INFO BROCHURE NIPD

FOR CRANIOSYNOSTOSIS

Non - Invasive Prenatal Diagnosis (NIPD) for Craniosynostosis

Craniosynostosis : Craniosynostosis is a condition in which one or more of the fibrous sutures in an infant skull prematurely fuses by turning into bone (ossification), thereby changing the growth pattern of the skull. Craniosynostosis can be caused by mutations in several genes, including FGFR2.
The FGFR2-related craniosynostosis syndromes are characterised by skull deformity such as cloverleaf skull, distinctive facial features, and variable hand and foot findings. These syndromes have been described as Crouzon syndrome, Pfeiffer syndrome, Jackson- Weiss syndrome, Antley-Bixler syndrome or isolated coronal synostosis.

Inheritance : The FGFR2-related craniosynostosis syndromes are autosomal dominant conditions caused by mutations in the FGFR2 gene encoding the Fibroblast Growth Factor Receptor 2. The FGFR2 mutation of the affected patient can be absent in the unaffected parents (sporadic cases). In familial cases the affected parent also has a mutation in one of the two FGFR2 genes and a risk of 50 % to get another affected child that inherited the FGFR2 mutation.FGFR2-related craniosynostosis syndromes show reduced penetrance and variable expressivity; testing of apparently unaffected parents is essential to determine recurrence risk.

Methods : 28 FGFR2 mutations causing Craniosynostosis 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. The 28 FGFR2 mutations analysed in this test include :

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.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>C, p.(Cys342Ser)
c.1025G>A, p.(Cys342Tyr)
c.1025G>T, p.(Cys342Phe)
c.1026C>G, p.(Cys342Trp)
c.1030C>G, p.(Ala344Pro)
c.1031C>G, p.(Ala344Gly)
c.1040C>G, p.(Ser347Cys)
c.1032G>A p.(=)

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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 from arrival of the sample at GENDIA.

Indications : NIPD for Craniosynostosis can be performed when :

1. The father has Craniosynostosis with one of the 28 FGFR2 mutations listed above.
The original test lab reports with documented FGFR2 mutation must be made available before NIPD can be planned.

2. A previous pregnancy has been confirmed to have Craniosynostosis, thus there is a very small risk of recurrence due to germline mosaicism.

3. None of the parents is affected, but Craniosynostosis in the fetus is suspected based upon fetal ultrasound findings.

Contraindications : NIPD for Craniosynostosis can NOT be performed when :

1. When the mother has Craniosynostosis no NIPD can be performed as the maternal FGFR2 mutation cannot be differentiated from the fetal mutation in maternal blood.

2. When the father has Craniosynostosis which is not due to one of the 28 FGFR2 mutations specified in the Methods.

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

Limitations of NIPD : Samples are analyzed for 28 FGFR2 mutations only.

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

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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 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 Craniosynostosis. The physician / genetic counseler will discuss the implications of this finding with the parents.

Price : 1400 Euros.

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