SickKids | Genome Diagnostics

CRANIOSYNOSTOSIS

Craniosynostosis occurs when the bones of a baby's skull fuse together before the brain has stopped growing. This can happen during pregnancy or the first few months of life. Fusion at one or more locations and excessive growth at others leads to distortion of the skull. This distortion may cause increased pressure and impaired blood flow in the brain, airway obstruction, impaired vision and hearing, learning difficulties and adverse psychological effects. Deformations in the skull may also be accompanied by abnormalities in the skeletal system, often in the hands and feet.

GENETICS

Both genetic and environmental factors contribute to craniosynostosis. Most cases that are genetic in origin arise from new mutations. Genetic craniosynostosis syndromes show autosomal dominant inheritance. Affected individuals have a 50% chance of transmitting the disorder to each child.

Common craniosynostosis disorders may be caused by mutations in the fibroblast growth factor receptor 1, 2 or 3 (*FGFR1*, *FGFR2*, *FGFR3*) genes or a transcription factor gene called *TWIST*. DNA-based testing of these genes may be helpful in establishing a diagnosis of non-syndromic craniosynostosis, Apert, Crouzon, Pfeiffer and Saethre-Chotzen syndromes.

WHO SHOULD BE TESTED?

- Individuals clinically suspected of being affected with craniosynostosis
- Pregnancies at risk due to abnormal ultrasound findings or a family history of craniosynostosis

TEST METHODS & SENSITIVITY

Apert Syndrome: Samples are analyzed by direct DNA sequencing for the presence of the two most common mutations in the *FGFR2* gene: p.Ser252Trp and p.Pro253Arg. This test detects ~98% of patients with Apert Syndrome.

Non-syndromic Craniosynostosis: Samples are analyzed for the presence of the defining mutation in the *FGFR3* gene: c.749C>G (p.Pro250Arg).

Crouzon Syndrome: Samples are analyzed by direct sequencing to detect mutations in exons 7 and 8 of *FGFR2*. This test will detect ~50% of patients clinically suspected to have Crouzon Syndrome. If no mutation is found in *FGFR2*, samples are tested for the presence of the non-syndromic craniosynostosis mutation in the *FGFR3* gene.

Pfeiffer Syndrome: Samples are analyzed by direct sequencing to detect mutations in exons 7 and 8 of *FGFR2*. This test will detect 60-70% of patients clinically suspected to have Pfeiffer Syndrome. If no mutation is found in *FGFR2*, samples are tested for the presence of the non-syndromic craniosynostosis mutation in the *FGFR3* gene.
For cases of familial Pfeiffer Syndrome, sequencing is used to detect the c.755C>G (p.Pro252Arg) mutation in *FGFR1*.

Saethre-Chotzen Syndrome: Samples are analyzed by direct sequencing to detect mutations in *TWIST*. This test will detect ~60% of patients clinically suspected to have Saethre-Chotzen Syndrome. If no mutation is found in *TWIST*, samples are tested for the presence of the non-syndromic craniosynostosis mutation in the *FGFR3* gene.

Dosage analysis and reflex testing: Quantitative testing for the *TWIST, FGFR2* (exons 7&8 only) and *FGFR3* (exons 6 & 7 only) genes are available upon request. Full sequencing of the FGFR2 and FGFR3 genes are also available—please consult with the Genome Diagnostics Laboratory before ordering this reflex testing.

POTENTIAL OUTCOMES & INTERPRETATION OF TEST RESULTS

Clinical Diagnosis	Gene Tested	Explanation
Apert Syndrome	*FGFR2* (exon 7)	• The detection of a mutation in the gene(s) indicated supports the associated clinical diagnosis. • When no mutation is detected in the gene(s) indicated, the associated clinical diagnosis is not supported by genetic testing. The absence of a mutation does not rule out the diagnosis.
Crouzon & Pfeiffer Syndromes	1. *FGFR2* (exon 7 & 8) 2. *FGFR3* (p.Pro250Arg)	
Familial Pfeiffer Syndrome	*FGFR1* (p.Pro252Arg)	
Saethre-Chotzen Syndrome	1. *TWIST* 2. *FGFR3* (p.Pro250Arg)	
Non-syndromic Craniosynostosis	*FGFR3* (p.Pro250Arg)	

For More Information

Online Mendelian Inheritance in Man (OMIM) http://www.ncbi.nlm.nih.gov/omim/
- Apert # 101200
- Crouzon # 123500
- Pfeiffer # 101600
- Saethre-Chotzen # 101400
- Non-syndromic # 602849

GeneReviews online clinical information resource http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=craniosynostosis

To locate a genetics center near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counsellors website at www.nsgc.org

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1. Molecular testing may not detect all possible mutations for this disease.

2. Test results should be interpreted in the context of clinical findings, family history, ethnic background and other laboratory data.

3. Chromosome analysis may identify patients with a translocation involving chromosome 7 or a microdeletion of band 7p21-22. These studies should be performed on all patients clinically suspected of being affected with Saethre-Chotzen Syndrome prior to molecular analysis.

4. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.