MOUNT SINAI SCHOOL OF MEDICINE

Department of Genetics and Genomic Sciences
Mount Sinai School of Medicine
One Gustave L. Levy Place
Box 1497
New York, NY 10029-6574

Tel: 212-241-7518
Fax: 212-241-0139

Mount Sinai Genetic Testing Laboratory – Molecular Genetics Laboratory

Autism Spectrum Disorder Sequencing Panel – Information Sheet

Clinical features:

Autism spectrum disorder (ASD) and autism are both general terms for a group of 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 0.9% 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. There are several genetic conditions that may have an autism spectrum disorder as part of the clinical phenotype. Those targeted in this genetic test are detailed here.

Autism spectrum disorder (ASD)	**Gene(s)**	**Common additional phenotypic traits**	**Inheritance pattern***	**Penetrance (for AD/AR only)****
Pitt-Hopkins-like/ Cortical Dysplasia-Focal Epilepsy Syndrome	*NRXN1, CNTNAP2*	intellectual disability (ID), seizures, specific brain anomaly, breathing irregularities	AR	*CNTNAP2*: complete, *NRXN1*: uncertain
Sotos syndrome	*NSD1*	typical facial appearance, overgrowth, and learning disability, sometimes seizures	AD	Complete
Joubert syndrome	*AHI1*	a distinctive brain malformation, developmental delay, breathing irregularities, atypical eye movements, ID	AR	Complete
Tuberous Sclerosis	*TSC1, TSC2*	abnormalities of the skin, brain, kidney, heart, and lungs, ID, seizures	AD	Complete
ASD + macrocephaly	*PTEN*	enlarged head circumference, *Note*: *PTEN* mutations can also cause non-ASD disorders	AD	Incomplete
Variable ASD and/or ID without a specific title	*CNTNAP2, NRXN1, SHANK2, SHANK3, NLGN4X, PTCHD1, ARX, ILRAPL1, KDM5C, OPHN1, PCDH19, UPF3B, GRIA3, RAB39B*	epilepsy, schizophrenia, cerebellar hypoplasia, etc	*CNTNAP2, NRXN1, SHANK2, SHANK3*: AD, *PCDH19*: XLD, rest: XL	*CNTNAP2, SHANK2*: incomplete, *NRXN1, SHANK3* : uncertain
Smith-Lemli-Opitz syndrome	*DHCR7*	growth retardation, small head size, ID	AR	Complete
Timothy syndrome	*CACNA1C*	cardiac, hand/foot, facial, neurodevelopmental abnormalities	AD	Complete
Angelman syndrome/Angelman-like	*UBE3A, CDKL5, SLC9A6*	ID, gait abnormalities, unique behavior, seizures	*UBE3A*: AD, *CDKL5:* XLD, *SLC9A6:* XL	*UBE3A*: complete
Fried syndrome	*AP1S2*	ID, delayed walking and speech, aggressive behavior, brain calcifications	XL	
OTC deficiency	*OTC*	In males: infantile lethargy, breathing irregularities, seizures, coma. In females: milder symptoms with a later onset	XL	
Simpson-Golabi-Behmel syndrome	*GPC3*	overgrowth, distinct facial characteristics, ID	XL	
Fragile X syndrome	*FMR1*	ID, connective tissue findings, a characteristic facial appearance	XL	
Creatine deficiency syndrome	*SLC6A8*	ID, seizures, behavior disorders	XL	
Rett syndrome/Variant Rett	*MECP2, CDKL5, SLC9A6*	progressive disorder characterized by 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	*SLC9A6:* XL, rest: XLD	

* AR = autosomal recessive, AD = autosomal dominant, XLD = X-linked dominant, XL = X-linked

** 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.

Inheritance Patterns:

We estimate that approximately 5% of ASD patients will have a mutation in one of the 30 genes on this sequencing panel. Eighteen of the 30 genes tested in this panel are X-linked, which means that the risk of male offspring with 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*, *CDKL5*, and *PCDH19* mutations in which females are commonly affected. Males with *MECP2* mutations are severely affected and typically die before birth. Both males and females with *CDKL5* mutations can be affected. For reasons that are not yet fully understood, males with *PCDH19* mutations are usually unaffected. 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.

Ten of the remaining genes can cause disease an autosomal dominant pattern. In these cases, an affected parent carrying the mutated gene has a 50% chance of passing it on to an offspring, regardless of gender. However, many of these genes are not fully penetrant and mutations can, in some cases, be carried by an unaffected parent. These parents also have a 50% chance of passing the mutation to an offspring. In most autosomal dominant disorders, a significant percentage of affected individuals are the first ones in their family to have the mutation. This is due to new or "*de novo*" DNA changes that occurred during the generation of the egg or sperm from which the affected individual developed.

The *UBE3A* gene is a unique case that follows a dominant inheritance pattern; however, the gene is imprinted and mutations in *UBE3A* can only cause disease if they inherited maternally or form *de novo* on the maternal chromosome 15.

Joubert syndrome, Cortical Dysplasia-Focal Epilepsy Syndrome, and Smith-Lemli-Opitz syndrome are autosomal recessive conditions, meaning each parent is a carrier of one mutated gene and the risk of having affected offspring is 25%.

Test-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, several of the genes on the panel are partially or fully subjected to Sanger sequencing due to inadequate sequence coverage during 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 each gene is a rare cause of ASD. Approximately 5% of patients are expected to have a positive results with this testing. This testing may fail to pick up certain types of DNA errors such as small insertions and deletions, which will affect the test sensitivity. A negative test 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.

Reasons for referral:
To determine whether a patient's ASD is caused by mutation in one of the genes on the panel after a test negative result for FMR1 expansion (Fragile X testing) and array comparative genomic hybridization (aCGH).

Specimen Requirements:
2 yellow (ACD) or lavender (EDTA) 5-10 ml tubes

Turn around time:
Results will be reported to the referring physician within 6 to 8 weeks from the receipt of the specimen.

Shipping Instructions:
Keep refrigerated or at room temperature, do not freeze

Include the following with each sample:

- Completed and signed test requisition form and informed consent
- Billing information or payment (include copy of insurance card)
- Contact information for referring physician
- Testing to be performed
- Indication for testing, patient's family history, ethnic background and prior relevant test results (must include Fragile X and aCGH)

Send same day *or overnight (check for morning delivery)* to:

Mount Sinai Genetic Testing Laboratory
Atran Laboratory Building
1428 Madison Avenue
Room AB2-32
New York, NY 10029