Cleft and Craniofacial Gene Panels

Genes Tested

Cleft and Craniofacial Gene Panel:

ABCC9, ACSS2, ACTB, ACTG1, ADAMTSL4, AHDC1, ALPL, ALX1, ALX3, ALX4, AMELX, AMER1, AMMECR1, AMOTL1, ANKH, ANKRD11, ARHGAP29, ARSB, ASPH, ASXL1, ASXL3, B3GAT3, B3GLCT, BCOR, BMP2, BMP4, BMPR1B, BPNT2, BRAF, BRD4, C2CD3, CBFB, CCNQ, CD96, CDC45, CDH1, CDKN1C, CDON, CENPF, CEP164, CHD5, CHD7, CILK1, CNOT1, COG1, COL11A1, COL11A2, COL2A1, COL9A1, COL9A2, COL9A3, COLEC10, COLEC11, CPLANE1, CREBBP, CTNND1, CTSK, CYP26B1, DDX59, DHCR7, DHODH, DISP1, DLL1, DLX4, DPF2, DPH1, DVL1, DVL3, EDN1, EDNRA, EFNA4, EFNB1, EFTUD2, EHMT1, EIF4A3, EP300, ERF, ESCO2, ESRP2, EVC, EVC2, EYA1, FAM20C, FBN1, FGD1, FGF10, FGF8, FGF9, FGFR1, FGFR2, FGFR3, FLNA, FLNB, FOXE1, FOXI3, FRAS1, FREM1, FST, FTO, FZD2, GAS1, GDF11, GJA1, GLI2, GLI3, GNAI3, GNAS, GNPTAB, GPC3, GPC4, GRHL3, GSC, GTF2E2, GZF1, HDAC8, HIST1H1E, HNRNPK, HUWE1, HYAL2, HYLS1, IDS, IDUA, IFT122, IFT140, IFT43, IGF1R, IGF2, IHH, IL11RA, INPPL1, IRF6, IRX5, ISM1, JAG1, KAT6A, KAT6B, KDM1A, KDM6A, KIAA0586, KIF7, KMT2D, KRAS, LOXL3, LRP2, LTBP1, MAFB, MAP3K7, MASP1, MED13L, MED25, MEGF8, MEIS2, MID1, MKS1, MN1, MSX1, MSX2, MTX2, MYCN, MYMK, MYT1, NBAS, NECTIN1, NEDD4L, NIPBL, OFD1, P4HB, PAX1, PAX3, PAX7, PDE4D, PGM1, PHEX, PHF21A, PHF8, PIEZO2, PIGN, PJA1, PLCB4, PLCH1, PLEKHA5, PLEKHA7, PLOD3, POLR1A, POLR1B, POLR1C, POLR1D, POR, PORCN, PPP1R12A, PRRX1, PSAT1, PTCH1, PTDSS1, PTPN11, RAB23, RAD21, RAX, RBM10, RECQL4, RIPK4, ROR2, RPGRIP1L, RPL5, RSPRY1, RUNX2, RYK, SATB2, SCARF2, SCLT1, SCN4A, SEC24D, SEMA3E, SF3B2, SF3B4, SHH, SHOC2, SHROOM3, SIN3A, SIX1, SIX2, SIX3, SIX5, SKI, SLC25A24, SMAD2, SMAD3, SMAD4, SMAD6, SMARCA4, SMARCB1, SMC1A, SMC3, SMG9, SMO, SMS, SMURF1, SNRPB, SON, SOST, SOX11, SOX6, SOX9, SPECC1L, SPRY1, SPRY4, STAG2, STIL, SUFU, SUMO1, TBC1D32, TBX1, TBX22, TCF12, TCOF1, TFAP2A, TFAP2B, TGDS, TGFB1, TGFB2, TGFB3, TGFBR1, TGFBR2, TGIF1, TLK2, TMCO1, TOPORS, TP63, TRAF7, TRRAP, TWIST1, TWIST2, TXNL4A, UBE3B, USP9X, VAX1, VCAN, WASHC5, WDR19, WDR35, WNT5A, YAP1, YWHAE, ZEB2, ZIC1, ZIC2, ZNF462, ZSWIM6

Stickler Syndrome Gene Panel:

BMP4, COL11A1, COL11A2, COL2A1, COL9A1, COL9A2, COL9A3, GZF1, LOXL3, LRP2, PLOD3, SOX9, VCAN

Treacher Collins Syndrome and Mandibulofacial Dysostosis Gene Panel

DHODH, EDNRA, EFTUD2, POLR1A, POLR1B, POLR1C, POLR1D, SF3B4, TCOF1, TXNL4A

Description:

Cleft lip with or without cleft palate (CL/P) is a common congenital malformation with genetic and environmental risk factors. CL/P occurs in about 1 in 1,000 births. Approximately 70% are isolated and multifactorial in etiology and 30% are syndromic with chromosomal or single-gene etiologies. Identifying a genetic etiology for patients with craniofacial malformations may assist in medical management and recurrence risk estimates. This Cleft and Craniofacial Gene Panel utilizes exome sequencing (ES) technology to analyze 288 genes, which were identified through careful curation to cover a wide variety of craniofacial indications from isolated and syndromic CL/P to other craniofacial malformations such as craniosynostosis and holoprosencephaly. Two sub-panels, Stickler Syndrome Gene Panel (13 genes) and Treacher Collins Syndrome and Mandibulofacial Dysostosis Gene Panel (10 genes) are also offered as individual tests. Trio analysis is available with the option to reflex from the sub-panels to the Cleft and Craniofacial Gene Panel or from any of the panels to whole exome analysis (see **Note** on page 2). This test will not include the identification of ACMG recommended actionable incidental findings.

Indications:

- Orofacial clefts (cleft lip and/or palate)
- Stickler syndrome
- Treacher Collins syndrome
- Mandibulofacial dysostoses
- Van der Woude syndrome
- Pierre Robin sequence

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- Craniofacial macrosomia
- Craniosynostosis
- Holoprosencephaly
- Ocular defects – myopia, cataracts, retinal detachment, vitreous anomalies, glaucoma
- Conductive or sensorineural hearing loss
- Craniofacial/skeletal abnormalities – midface hypoplasia, spondyloepiphyseal dysplasia, early-onset arthritis

What Is Reported?

Variants that will be discussed in detail in the report:

- Pathogenic and likely pathogenic variants
- Variants of uncertain clinical significance may be discussed in detail on a case-by-case situation

Variants that will be listed in the report:

- Variants of uncertain clinical significance
- Variants that predict an increased risk of diseases, but do not cause a disease by themselves (risk alleles)

What is not reported:

- Variants in genes not included in the predefined gene list
- Variants classified as benign or likely benign

Note: Cleft and Craniofacial, Stickler and Treacher Collins Syndrome and Mandibulofacial Dysostosis Gene Panel cases with negative or uncertain findings can be reflexed to Whole Exome Sequencing (WES). A separate test order and a signed consent form is required for all WES testing. In addition, including biological parental samples is strongly encouraged to assist with the analysis of WES and to increase test yield. Reflex to WES orders can either be placed simultaneously or separately. Separate reflex to WES orders are subject to review prior to the initiation of testing. Please see our website at www.cincinnatichildrens.org/exome to obtain a WES test requisition and consent form.

Methodology:

The Cleft and Craniofacial Gene Panel uses the Human Comprehensive Exome kit to capture the exonic regions of genes from the genomic DNA extracted from the patient. Targeted regions are sequenced using an Illumina sequencing system with paired end reads. Sequence reads are aligned to the human reference genome (build UCSC hg19). Variants within exons and flanking sequences are identified and evaluated by a validated in-house developed bioinformatics analysis pipeline and Fabric Genomic Analysis platform. Data quality is assessed to confirm it has a minimum coverage of 20X for >95% of targets of interest.

Technical Limitations:

- Pathogenic variants may be present in a portion of the genes not covered by this test or in regions with suboptimal data due to homologous issue, poly-nucleotides, or nucleotide repeats, and therefore may not be identified. Thus, the absence of identified pathogenic variants does not exclude the possibility of a genetic etiology for the patient's symptoms.
- Certain types of variants are not detected. Only single base pair changes or small insertions or deletions of DNA are detected. Large deletions, duplications, or rearrangements, mitochondrial genome mutations, repeat expansions, low level mosaicism and many epigenetic defects may not be detected by this test.

Regions of Homology

These gene regions with homology may generate suboptimal data with potential false negative results.

GENE	TRANSCRIPT	EXON	CHROM	EXON_START	EXON_END
IDS	NM_000202	3	X	148584841	148585019
PIEZO2	NM_022068	4	18	10911183	10911226
SMS	NM_004595	11	X	22012429	22012469
SUMO1	NM_003352	1	2	203103162	203103174
TLK2	NM_006852	4	17	60599564	60599634
TLK2	NM_006852	6	17	60601596	60601692
TLK2	NM_006852	10	17	60637376	60637487
TLK2	NM_006852	22	17	60689752	60689926

Low coverage (<20X) regions

GENE	REGION	LENGTH	CHROM	EXON_START	EXON_END
AMMECR1	NM_015365:c.888-8_894	15 bps	X	109441856	109441870
CCNQ	NM_152274:c.-8_34	42 bps	X	152864496	152864537
EHMT1	NM_024757:c.-8_21+8	37 bps	9	140513473	140513509
EVC	NM_153717:c.32_174+8	151 bps	4	5713139	5713289
GPC3	NM_004484:c.1166+1_1166+8	8 bps	X	132833915	132833922
GPC4	NM_001448:c.320-8_331	20 bps	X	132458553	132458572
HUWE1	NM_031407:c.11633-8_11634	10 bps	X	53566040	53566049
KDM6A	NM_021140:c.1393_1425+8	41 bps	X	44920632	44920672
KIAA0586	NM_001244189:c.4655-8_4739+8	101 bps	14	59010593	59010693
KIAA0586	NM_001244189:c.447-8_569+8	139 bps	14	58907931	58908069
PHEX	NM_000444:c.1483-8_1586+8	120 bps	X	22196382	22196501
PHEX	NM_000444:c.733-8_760	36 bps	X	22112093	22112128
RPGRIP1L	NM_015272:c.3413_3432+8	28 bps	16	53656123	53656150
RYK	NM_001005861:c.-8_23	31 bps	3	133969474	133969504
STAG2	NM_001042749:c.2925-8_2946	30 bps	X	123217263	123217292

Low coverage (<20X) regions (continued)

GENE	REGION	LENGTH	CHROM	EXON_START	EXON_END
STAG2	NM_001042749:c.2989_3053+8	73 bps	X	123217335	123217407
STAG2	NM_001042749:c.289-8_296	16 bps	X	121526213	121526227
STAG2	NM_001042749:c.369_385+8	25 bps	X	123171457	123171481
TBC1D32	NM_152730:c.2564_2570+8	15 bps	6	121526213	121526227
TBX1	NM_080646:c.89_209	121 bps	22	19748482	19748602
USP9X	NM_001039590:c.2626_2636+3	14 bps	X	41027461	41027474
ZSWIM6	NM_020928:c.426_562	137 bps	5	60628525	60628661

Please note: *These regions represent the low coverage (<20X) regions identified during our test validation. For specific patient cases, these regions may vary.*

Turn-Around Time:

56 days (8 weeks)

Prenatal samples: 28 days (4 weeks)

Specimen:

At least 3 mls whole blood in a lavender top (EDTA) tube, saliva in an Oragene saliva kit, or 25 mL amniotic fluid or two (2) T25 flasks grown to confluence. Please call the lab at 513-636-4474 for a free saliva collection kit. Label the tube with the patient's name, birth date, and date of collection. Alternatively, 10 mcg of DNA extracted by a CLIA certified lab may be submitted.

CPT Codes:

Cleft and Craniofacial Gene Panel: **81404 81405, 81406, 81479**

Stickler Syndrome Gene Panel: **81479(x4)**

Treacher Collins Syndrome and Mandibulofacial Dysostosis Gene Panel: **81479(x4)**

Shipping Instructions:

Please enclose **test requisition** with sample. **All information must be completed before sample can be processed.**

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Saturday.

Ship to:

Genetics and Genomics Diagnostic Laboratory
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474

References:

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