Diagnosis (NIPD) for Apert syndrome**

**Apert syndrome** : Apert syndrome is a congenital disorder characterized primarily by craniosynostosis, midface hypoplasia, and syndactyly of the hands and feet. The primary anomaly is a tendency to fusion of bony structures in the skull (leading to craniosynostosis) and in the extremities (leading to syndactyly). Apert syndrome can be detected prenatally by ultrasound of the fetus.

**Inheritance** : Apert syndrome is an autosomal dominant condition caused by mutations in the FGFR2 gene encoding the Fibroblast Growth Factor Receptor. Usually, the FGFR2 mutation of the affected patient is not present in the unaffected parents (sporadic cases); in these cases there is a small recurrence risk due to the possibility of germline mosaicism in one parent

In familial cases the affected parent also has a mutation in the FGFR2 gene; in these cases there is a 50% risk of any future children inheriting the FGFR2 mutation.

Two mutations in FGFR2 exon 8, c.755C>G (p.Ser252Trp) and c.758C>G (p.Pro253Arg), account for over 98% of reported cases. A third FGFR2 mutation (c.755\_756delinsTT - p.Ser252Phe) is less common.

**Methods** : The 3 specific FGFR2 mutations causing Apert syndrome (p.Ser252Trp, p.Pro253Arg p.Ser252Phe) can be analysed in DNA isolated from maternal blood (cell free DNA - cfDNA) which also contains fetal DNA. Such **Non - Invasive Prenatal Diagnosis** 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.

**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.

**Testing must be arranged in advance by emailing 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 Apert syndrome can be performed when :

1. Neither parent is affected with Apert syndrome, but Apert syndrome in the fetus is suspected based upon fetal ultrasound findings of acrocephaly with syndactyly.
2. The father has Apert syndrome with a documented FGFR2 mutation. **The original test lab reports with documented FGFR2 mutation must be made available before NIPD can be planned.**
3. A previous pregnancy has been confirmed to have Apert syndrome, thus there is a very small risk of recurrence due to germline mosaicism.

**Contraindications** : NIPD for Apert syndrome can NOT be performed when :

1. When the mother has Apert syndrome no NIPD can be performed as the maternal FGFR2 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 3 FGFR2 mutations associated with Apert syndrome only.

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

**Results** : NIPD results will be sent to the physician / genetic counselor 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 FGFR2 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 FGFR2 mutation is found in the maternal blood the fetus is affected with Apert syndrome, and the physician / genetic counselor will discuss the implications of this finding with the parents.

**Price** : 1400 Euros.