Autism Spectrum Disorder
Sequencing Panel

Autism spectrum disorders (ASD) are complex disorders of brain development. These disorders are characterized, in varying degrees, by difficulties in social interaction, verbal and nonverbal communication and repetitive behaviors. These disorders affect about 1% of the population with an overrepresentation in males. In some cases, autism is part of a more complex genetic syndrome with other characteristics, whereas in other cases, it is an isolated finding; for this reason our sequencing panel is best utilized in conjunction with FMR1 expansion (Fragile X) testing and array comparative genomic hybridization (aCGH) analysis.

Genetics: Eighteen of the 42 genes tested in this panel are X-linked, which means that the risk of male offspring with an ASD from a mother carrying a mutation is 50%. Depending on the X-inactivation pattern of the gene, a mother and her daughters may rarely be affected. Exceptions to this are:

- *MECP2:* Males with MECP2 mutations are severely affected and typically die before birth; females are commonly affected
- *CDKL5:* Both males and females with CDKL5 mutations can be affected
- *PCDH19:* Males with PCDH19 mutations are usually unaffected (for reasons that are not yet fully understood); females are commonly affected

Although X-linked diseases are normally transmitted from mother to son, transmission of an X-linked mutation will occur from an affected father to each daughter, but will not occur from father to son.

Twenty two of the remaining genes can cause disease 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. Many of these genes are not fully penetrant (implying that an individual may have a mutated gene but not display any of the signs/symptoms of the disorder).

A person can harbor a mutation from one of two sources:

- either the person inherited this mutation from an affected (or unaffected, non-penetrant) parent
- or the mutation was a "de novo" DNA change that occurred in the egg or sperm from which the affected individual developed

The *UBE3A* gene is unique in that it follows a dominant inheritance pattern but is imprinted. Mutations in *UBE3A* can only cause disease when maternally inherited or when formed de novo on the maternal chromosome 15.

Joubert syndrome, Cortical Dysplasia-Focal Epilepsy Syndrome, and Smith-Lemli-Opitz syndrome are autosomal recessive conditions. 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: A blood sample is drawn and DNA is obtained from the white blood cells. High-throughput, next generation sequencing is performed to examine a large number of genes at one time. In addition, some of the genes on the panel may be partially subjected to Sanger sequencing due to inadequate sequence coverage by next generation sequencing.

Test Sensitivity and Limitations: High-throughput sequencing will pick up >97% of DNA mutations at the level of a few base-pairs. Larger genomic rearrangements and DNA insertions or deletions will likely be missed by this testing method. For the majority of the genes on this panel, the clinical sensitivity of this assay cannot be estimated individually because each gene is a rare cause of ASD. Approximately 5% of patients are expected to have a positive result with this testing. A negative test result does not exclude a genetic cause for ASD. The patient may still have a mutation in one of the genes on the panel that was not identified by this testing or may have a mutation(s) in a gene not included in this panel.

Turnaround Time: Results are reported to the referring physician within 10 to 12 weeks from the receipt of the specimen.

Specimen and Shipping Requirements: 2 yellow-top (ACD-A or ACD-B) or 2 lavender-top (EDTA), 5-10 ml tubes of blood from the patient and both of his/her parents are required. Tubes should be kept and shipped refrigerated or at room temperature *(do NOT freeze)*.

Mount Sinai

Mount Sinai Genetic Testing Laboratory
1428 Madison Avenue, Atran Building, Room 2-25
New York, NY 10029

T: 212-241-7518
F: 212-241-0139
icahn.mssm.edu/genetictesting

Autism Spectrum Disorder Sequencing Panel

There are several genetic conditions that may have ASD as part of the clinical phenotype.
Our ASD sequencing panel can test for the following disorders:

ASD	Common Additional Phenotypic Traits	Gene(s): Inheritance Pattern*	Penetrance
Angelman Syndrome /Angelman-Like	ID, gait abnormalities, unique behavior, seizures	*UBE3A:* AD *CDKL5:* XLD; *SLC9A6:* XL	*UBE3A:* – Complete**
ASD + Macrocephaly	Enlarged head circumference, *Note: PTEN* mutations can also cause non-ASD disorders	*PTEN:* AR	Incomplete
Creatine Deficiency	ID, seizures, behavior disorders	*SLC6A8:* XL	**
Fragile X Syndrome	ID, connective tissue findings, characteristic facial appear.	*FMR1:* XL	**
Fried Syndrome	ID, delayed walking and speech, aggressive behavior, brain calcifications	*AP1S2:* XL	**
Joubert Syndrome	ID, distinctive brain malformation, developmental delay, breathing irregularities, atypical eye movements	*AHI1* AR	Complete
OTC Deficiency	**Males:** infantile lethargy, breathing irregularities, coma, seizures. **Females:** milder symptoms with a later onset	*OTC:* XL	**
Neurofibromatosis Type 1^	Short stature, learning disability, multiple café au lait, axillary, inguinal freckling, neurofibromas, iris Lisch nodules, facial dysmorphisms, macrocephaly, increased risk of malignancy	*NF1*	Complete
Noonan Specturm Disorders^	Depending on gene involved: congenital heart defects, hypertrophic cardiomyopathy, developmental delay, ID, macrocephaly, sensorineural deafness, progressive cerebellar overgrowth, hyperactive behavior, webbed neck, facial dysmorphisms, abnormalities of the skin and hair, musculoskeletal abnormalities, hypernasal voice, postnatal feeding difficulties, lymphatic dysplasias, bleeding diathesis, cryptorchidism in males, increased risk of malignancy	All *AD* *PTPN11, KRAS, SOS1, RAF1, NRAS, BRAF, MAP2K1, MAP2K2, CBL, HRAS, SHOC2*	Incomplete
Pitt-Hopkins-like/ Cortical Dysplasia-Focal Epilepsy Syndrome	ID, seizures, specific brain anomaly, breathing irregularities	*NRXN1:* AR *CNTNAP2:* AR	*CNTNAP2:* – complete *NRXN1:* – uncertain
Rett Syndrome/ Variant Rett Synd.	Progressive disorder (normal development in the first year of life followed by regression) patients develop repetitive hand movements, panic attacks, gait problems, seizures, and a small head size	*MECP2:* XLD *CDKL5:* XLD *SLC9A6:* XL	**
Simpson-Golabi-Behmel Syndrome	ID, overgrowth, distinct facial characteristics	*GPC3:* XL	**
Smith-Lemli-Opitz	ID, growth retardation, small head size	*DHCR7:* AR	Complete
Sotos Syndrome	Typical facial appearance, overgrowth, and learning disability, sometimes seizures	*NSD1:* AD	Complete
Timothy Syndrome	Cardiac, hand/foot, facial, and/or neurodevelopmental abnormalities	*CACNA1C:* AD	Complete
Tuberous Sclerosis	ID, seizures, abnormalities of the skin, brain, kidney, heart, and lungs	*TSC1:* AD *TSC2:* AD	Complete
Variable ASD and/or ID without a specific Title	Depending on gene involved: epilepsy, schizophrenia, cerebellar hypoplasia	AD: *CNTNAP2, NRXN1, SHANK2, SHANK3* XLD: *PCDH19* XL: *NLGN4X, PTCHD1, ARX, OPHN1, UPF3B, GRI3, RAB39B*	*CNTNAP2:* *SHANK2:* – incomplete** *NRXN1:* *SHANK3:* – uncertain**

* AR = autosomal recessive AD = autosomal dominant XLD = X-linked dominant XL = X-linked ID = Intellectual Disability

** *Penetrance not applicable for an XL mutation in a female. This is difficult to predict due to random inactivation of one X chromosome in females. Penetrance is presumably complete for an XL mutation in a male.*

^ *Testing for genes associated with these conditions can be ordered separately as part of our* ***Noonan Spectrum Disorders Sequencing Panel****.*

Mount Sinai

Mount Sinai Genetic Testing Laboratory
1428 Madison Avenue, Atran Building, Room 2-25
New York, NY 10029

T: 212-241-7518
F: 212-241-0139
icahn.mssm.edu/genetictesting