Rapid Mendelian Genes Sequencing Panel, Trio

Mendelian diseases are inherited conditions linked to individual genes. This test entails rapid sequencing of ~4,900 genes of known function from a critically ill individual and both parents to quickly diagnose a Mendelian disease to improve medical management.

Tests to Consider

Rapid Mendelian Genes Sequencing Panel, Trio 2012849

Method: Massively Parallel Sequencing

Order for rapid diagnosis of a critically ill individual suspected to be affected with a Mendelian genetic condition

See Related Tests

Test Overview

- Although humans have ~19,000 genes, the function of only ~4,900 genes is known.
  - This test only sequences genes with known function
- See Rapid Mendelian Sequencing Gene List for genes included in this panel.
- Parental specimens are required to identify de novo variants and to determine phase and clinical significance of variants detected in proband.

Required for Testing

- Blood specimens from the proband and both parents
- Completed Informed Consent for Rapid Mendelian Genes Sequencing Panel, Trio form for proband
- Completed Patient History for Rapid Mendelian Genes Sequencing Panel, Trio form
- Clinical summary from genetic consultation (if available)
- Three-generation medical pedigree
- Copy of abnormal results, which may include:
  - Genomic microarray
  - Skeletal survey
  - Magnetic resonance imaging (MRI)

Test Interpretation

Clinical Sensitivity

50% for infants[1,2]

Reporting and Interpretation

- Accurate representation of biological relationships between family members is imperative for correct test interpretation.
- Only variants predicted to be related to the patient's medical issues are reported.
- Interpretation is based on information available at the time of testing and may change in the future.
- Results are typically reported in 14-28 days.

Secondary Findings

- American College of Medical Genetics and Genomics (ACMG) recommends that disease-causing variants in specific genes (see ACMG list in table below) be reported whether or not they are related to the patient's medical issues.[3]
  - This information may enable disease monitoring or early treatment.
  - Single pathogenic variants in autosomal recessive genes from this list are not reported.
- Additional medically actionable secondary findings may be reported at ARUP's discretion.
- Pathogenic variants in genes recommended by ACMG, or other medically actionable secondary findings in non-ACMG genes, are reported if elected on the consent form.
- Parental inheritance is not reported for secondary variants detected in the proband.
- Parents are not issued reports of secondary findings.
- Familial Mutation, Targeted Sequencing (2001961) can be ordered on the parents to test for a medically actionable secondary finding reported in the proband.

Limitations

- A negative result does not exclude the possibility of a genetic condition.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual or his/her parents have had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Genes with unknown function
  - Variants outside coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Large deletions/duplications
  - Noncoding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Pathogenic ACMG variants that cannot be detected by massively parallel sequencing
  - Low-level mosaic variants

Analytic Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

ACMG Recommends Reporting Secondary Findings for These Genes[3]		
Conditions		**Associated Genes**
Tumors/cancer syndromes	Familial adenomatous polyposis	*APC*
	Familial medullary thyroid cancer Multiple endocrine neoplasia type 2	*RET*
	Hereditary breast and ovarian cancer	*BRCA1, BRCA2*
	Hereditary paraganglioma/pheochromocytoma	*SDHD, SDHAF2, SDHC, SDHB*
	Juvenile polyposis	*BMPR1A*, *SMAD4*
	Li-Fraumeni syndrome	*TP53*
	Lynch syndrome	*MLH1, MSH2, MSH6, PMS2*
	Multiple endocrine neoplasia type 1	*MEN1*
	MUTYH-associated polyposis	*MUTYH*
	Neurofibromatosis type 2	*NF2*
	Peutz-Jeghers syndrome	*STK11*
	PTEN hamartoma tumor syndrome	*PTEN*
	Retinoblastoma	*RB1*
	Tuberous sclerosis complex	*TSC1, TSC2*
	Von Hippel-Lindau syndrome	*VHL*
	WT1-related Wilms tumor	*WT1*

Conditions		Associated Genes
Cardiovascular conditions/syndromes	Arrhythmogenic right-ventricular cardiomyopathy	*PKP2, DSP, DSC2, TMEM43, DSG2*
	Brugada syndrome Romano-Ward long QT syndrome types 1, 2, and 3	*KCNQ1, KCNH2, SCN5A*
	Catecholaminergic polymorphic ventricular tachycardia	*RYR2*
	Ehlers-Danlos syndrome, vascular type	*COL3A1*
	Familial hypercholesterolemia	*LDLR, APOB, PCSK9*
	Familial thoracic aortic aneurysms and dissections	*SMAD3, ACTA2, MYLK, MYH11*
	Hypertrophic cardiomyopathy, dilated cardiomyopathy	*MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA*
	Loeys-Dietz	*TGFBR1*, *TGFBR2*
	Marfan syndrome	*FBN1*
Other conditions	Malignant hyperthermia susceptibility	*RYR1, CACNA1S*
	Ornithine transcarbamylase deficiency	*OTC*
	Wilson disease	*ATP7B*

References

1. Willig LK, Petrikin JE, Smith LD, et al. Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings. Lancet Respir Med. 2015; 3 (5): 377-87. PubMed

2. Daoud H, Luco SM, Li R, et al. Next-generation sequencing for diagnosis of rare diseases in the neonatal intensive care unit. CMAJ. 2016; 188 (11): E254-60. PubMed

3. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics Genet Med. 2016; PubMed

Related Tests

Exome Sequencing, Proband 2006336

Method: Massively Parallel Sequencing

Exome Sequencing, Trio 2006332

Method: Massively Parallel Sequencing

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