The Children's Hospital of Philadelphia® | RESEARCH INSTITUTE

PEDI SEQ: The CHOP Pediatric Genetic Sequencing Project

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Patient Name:	XXXXX	**Medical Record:**	XXXXX
Date of Birth:	XXXXX	**Date of Report:**	XX/XX/XXXX
Gender:	FEMALE/MALE	**Ordering Clinician:**	XXXXX, MD (CHOP)
Date of Receipt:	XX/XX/XXXX	**Specimen Type:**	Genomic DNA

Research Test Performed: Exome sequencing

Clinical Indication Provided: This individual is a 9-year-old male with a history of isolated bilateral sensorineural hearing loss. Parental samples were also submitted.

RESULTS SUMMARY

I. Results Related to Clinical Indication *[Details in Section I]*

* **POSITIVE**: **Two heterozygous pathogenic variants in *XXXX* gene** [autosomal recessive]

The patient was found to have two pathogenic variants in the *XXXX* gene. Exome sequencing identified a pathogenic variant in one copy of the *XXXX* gene, which is consistent with the patie **bilateral sensorineural hearing loss.** Parental testing is needed to determine if these two pathogenic variants are located on different alleles (compound heterozygosity) or on the same allele.

II. Results Possibly Related to Clinical Indication *[Details in Section II]*

* **Heterozygous pathogenic variants in the *XXXX* gene** [autosomal recessive]
* **Heterozygous variants of uncertain significance (VUS) in 2 genes *(XXXXXX, XXXXX)*** [autosomal recessive]

This testing also identified multiple other findings related to PHENOTYPE. This individual carries a heterozygous pathogenic variant in the *XXXXX* gene (associated with CONDITION). A se variant was not identified in this gene. This patient also has variants of uncertain significance (VUSs) in two genes known to be associated with PHENOTYPE. These findings are less likely be the cause of this patient's condition because a second disease-causing variant was not identified for these recessive conditions and/or they do not fit with the patient's phenotype.

III. Incidental Findings Unlikely to be Related to Clinical Indication *[Details in Section II]*

A. Immediately Medically Actionable Disease-Causing Variants Not Related to Clinical Indication

* Heterozygous likely pathogenic variant in the *XXXX* gene possibly related to PHENOTYPE was detected.

B. Medically Actionable Childhood Onset Disease-Causing Variants Not Related to Clinical Indication

* None detected. This result does not rule out the possibility that this patient has a variant that was not identified by this test.

C. Medically Actionable Adult Onset Disease-Causing Variants Not Related to Clinical Indication

* None detected. This result does not rule out the possibility that this patient has a variant that was not identified by this test.

D. Carrier Status for Recessive Diseases Not Related to Clinical Indication

* **Carrier of heterozygous pathogenic variants** in XXXX genes associated with autosomal recessive diseases*: XXXXX* (as noted above), *XXXXX, XXXX, XXXX*

RECOMMENDATIONS

* Appropriate medical follow up is recommended for this patient's PHENOTYPE, as well as the XXXX variant previously associated with CONDITION.
* Correlation with the patient's features is recommended to clarify the relevance of the identified variants.
* Genetic consultation is recommended. Consider additional testing (details below) for variants that possibly correlate with the patient's phenotype and any incidental findings that the family intenc use for future medical decisions.
* General information about sequencing can be found in the Supplemental Information at the end of this report. Additional information regarding genes and genetic conditions is available at www.omim.org and www.genetests.org. Information for the family may be available at Genetics Home Reference (www.ghr.nlm.nih.gov).

LIMITATIONS

This test does not identify all genetic variants. We cannot exclude the possibility that this patient has additional disease-associated variants that were not identified or reported.

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I. INTERPRETATION OF RESULTS RELATED TO CLINICAL INDICATION

A molecular cause for this patient's hearing loss **was identified**. This test also identified multiple variants that are possibly related to this patient's condition (See *Table II*). Clinica correlation with the patient's phenotype is recommended.

POSITIVE: Two heterozygous pathogenic variants in *XXX* associated with CONDITION.

- Two heterozygous variants in the *XXXX* gene were found in this individual (See *Table I)*. **These findings are most likely the cause for this patient's PHENOTYPE.** The *GJB* gene encodes for connexin 26, a gap junction protein implicated in nonsyndromic hearing loss, which presents with prelingual mild to profound sensorineural hearing loss.
- The first variant (c.XXXX, p.XXXX) is a frameshift variant resulting in the truncation of the XXXX protein after 2 amino acids. This variant has been previously reported as pathogenic in individuals with CONDITION (REFERENCE). This variant is also carried by the patient's PARENT.
- The second variant (c.XXXX, p.XXXX) is a missense variant that changes a methionine to a threonine at amino acid position 34 in the XXXXX protein. This variant has been previously reported as a pathogenic substitution (REFERENCE). This variant is also carried by the patient's PARENT.

- **Validation:** These variants were confirmed by Sanger sequencing in a CAP-certified laboratory, and separate clinical report was generated by the CLIA-certified Division of Genomics Diagnostics laboratory, accession # MBXXXXX.

* ***RECOMMENDATION***: Clinical correlation with the patient's phenotype, appropriate medical management, and genetic counseling for this patient's parents and other family members is recommended. Due to the limitations of this test not all variants in these genes will be identified. If there is a strong clinical suspicion for these conditions, further studi may be warranted to determine if a second variant is present on the other allele.

TABLE I. Details of Results Related to Clinical Indication

Variant Pathogenicity Call	Disease* (OMIM #)	Gene	Gene Coverage 100% **	Isoform	Position (hg19)	Inherit-ance Pattern	Zygo-sity	Variant Type	Location	cDNA (Amino Acid)	Evidence ***	EVS ****	1000 Genomes ****	Parental Origin	References/ Comments
Pathogenic	Deafness, Autosomal Recessive 1A (MIM:220290]	*GJB2*	No	NM_004004.5	Chr13: 20763650	AR	Het	Nonsense	Ex 2	**c.71G>A (p.W24*)**	1,2,3,9	N/A	N/A	Not found in mother	rs104894396 PMIDs: 9139825, 12833397, 15113126, 15070423, 15146474 16088916, 18294064
Pathogenic	Deafness, Autosomal Recessive 1A (MIM:220290]	*GJB2*	No	-	-	AR	Het	-	-	**c.-23+1G>A**	N/A	N/A	N/A	Not tested	Reported by outside laboratory; detected by the current test

The OMIM number designates the number of this condition in the Online Mendelian in Man database (www.omim.org). ****The Gene Coverage** column indicates whether or not the nucleotides contained within the gene's exons and splice were covered at 20x or higher, including all known gene transcripts for the given gene. ***** The Evidence Column** displays evidence used to assign determination of pathogenicity: 1 = reported pathogenic; 2 = predicted loss of function mutati = mutation segregates with phenotype in the literature; 4 = Change causes a non-conservative amino acid change; 5 = Change occurs at an amino acid position that is highly conserved across species; 6 = Change occurs at a nucleotide position th highly conserved across species; 7 = Change present in a functional domain of the protein; 8 = Enrichment in cases over controls; 9 = functional or animal study. ***** **ExAC** displays the frequency (%) of alleles in whom the variant was report the ExAC database. NR = Not reported in database. **Other**: ND = Not done. Mat = Inherited from the mother; Pat = Inherited from the father. **References** The reference SNP identification number (rs#) indicates the variant's reference numb NCBI's SNP database (dbSNP: www.ncbi.nlm.nih.gov/SNP). The PMID indicates the reference number for a Pubmed article describing the variant (www.ncbi.nlm.nih.gov/pubmed)

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II. INTERPRETATION OF RESULTS POSSIBLY RELATED TO CLINICAL INDICATION

A molecular cause possibly related to this patient's symptoms was identified.

- **Variant of unknown significance (VUS) in the *XXXX* gene –**
  - This test identified a novel heterozygous variant (c.XXXX) in the XXXX gene. Variants in XXXX have been associated with PHENOTYPE (MIM XXXX). There are two isoforms characterized for this gene: a shorter isoform of unknown function (XXXX*1*) and a longer isoform, which is involved in auditory and vestibular functions (XXXX*2 or* XXXX*2*). The XXXX*2* transcript contains a catechol-O-methyl transferase domain wherein most variants have been reported (REFERENCE). To date, all variants implicated in causing PHENOTYPE have been found in the longer isoform.
  - There are 3 transcripts for XXXX. The heterozygous G to A mutation at position XXXX (c.XXXX) occurs at a canonical splice site of a noncoding exon in two of the three known transcripts of XXXX (NM_ XXXX and NM_ XXXX). The effect of this variant on any transcript is unknown and considered a variant of unknown significance.

- **Validation:** This variant was confirmed by Sanger sequencing in a CAP-certified laboratory, and separate clinical report was generated by the CLIA-certified Division of Genomics Diagnostics laboratory, accession # XXXXXX

* ***RECOMMENDATION***: Clinical correlation with the patient's phenotype, appropriate medical management, and genetic counseling for this patient's parents and other family members is recommended. Due to the limitations of this test not all variants in these genes will be identified. If there is a strong clinical suspicion for these conditions, further studies may be warranted to determine if a second variant is present on the other allele.

TABLE II B. Details of Results Possibly Related to Clinical Indication

Variant Pathogenicity Call	Disease* (OMIM #)	Gene	Gene Coverage 100% **	Isoform	Position (hg19)	Inherit-ance Pattern	Zygo-sity	Mutation Type	Location	cDNA (Amino Acid)	Evidence ***	ExAC ****	Parental Origin	Reference Comment
VUS	Deafness, autosomal recessive 63 (MIM: 611451)	*LRTOMT*	No	NM_001145309.3	Chr11: 71799427G>A	AR	Het	Splice site	Intron 2	c.-459+1G>A	N/A	N/A	Unknown	N/A

*** The OMIM number** designates the number of this condition in the Online Mendelian in Man database (www.omim.org). ****The Gene Coverage** column indicates whether or not the nucleotides contained within the gene's exons and splic sites were covered at 20x or higher, including all known gene transcripts for the given gene. ***** The Evidence Column** displays evidence used to assign determination of pathogenicity: 1 = reported pathogenic; 2 = predicted loss of functio mutation; 3 = mutation segregates with phenotype in the literature; 4 = Change causes a non-conservative amino acid change; 5 = Change occurs at an amino acid position that is highly conserved across species; 6 = Change occurs at nucleotide position that is highly conserved across species; 7 = Change present in a functional domain of the protein; 8 = Enrichment in cases over controls; 9 = functional or animal study. ****** ExAC** displays the frequency (%) of alleles i whom the variant was reported in the ExAC database. NR = Not reported in database. **Other**: ND = Not done. Mat = Inherited from the mother; Pat = Inherited from the father. **References** The reference SNP identification number (rs# indicates the variant's reference number in NCBI's SNP database (dbSNP: www.ncbi.nlm.nih.gov/SNP). The PMID indicates the reference number for a Pubmed article describing the variant (www.ncbi.nlm.nih.gov/pubmed)
)

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III. INTERPRETATION OF INCIDENTAL FINDINGS UNLIKELY TO BE RELATED TO CLINICAL INDICATION

Incidental findings are divided into 4 categories:

- A) Immediately Medically Actionable -Results that suggest an immediate change in medical care, including screening or intervention, based purely on diagnosis (not symptoms) that may have a significant and permanent impact on morbidity or mortality.
- B) Medically Actionable Childhood Onset - Childhood onset results that could cause a serious health risk and have known options for improving health or remaining healthier through changes in treatment or management of a person's health care.
- C) Medically Actionable Adult Onset - Adult onset results that could cause a serious health risk and have known options for improving health or remaining healthier through changes in treatment or management of a person's health care.
- D) Carrier Status for Recessive Disease - Carriers of a variant for an autosomal recessive disease do not generally have any symptoms, but they have a risk of having a child with a recessive disease if their partner is also a carrier of a pathogenic variant in the same gene. More information on the variants identified in this patient is described below, and in Table IIID.

In this patient, *a likely pathogenic* variant was found in genes from the ***Medically Actionable Adult Onset*** and ***Carrier Status*** result category. These variants have been previously reported as pathogenic in variant databases and scientific literature. Variants of uncertain significance are not reported for incidental findings.

IIIA. Immediately Medically Actionable Disease-Causing Variants Not Related to Clinical Indication

None detected. This result does not rule out the possibility that this patient has a variant that was not identified by this test.

POSITIVE: Heterozygous pathogenic variant in the *XXXXX* gene (autosomal dominant) associated with CONDITION

- A heterozygous variant in *XXXXX* was identified in this individual (See *Table IIIA)*, **consistent with a diagnosis of CONDITION in this patient.**
- The variant (c.XXXX, p.XXXXX) is a missense variant resulting in the substitution of a serine with a proline. This variant has been previously reported as pathogenic in at least one family of Dutch ancestry with CONDITION (REFERENCE). In this family, the variant segregated with disease and was associated with CONDITION.
- Validation: This variant was confirmed by Sanger sequencing in a CAP-certified Laboratory, and a separate clinical report was generated.

* ***RECOMMENDATION***: Clinical correlation, genetic counseling, and appropriate medical follow up, including evaluation for cardiac disease, for the patient and family members is strongly recommended.

TABLE IIIA. Details of Immediately Medically Actionable Disease-Causing Variants Not Related to Clinical Indication

Variant Pathogenicity Call	Disease* (OMIM #)	Gene	Gene Coverage 100%** (all exons)	Isoform	Position (hg19)	Inheritance Pattern	Zygosity	Mutation Type	Location	cDNA (Amino Acid)	Evidence***	ExAC ****	References/ Comments
Likely pathogenic	Familial hypercholesterolemia (MIM:143890]	*LDLR*	No	NM_000527.4	Chr19:11221390G>A	AD	Het	Missense	Ex7	c.1003G>A (p.Gly335Ser)	1,5,6,7,9	0.00005	PMIDs: 1301956 11668627; 15556094; 23375686

*** The OMIM number** designates the number of this condition in the Online Mendelian in Man database (www.omim.org). ****The Gene Coverage** column indicates whether or not the nucleotides contained within the gene's exons and splice sites were covered at 20x or higher, including all known gene transcripts for the given gene. ***** The Evidence Column** displays evidence used to assign determination of pathogenicity: 1 = reported pathogenic; 2 = predicted loss of function mutation; 3 = mutation segregates with phenotype in the literature; 4 = Change causes a non-conservative amino acid change; 5 = Change occurs at an amino acid position that is highly conserved across species; 6 = Change occurs at a nucleotide position that is highly conserved across species; 7 = Change present in a functional domain of the protein; 8 = Enrichment in cases over controls; 9 = functional or animal study. ****** ExAC** displays the frequency (%) of alleles in whom the variant was reported in the ExAC database. NR = Not reported in database. **Other**: ND = Not done. Mat = Inherited from the mother; Pat = Inherited from the father. **References** The reference SNP identification number (rs#) indicates the variant's reference number in NCBI's SNP database (dbSNP: www.ncbi.nlm.nih.gov/SNP). The PMID indicates the reference number for a Pubmed article describing the variant (www.ncbi.nlm.nih.gov/pubmed) (www.ncbi.nlm.nih.gov/pubmed)

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IIIB. Medically Actionable Childhood Onset Disease-Causing Variants Not Related to Clinical Indication

None detected. This result does not rule out the possibility that this patient has a variant that was not identified by this test. OR
Not Analyzed - Category was not requested by the family on test consent form.

IIIC. Medically Actionable Adult Onset Disease-Causing Variants Not Related to Clinical Indication

None detected. This result does not rule out the possibility that this patient has a variant that was not identified by this test. OR
Not Analyzed - Category was not requested by the family on test consent form.

IIID. Carrier Status for Recessive Diseases Not Related to Clinical Indication

Carrier of one heterozygous likely pathogenic variant in the XXXX gene.

- This patient is a carrier of a heterozygous likely pathogenic variant in the XXXX gene associated with CONDITION (MIM XXXX). The XXXX variant (c. XXXX) was identified in several patients in the literature (reference). Molecular analysis of mRNA from a homozygous patient's fibroblast cell line showed that the variant generated an in-frame exonic deletion, skipping exon 6 (reference). This supports pathogenicity.
- Carriers of a variant for an autosomal recessive disease do not generally have significant symptoms, but they have a risk of having a child with a recessive disease if their partner is also a carrier of a variant in the same gene.

Validation: This variant was confirmed by Sanger sequencing in the PediSeq Research Laboratory. A separate clinical report was **NOT** generated.

* ***RECOMMENDATION***: If the above information is to be used for future medical decisions or family planning, variant-specific Sanger confirmation in a CAP/CLIA-certified lab is indicated and referral to a genetics professional could be considered. Since exome sequencing can miss deletions, duplications and certain types of point variants, additional testing, such as Sanger sequencing of the entire gene or deletion/duplication analysis by MLPA or microarray, should be considered if the diagnosis is relevant to the patient's clinical presentation. Carrier testing of family members and their partners could help clarify the likelihood of having a child with one of the above conditions.

TABLE IIID. Details of Clinical Indication for Carrier Status

Variant Pathogenicity Call	Disease* (OMIM #)	Gene	Gene Coverage 100%** (all exons)	Isoform	Position (hg19)	Inheritance Pattern	Zygosity	Variant Type	Location	cDNA (Amino Acid)	Evidence ***	References/Comments
Likely pathogenic	Glycogen storage disease 3 (MIM:232400)	*AGL*	No	NM_000028.2	Chr1: g.100330148A>G	AR	Het	Splice site	Intron 7	c.664+3A>G	1,2,3,9	rs370792293 PMID: 12442284; 16705713

*** The OMIM number** designates the number of this condition in the Online Mendelian in Man database (www.omim.org). ****The Gene Coverage** column indicates whether or not the nucleotides contained within the gene's exons and splic sites were covered at 20x or higher, including all known gene transcripts for the given gene. ***** The Evidence Column** displays evidence used to assign determination of pathogenicity: 1 = reported pathogenic; 2 = predicted loss of functio variant; 3 = variant segregates with phenotype in the literature; 4 = Change causes a non-conservative amino acid change; 5 = Change occurs at an amino acid position that is highly conserved across species; 6 = Change occurs at a nucleotid position that is highly conserved across species; 7 = Change present in a functional domain of the protein; 8 = Enrichment in cases over controls; 9 = functional or animal study. ****** ExAC** displays the frequency (%) of alleles in whom th variant was reported in the ExAC database. NR = Not reported in database. **Other**: ND = Not done. Mat = Inherited from the mother; Pat = Inherited from the father. **References** The reference SNP identification number (rs#) indicates th variant's reference number in NCBI's SNP database (dbSNP: www.ncbi.nlm.nih.gov/SNP). The PMID indicates the reference number for a Pubmed article describing the variant (www.ncbi.nlm.nih.gov/pubmed)

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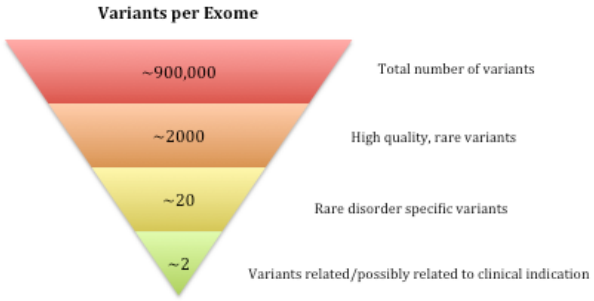
GENERAL FILTERING SCHEMA FOR RESULTS RELATED TO CLINICAL INDICATION:



Methodology

After extraction of genomic DNA, targeted exons were captured with the Agilent SureSelect XT Human All Exon V4 kit and were sequenced on the Illumina HiSeq 2000 platform with 100bp paired-end reads in the CHOP@BGI Sequencing Facility. The mitochondrial genome was not analyzed. Mapping and analysis were based on the human genome build UCSC hg19 reference sequence. Samples were sequenced at a minimum average coverage of 100x. All DNA variants associated with the clinical indication and reported here were confirmed via Sanger sequencing in the patient and the family members, when available. Variants that were incidental findings were Sanger confirmed in the patient. Variants and VUSs associated with the primary diagnosis (Table I and II) were validated in the Division of Genomics Diagnostics at CHOP (CLIA#39D0198678), as were incidental finding variants that were deemed to be immediately medically actionable (Table IIIA). Variants of uncertain significance are only reported for genes related to the clinical phenotype. Variants related to traits, low risk for common disease, or untreatable adult onset degenerative diseases are not analyzed or reported. Common benign polymorphisms are also not reported.

Limitations

This test does not capture or analyze all regions of the exome/genome. Approximately 95% of the exome is captured consistently at 10x or greater. In addition, this test may not identify certain types of DNA variants, including large structural deletions/ duplications, triplet repeats or other repetitive DNA sequences, insertions or deletions >15 basepairs or variants in genes with associated pseudogenes. Lack o a definite disease-causing variant does not exclude the possibility that a patient may have a genetic variant that was unable to be identified by this test due to failure to capture or sequence that region of the genome. This analysis is based on current understanding of this test and of genetic disease. It is possible that the variant responsible for this patient's condition was not identified or reported because it is not ye understood to be associated with disease based on current scientific knowledge.

Versions

GATK 2.2-5	1000 Genomes Phase 1 v3, Exome Variant Server 0.0.9, ExAC 0.3
Human Reference Genome: hg19	PediSeq Hearing Loss Genelist v1
Novalign 2.08.02	Picard 1.79

The PediSeq Laboratory is a CLIA-compliant research laboratory. This test was performed as part of a research project. Therefore, **results of this test should not be placed in the medical record or used to make medical decisions without first being confirmed in a CAP or CLIA-certified laboratory.** For questions related to this analysis or results, please contact the PediSeq Laboratory at 267-426-8379 or biswass1@email.chop.edu. The Division of Genomic Diagnostics at CHOP (a CAP and CLIA-certified facility) validated variants associated with the primary diagnosis and immediately medically actionable incidental findings and issued a separate clinical diagnostic report. For questions relating to the CAP/CLIA-certified results, please contact the Division of Genomic Diagnostics at 267-426-1147 or DGDgeneticcounselor@email.chop.edu. **References and other information about this test can be found at** http://www.research.chop.edu/programs/pediseq/**.**

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Laura Conlin, PhD
Laboratory Director

_____
Ian Krantz, MD
Medical Director

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EXOME SEQUENCING

All the genetic material in a person is referred to as their genome. Whole genome sequencing attempts to look at the sequence of the entire DNA in a person's body. The portion of the DNA that is needed to make proteins is referred to as the exome. The majority of genetic diseases for which we know the molecular cause result from variants in the exome. Exome sequencing only looks at the portion of DNA, about 1.5% of the total DNA that is used to make proteins.

Exome and genome sequencing cannot identify all of a person's genetic variants because of the complexity of our genomes and the current limitations of test technology and knowledge. There are some areas of the exome or genome that will not be sequenced, partially due to the inability to capture all genes consistently and misalignment of DNA sequences with existing pseudogenes (copies of genes with a very similar sequence). In addition, exome sequencing is unable to identify certain types of genetic variants, particularly larger regions of missing or extra DNA (deletions/duplications), repeated sequences (including repeats associated with triplet repeat disorders, such as Fragile X syndrome and Huntington disease), and regions of the genome that are rearranged (structural rearrangements, such as inversions and translocations). Exome or genome sequencing may not identify the genetic basis of a patient's condition, even if that person has a genetic condition. If results of exome or genome sequencing do not identify a causative variant, it is important to consider additional testing options.

INTERPRETING RESULTS OF EXOME/GENOME SEQUENCING

Interpreting results of exome and genome sequencing can be complex. There are several steps that may be helpful. These steps include:

Correlation with your patient's symptoms

One of the most important steps in interpreting the results of exome or genome sequencing is to consider the meaning of the identified genetic variants in relation to the current symptoms and features of the patient, as well as the expected age of onset of the associated conditions. For example, if a child with hearing impairment has a pathogenic variant in a gene associated with hearing loss and onset of visual issues in adolescence, this variant may be relevant to the child's future health, even if the child does not currently have any visual issues.

Determining if the mode of inheritance makes sense

In addition, it is important to consider the mode of inheritance of the genetic disorders associated with each gene or genetic variant. We have two copies of most of our genes. **Autosomal dominant** conditions are expressed when only one copy of a gene has a pathogenic variant, while **autosomal recessive** conditions are expressed when both copies of the gene have a pathogenic variant. For recessive diseases for which testing identified a single variant, it is important to consider the possibility that a second variant could have been missed due to lack of sequencing coverage. Many **X-linked** diseases are primarily expressed in boys, since males usually only have one copy of the X chromosome and females have two. Therefore, a female may carry a pathogenic variant in a gene on the X chromosome but have no symptoms of disease. **Mitochondrial** diseases can be inherited through recessive, dominant, or X-linked inheritance. In addition, mitochondrial diseases can be caused by pathogenic variants in the mitochondrial DNA. Mitochondrial DNA is located in the mitochondria and may not be tested through exome or genome sequencing of the nuclear DNA. Therefore, it is important to consider whether or not the mitochondrial DNA has been tested in patients in whom you suspect a mitochondrial disease.

Verifying that genes relevant to the patient's condition were tested

As described above, exome and genome sequencing may not test all areas of the genome and may not test certain genes consistently. Therefore, if you know of certain genes that you feel are highly likely to be associated with your patient's symptoms, it is important to verify that the testing covered these genes and to consider additional testing of these genes. It is particularly important to remember that exome and genome sequencing may not identify large deletions or duplications.

GENETIC CONSULTATION

Genetic consultation is the process of evaluating the genetic etiology of a patient's condition and providing recommendations for additional testing and future medical management. Board-certified MD or PhD geneticists, genetic counselors, or specialists often provide genetic consultations with expertise in the genetics of a specific type of disorder. A directory of board-certified geneticists can be found at www.acmg.net and a directory of genetic counselors can be found at www.nsgc.org.

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TERMINOLOGY

Coverage refers to the *average* depth or the average number of times the DNA was sequenced over a specific region of the exome/genome or over the entire exome/genome OR the average percentage of a given gene, region, exome or genome that was sequenced.

Depth refers to the number of times a specific nucleotide/base (location in the DNA) is sequenced. The more times the variant is sequenced, the greater the depth, and the more likely that the result is accurate.

Exon refers to the segments of a gene that are "expressed" or made into RNA and proteins. During the production of a protein, the exons of a gene are spliced and put together.

Intron refers to the segments of a gene that are NOT "expressed" and NOT made into RNA and proteins. During the production of a protein, the introns of a gene are spliced out and discarded while the exons are put together to produce the protein. Introns help regulate splicing and gene expression.

Variant is often used to refer specifically to genetic variants that are associated with disease. However, a variant is actually any variant or change in the sequence of DNA that differs from the standard sequence.

MLPA (Multiplex Ligation-dependent Probe Amplification) is often used to rapidly look at genomic DNA for copy number changes (deletions and duplications) of small to moderate size. For this method, probes are matched to DNA and amplified. The amounts of amplified products are then compared to a reference to determine how many copies of each DNA segment are present.

Sanger Sequencing is the "gold standard" of genetic testing used to sequence a single gene, a specific region of a gene, or a small number of genes. Because exome and whole genome sequencing are new technologies, Sanger sequencing is often used to verify the presence of specific variants in a person's genes.

SNP, a single nucleotide polymorphism, is a change of one nucleotide for a different nucleotide in DNA.

SNP Array looks at a large number of **SNPs** that are common in the general population. The presence or absence of these SNPs can identify missing segments or additional copies of regions in the genome. Some of these large changes cause disease, while others do not.

Variant refers to a change or variation in the DNA sequence that differs from the standard reference sequence.

Variants of Uncertain Significance (VUSs) are genetic changes that are not fully understood. These variants either do not have a definite association with disease, not understood enough to be deemed benign or there is limited information to make a clear judgment. More information gathered in the future, such as a report of the VUS in another patient or in a control population, may help determine whether or not these VUSs are truly associated with disease.

Likely Pathogenic Variant is a variant that shows some evidence that it is associated with disease, but the evidence may not be well understood at the current time, or only a few reports of evidence have been published in the literature. More information gathered in the future may confirm that this variant is definitely associated with disease.

Pathogenic Variant is a variant that has published evidence that it is associated with disease. In some cases, the exact variant has not been previously identified in the literature; however there is abundant evidence that the disease is associated with a certain type of variant that results in a loss of the protein product from that allele (loss of function).

Heterozygous refers to a genetic variant or change that is only found in one copy of a person's gene and is not found in the second copy.

Homozygous refers to a genetic variant or change that is found in both copies of a person's gene.

Hemizygous refers to a genetic variant or change that is found in a gene on the X chromosome of a male. Because males only have one copy of the genes on the X chromosome, males are considered hemizygous for these variants instead of heterozygous or homozygous.

ANALYSIS DETAILS

OMIM (Online Mendelian Inheritance in Man) is an online database that details what is currently known about the majority of genes and genetic conditions.

EVS (Exome Variant Server) contains data about variants identified through the NHBLI GO Exome Sequencing Project (ESP). This server can be used to filter variants based on their frequency. For more information, visit http://evs.gs.washington.edu/EVS/

1000 Genomes is a catalog of sequence data from over 1000 genomes. Like EVS, this data can be used to filter variants based on their frequency. For more information, visit http://www.1000genomes.org/

ExAC (Exome Aggregation Consortium) is a data set provided on 60,706 unrelated individuals sequenced as part of genetic studies, including data from EVS and 1000 Genomes, that can be used to filter variants based on their frequency. For more information, visit http://exac.broadinstitute.org/