Autism / Intellectual Disability / Multiple Anomalies
Indication-Specific Gene Panel

Including: sequencing and high resolution deletion/duplication analysis

PANEL DESCRIPTION:
Individuals with autism spectrum disorder, developmental delays, intellectual disabilities, and/or congenital birth defects may have an identifiable underlying genetic cause. This panel is designed to interrogate 117 genes of interest for both sequence-based mutations and small-scale deletions or duplications.

PANEL OVERLAP:
This panel covers all genes included in other panels offered by our laboratory, as well as additional genes of clinical significance.
- Noonan Syndrome/RASopathy Disorders Panel, and
- Rett/Atypical Rett/Angelman/Angelman-like Syndromes Panel

PANEL DETAILS:
- This panel includes both sequencing and high resolution deletion/duplication analysis of the genes specified.
  - Sequencing is performed using a customized next generation sequencing library. Analysis includes the coding exons of all genes in the panel plus ten bases into the introns and untranslated regions (5' and 3'). Sanger sequencing is performed to confirm variants suspected or confirmed to be pathogenic.
  - Deletion/duplication analysis is performed using a high resolution, custom microarray platform designed to target the genes of interest at the exon level.
- Detection rates are limited to the genes specified; this test does not provide whole genome analysis.
- Gene panels are a more cost-effective approach than single gene testing to confirm or establish a diagnosis. However, if single gene testing is desired for the patient or family members of an individual with a known mutation, that must be ordered separately.

ADDITIONAL TESTING DETAILS:
- If microarray analysis is performed, it will be done using a high resolution, single nucleotide polymorphism (SNP) platform designed to interrogate the whole genome at a resolution much higher than is possible using traditional karyotyping or fluorescence in situ hybridization (FISH) methodologies. Our High Density SNP array contains a total of 2.6 million markers distributed throughout the genome for the detection of both genomic dosage anomalies (deletions and duplications) and regions of homozygosity (ROH; regions lacking typical amounts of genetic variation). This marker density provides a global resolution of 10 Kb to 20 Kb for copy number changes and 5 Mb resolution for ROH.
- If methylation analysis is performed, it will be done using a methylation-specific PCR assay to identify imprinting abnormalities of chromosome 15. Methylation analysis is used to detect and identify the parental origin of deletions, uniparental disomy (UPD), and methylation defects occurring in the imprinted promoter regions of chromosomes 14 and 15.

RECOMMENDED TESTING STRATEGY:
Tests below can be ordered individually, however our laboratory’s recommended Comprehensive Testing for autism, intellectual disability, and multiple anomalies includes the following three tests:
- High Density SNP Microarray
  - Between 10% and 20% of individuals with developmental disabilities, autism, or congenital anomalies have copy number changes, microdeletions, or microduplications, detected by microarray analysis. The American College of Medical Genetics recommends microarray as a first tier test for individuals with these indications due to its increased diagnostic yield compared to traditional chromosome analysis1.
Next Generation Sequencing
- Single gene disorders cause developmental disabilities, autism, or congenital anomalies in an additional number of individuals. Next generation sequencing (NGS) analyzes multiple genes at once, making this a cost-effective method of testing genes known to be as associated with these indications.

Targeted Deletion/Duplication Analysis
- If SNP Microarray Analysis and NGS are normal, Deletion/Duplication Analysis is performed to identify partial or whole gene deletions and duplications in the associated genes, another potential cause of developmental disabilities, autism, or congenital anomalies.

IF INDICATED, add Methylation 15 studies
- For patients with suspected Angelman or Prader-Willi syndromes, Methylation Analysis of chromosome 15 will identify abnormalities in patients who have methylation errors that cannot be detected by SNP Microarray Analysis.

DISORDERS INCLUDED IN THIS PANEL:
- Aarskog (Faciogenital dysplasia)
- Opitz
- X-linked hydrocephalus, including L1 GeneReviews® http://www.ncbi.nlm.nih.gov/books/NBK1484/
INDICATIONS FOR TESTING:
- Developmental delay, learning disability, or intellectual disability
- Autism spectrum disorder
- Abnormal growth parameters such as failure to thrive, short stature, and overgrowth
- Macrocephaly and microcephaly
- Birth defects
- Structural brain anomalies, including lissencephaly
- Seizure disorders
- Vision/hearing problems
- Low muscle tone
- Dysmorphic facial features
- Certain dermatologic findings

SPECIMEN COLLECTION & TRANSPORT:
Complimentary test kits are available upon request, but are not required.

SAMPLE TYPE and REQUIREMENTS:
- blood, > 3 months of age: 3-5 ml whole blood in an EDTA tube (purple top)
- blood, newborn: 1-3 ml whole blood in an EDTA tube (purple top)
- buccal swab: 5 swabs
- extracted DNA: 5 µg in a DNA microcentrifuge tube

SHIPPING:
- Maintain and ship samples at room temperature.
- Coordinate transport for sample to be received in our laboratory within 24-48 hours of collection.
  - LOCAL: Call 402-559-5070 (option 1)
  - OUT OF AREA: Prior to shipment, please fax the completed test request form to 402-559-7248, including the FedEx® airbill tracking number.
    - Saturday delivery MUST be checked when sending FedEx® on Friday.
    - Please include Internal Billing Reference # 3155070600 on the FedEx® airbill.
    - Ship To: Human Genetics Laboratory – Zip 5440
      UNMC Shipping & Receiving Dock
      601 S. Saddle Creek Road
      Omaha, NE 68106

REQUIRED FORM: The following form can be downloaded via our website.
- Postnatal Test Request Form

OPTIONAL FORM:
- Informed Consent for Genetic Testing

POTENTIAL TEST RESULTS:
Once a variant is confirmed, our laboratory team interprets this information in conjunction with the patient’s clinical findings and the scientific literature in order to classify a finding. There are three possible results:
- A normal result indicates that sequencing or deletion/duplication analysis of the genes analyzed did not find any pathogenic mutations or variants of uncertain clinical significance (or no clinically-significant chromosome anomalies were identified by microarray analysis).
- An abnormal (or pathogenic) result indicates that a pathogenic mutation was identified (or microarray analysis identified a genomic dosage anomaly [deletion or duplication] or ROH that likely provides an explanation for the individual’s clinical findings). Any available information regarding the phenotype associated with that mutation will accompany the technical details on the report.
• In some cases, the clinical significance of an identified sequence variant (or chromosomal anomaly detected by microarray) may not be well understood. These variants (anomalies) will be reported as **variants of uncertain clinical significance (UCS)**. Any available information about the molecular characteristics of the genetic change and the relationship of the genetic change to phenotype will be included on the report. Over time, as more patients are reported, a variant of uncertain clinical significance may be revised to an informative result, and a revised report will be generated.

• Parental testing may be recommended in order to classify the result as **de novo** or familial for the purpose of recurrence risk calculation.

**TURN-AROUND-TIMES:** For all sample types, results are typically available in 2-6 weeks.

**BILLING:** Our laboratory offers patient/self-pay, insurance (including Medicare/Medicaid), and client/institution billing options. Verifying coverage requirements or obtaining preauthorization PRIOR TO OR AT THE TIME OF SPECIMEN COLLECTION is often necessary. We provide preauthorization services upon request by calling 402-559-5070 (option 3); the following form is helpful for obtaining the information required by insurance providers and can be downloaded via our website.

• Request for Pre-Authorization for Genetic Testing (Postnatal Diagnoses on Peripheral Blood)

In some circumstances, a test may be warranted even though insurance coverage is denied or not guaranteed. For these situations, we request the following form be signed by the patient and submitted with the sample. This helps inform patients of their potential financial responsibility, should the costs of genetic testing not be paid by their insurance provider.

• Advanced Beneficiary Notice of Noncoverage (ABN) – required when billing Medicare

**CPT CODES:**

• **High Density SNP Microarray:** 81229, 88230

• **Next Generation Sequencing** (Gene List: expanded panel, version 3_117):
  - For patients who have **not** been tested on previous version gene lists: 81407(x2)

• **Targeted Deletion/Duplication Analysis:** 81228

• **Methylation Analysis (of chromosome 15):** 81331

**PRICING:** For current costs contact the laboratory billing staff at 402-559-5070 (option 3).
GENE LIST: (expanded panel, version 3_117)
This 117 gene panel is applied to all testing performed on and after November 5, 2014.

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updated 6/2015