Craniosynostosis Syndromes
Sequencing

Craniosynostosis is the early fusion of bones or premature ossification of sutures (the tissues between bones) of the skull. This developmental anomaly often leads to an abnormal head shape. Craniosynostosis is relatively common, occuring in approximately 1 in 2500 live births. There is considerable variability in physical appearance between patients with craniosynostoses. A common finding is brachycephaly (a shortened distance between the front and back of the head) due to early closure of one or both coronal sutures. Other sutures can be involved as well, and the most dramatic appearance would be that of a cloverleaf skull (kleeblattschädel) deformity when multiple sutures are affected. Some individuals have isolated craniosynostosis and are mildly affected; with an abnormal head shape being their only health concern. Others are clinically diagnosed with one of the more than 100 inherited conditions where craniosynostosis is one of several features of the disorder in question. Testing for one (or more) genes from our offering can aid in confirming a clinical diagnosis and genetic counseling. Once a mutation is identified in an affected individual, this information can be used for future prenatal diagnosis.

Genetics:
Most of the conditions we offer testing for are inherited in an autosomal dominant inheritance pattern. In these cases, a parent carrying the mutated gene has a 50% chance of passing it on to an offspring, regardless of gender. A person can harbor a mutation from one of two sources:

- either the person inherited this mutation from an affected parent
- or the mutation was a *"de novo"* DNA change that occurred in the egg or sperm from which the affected individual developed

Carpenter syndrome and POR deficiency syndromes are inherited differently; these two conditions follow an autosomal recessive pattern. If a child is affected with one of these conditions, it is implied that each parent is a carrier of one mutated gene and the risk of having future affected offspring is 25% with each pregnancy. A person who is a carrier for an autosomal recessive condition does not display features of the disorder in question.

Testing Methods:
DNA is obtained from a blood (postnatal) sample or a prenatal specimen (direct or cultured Chorionic Villus Sampling or amniocytes). Sequencing is performed on sections of the requested gene(s) that are thought to contain most known mutations. For three syndromes (CFNS, CRS2 and SCS), deletions or duplications of the target genes will also be determined by MLPA (since deletions/duplications are responsible for some cases).

Test Sensitivity and Limitations:
Some of these syndromes can be caused by different mutations in more than one gene. Some of these syndromes are caused by mutations in only one gene with specific mutations in that gene. For example, the *FGFR2* gene has been identified as a Crouzon syndrome disease gene. It accounts for about 90% of cases of Crouzon syndrome. Therefore, this test will be negative 10 percent of the time but that does not mean that the diagnosis of Crouzon syndrome is wrong. If a *FGFR2* mutation has been identified in a person with Crouzon syndrome, this test can determine whether or not a family member or his/her fetus has the disorder with nearly 100% accuracy. On the other hand in Apert syndrome, the p.S252W and p.P253R mutations in *FGFR2* account for almost 100% of patients.

Turnaround Time:
Results are reported to the referring physician within 4 weeks from the receipt of the specimen.

Specimen and Shipping Requirements:
For Postnatal Cases: 2 yellow-top (ACD-A or ACD-B) or 2 lavender-top (EDTA), 5-10 ml tubes of blood.

For Prenatal Cases: 2 confluent T-25 flasks of cultured cells (originating from amniotic fluid or chorionic villi) or more than 4 mg of direct CVS tissue, or 10 ml of direct amniotic fluid (AF) as well as 2 lavender-top (EDTA), 5-10 ml tubes of blood from the pregnant patient and her partner are required. Note: parental blood samples are requested for confirmation studies necessary in some cases; maternal blood is also used for maternal cell contamination studies.

Tubes of blood, cultured cells, direct CVS, and direct AF should be kept and shipped refrigerated or at room temperature *(do NOT freeze)*.

Mount Sinai

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Sequencing for Craniosynostosis Syndromes

Gene Testing:

The genes for which Mount Sinai Genetic Testing Laboratory offers testing are
(Exon numbering according to ENSEMBL database – www.ensembl.org/Homo_sapiens/index.html):

Syndrome	Common Phenotypic Traits	Gene(s) Exon(s) Sequenced *(Also, MLPA if applicable)*	Molecular Diagnostic Rate	References
Antley-Bixler syndrome	Midfacial hypoplasia, camptodactyly, bowing of femoral bones, fractures, cardiac malformations, no genitalia anomalies and no disorders of steroidogenesis	*FGFR2*; exons 7,8	30-50%	Chun et al (1998) Am J Med Genet 77:219.
Apert syndrome	Severe craniofacial features, symmetric hand and feet syndactyly, and >50% have learning problems	*FGFR2*; exon 7	99-100%	Wilkie et al. (1995) Nat Genet 9:101.
Beare-Stevenson syndrome	Acanthosis nigricans and cutis gyrata	*FGFR2*; exon 9	99%	Przyelpa et al (1997) Nat Genet 13:492.
Crouzon syndrome	Prominent eyes or ocular proptosis, flat midface, prominent mandible, strabismus, dental abnormalities, cleft palate, hearing loss, and cervical spine problems	*FGFR2*; exons 7, 8 (**FGFR3*; exon 6)	90%	Lewanda & Jabs (2002)
Crouzon and acanthosis syndrome (Crouzonodermo-skeletal syndrome)	Acanthosis nigricans and choanal atresia and hydrocephalus	*FGFR3*; exon 8	99%	Meyers et al (1995) Nat Genet 11:462.
Jackson-Weiss syndrome	Large great toes or other bony foot deformities	*FGFR2*; exons 7, 8 (**FGFR3*; exon 6)	90%	Jabs et al (1994) Nat Genet 8:275.
Muenke syndrome	Highly variable, but may include: bone deformities (such as carpal and tarsal bony fusion), ocular proptosis, strabismus, dental abnormalities, cleft palate, hearing loss	*FGFR3*; exon 6	100%**	Lewanda & Jabs (2002)
Non-syndromic coronal synostosis	Isolated coronal synostosis	*FGFR2*; exons 7, 8	Familial 74%	Lajeunie et al (1999) J Med Genet. 36:9.
		FGFR3; exon 6	Sporadic 15%	Renier et al (2000) J Neurosurg. 92:631
Pfeiffer syndrome	Hand and feet abnormalities with broad thumbs and great toes, brachydactyly (short phalanges) and syndactyly (webbing), and more severe cases have upper arm (radioulnar) synostosis and other organ system abnormalities	*FGFR1*; exon 7 *FGFR2*; exons 7, 8 (**FGFR3*; exon 6)	85%	Lewanda & Jabs (2002)
Carpenter syndrome	Polydactyly (extra digits)	*RAB23* cds	less than 100%	Jenkins et al (2007) Am J Hum Genet 80:1162.
Craniofrontonasal syndrome (CFNS)	Midline problems including hypertelorism and broad nasal tip	*EFNB1* cds (MLPA)	93%	Wieland et al Hum Mutat 26:113.
Craniosynostosis, Boston Type (CRS2)	Forehead retrusion, recession of the superorbital region and digital abnormalities	*MSX2* cds† (MLPA)	Some cases	Jabs et al. (1993) Cell 75:443.
Craniosynostosis with radial defects (phenotypic overlap with Baller-Gerold syndrome)	Radial ray defects and visceral organ abnormalities	*TWIST1* cds (*RECQL4* mutations are associated with Baller-Gerold syndrome)	Some cases	Gripp et al (1999) Am J Med Genet 82:170.
Saethre-Chotzen syndrome (SCS)	Facial asymmetry, eyelid ptosis (drooping), and mild hand and foot brachydactyly and syndactyly	*TWIST1* cds (**FGFR2*; exon 7. *FGFR3*; exon 6) (MLPA)	79%	Paznekas et al (1998) Am J Hum Genet 62: 1370.
POR deficiency (cytochrome P450 reductase)	Antley-Bixler-like features with genitalia anomalies and disorders of steroidogenesis, cytochrome P450 reductase deficiency	*POR* coding sequence (cds)	50-70%	Miller et al (2005) Ann N Y Acad Sci 061:100.

* *If preceding exons are negative for any mutations, then the following exon(s) will be sequenced.*

** *Syndrome is defined by mutation, not phenotype*

† *MLPA may detect a duplication correlated to CRS2; however, MLPA may detect a deletion that would be associated with a distinct condition, Parietal formina.*

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