PowerXomeGS

Action Packed Whole-Exome Sequencing

Client Information

Client Name: Jane Doe

Client DOB: 24-03-1965

Client Sex: Female

Ordering Physician: Dr. Annie Abble

Test Information

Panel Name: PowerXomeGS

Client ID: 123456789123

Collection Date: 06-10-2017

Sequencing Date: 08-10-2017

Report Date: 08-10-2017

Specimen Type: Buccal

Panel Metrics

Phenotypes Extracted from HPI: 16

Direct Gene Relations: 7

Inirect Gene Relations: 15

Median Depth of Coverage: 204x

Provided Clinical Presentation (HPI)

Debilitating fatigue, (exercise causes further fatigue instead of energizing like it used to), memory issues, confusion, short attention span, difficulty focusing, frequent sore throat or feeling of getting the flu on a regular basis. Chronic joint pain and/or tendon pain (mostly in hands with no joint swelling) I have been enduring this for years, thyroid issues, Vulvodynia (sever inflammation of the vestibule) Chronic joint and/or tendon pain (does not include swelling of the joints) pain moves throughout body but mostly in hands. Weight issues just started since menstruation stopped Heart Attack and Atherosclerosis

Extracted Phenotype Terms

Fatigue, dysbiosis, constipation, diarrhea, hypoglycemia, chronic cough, autoimmune, inflammation, PANS, sore throat, PANDAS, allergies, nausea, dopamine, serotonin, mood

Related ICD-10 Codes

Abdominal Pain R53.32, IBS R53.32, Chronic fatigue, unspecified R53.82, Unspecified mood F39, Cough R05, Other specified disorders involving the immune mechanism D89.89

Report Overview

Some variant of significance to the clients clinical presentation are present based on well documented gene to disease databases. Further action should be taken on those genes to develop personalized treatment options. Detailed gene information including function and potential treatment options can be found on your GeneSavvy online portal.

Potential Next Steps

- As with all genetic testing, genetic counseling is recommended to review both positive and negative results. Counselors can be found at www.nsgc.org.
- Functional labs and other diagnostic tools should be used in tandem with these results to verify current gene function.
- Supplements, drugs, and other treatment options can be used to enhance the functionality of genes. If you need help deciding on treatment options, please contact GeneSavvy and our team can review and assist in guiding actionable movement based on these results.
- To help further classify gene variants, please fax or email information regarding any outcomes based on these results, including clinical diagnosis, impact on medical management, treatment trials, or other pertinent test results.

Variants with Indirect Relation

Variants of unknown significance are not included in this report. Your variants of unknown significance are available by request. Please contact us at info@genesavvy.com for more information.

FOR RESEARCH PURPOSE ONLY

Main finding: Variant Identified in **SERPINA1**

Details about E288V (NM_000295.4) [Dominant HET] - Relevance: High - Pathogenic

- The heterozygote T->A substitution at chr14:94847262 is predicted to result in abnormal protein translation of the SERPINA1 protein at amino acid position 288.
- Predicted effect(s) on the protein: Missense
- The quality and reliability of the variant calling is High and the severity of the impact on the protein is High.
- The maximal allele frequency of this specific variant in healthy control population was found in the ESP (European Americans) and is 4.14e-2.
- This variant is annotated in ClinVar as: other, Pathogenic, other, Pathogenic.

Variant Note:

Clinical correlation is indicated. Presence of COPD signs and symptoms need to be confirmed.

CONDITION	CLINICAL SIGNIFICANCE	ACCESSION
• PI S • Alpha-1-Antitrypsin Deficiency • Not Provided	• Other • Pathogenic • Pathogenic, Other	• RCV000019569 • RCV000148878 • RCV000177031

Main finding: Variant Identified in **ACSF3**

Details about E359K (NM_174917.4) [Dominant HET] - Relevance: High – Pathogenic

- The heterozygote G->A substitution at chr16:89180844 is predicted to result in abnormal protein translation of the ACSF3 protein at amino acid position 359.
- Predicted effect(s) on the protein: Missense
- The quality and reliability of the variant calling is High and the severity of the impact on the protein is High.
- The maximal allele frequency of this specific variant in healthy control population was found in the ExAC database and is 6.80e-4.
- This variant is annotated in ClinVar as: Pathogenic, Uncertain significance.

Variant Note:

Clinical correlation is indicated. Further evaluation is advised. Laboratory assessment of both malonic and methylmalonic acid is indicated.

CONDITION	CLINICAL SIGNIFICANCE	ACCESSION
• Combined Malonic and Methylmalonic Aciduria	• Pathogenic	• RCV000024132

Main finding: Variant Identified in MC1R

Details about R151C (NM_002386.3) [Dominant HET] - Relevance: Medium - Likely Pathogenic

- The heterozygote C->T substitution at chr16:89986117 is predicted to result in abnormal protein translation of the MC1R protein at amino acid position 151.
- Predicted effect(s) on the protein: Missense
- The quality and reliability of the variant calling is High and the severity of the impact on the protein is Med.
- The maximal allele frequency of this specific variant in healthy control population was found in the ESP (European Americans) and is 7.62e-2.
- This variant is annotated in ClinVar as: association, Affects, risk factor, Pathogenic, Likely benign, Benign.

Variant Note:

Clinical correlation is indicated. Confirm clinical history. Further evaluation is advised.

CONDITION	CLINICAL SIGNIFICANCE	ACCESSION
• Increased analgesia from kappa-opioid receptor agonist, female-specific • Malignant Melanoma Susceptibility	• Affects • Likely benign	• RCV000015386 • RCV000395364

Main finding: Variant Identified in FMO3

Details about E158K (NM_006894.5) [Dominant HET] - Relevance: Medium - Likely Pathogenic

- The heterozygote G->A substitution at chr1:171076966 is predicted to result in abnormal protein translation of the FMO3 protein at amino acid position 158.
- Predicted effect(s) on the protein: Missense
- The quality and reliability of the variant calling is High and the severity of the impact on the protein is Med.
- The maximal allele frequency of this specific variant in healthy control population was found in the ESP (African (European Americans) and is 4.65e-1.
- This variant is annotated in ClinVar as: Pathogenic, Benign, Likely pathogenic.

Variant Note:

Clinical correlation is indicated. Further evaluation is advised. Clinical testing of urine advised.

CONDITION	CLINICAL SIGNIFICANCE	ACCESSION
• Trimethylaminuria, mild • Trimethylaminuria • Trimethylaminuria	• Pathogenic • Likely pathogenic • Pathogenic	• RCV000017711 • RCV000201276 • RCV000201278

Main finding: Variant Identified in **FMO3**

Details about E308G (NM_006894.5) [Dominant HET] - Relevance: Medium - Likely Pathogenic

- The heterozygote A->G substitution at chr1:171083242 is predicted to result in abnormal protein translation of the FMO3 protein at amino acid position 308.
- Predicted effect(s) on the protein: Missense
- The quality and reliability of the variant calling is High and the severity of the impact on the protein is Med.
- The maximal allele frequency of this specific variant in healthy control population was found in the ESP (European Americans) and is 1.88e-1.
- This variant is annotated in ClinVar as: Pathogenic, Benign, Likely pathogenic.

Variant Note:

SERPINA1 (Serpin Family A Member 1) is a Protein Coding gene. Diseases associated with SERPINA1 include Emphysema Due To Aat Deficiency and Hemorrhagic Disease Due To Alpha-1-Antitrypsin Pittsburgh Mutation. Among its related pathways are Transport to the Golgi and subsequent modification and Innate Immune System. GO annotations related to this gene include identical protein binding and protease binding. An important paralog of this gene is SERPINA4.

CONDITION	CLINICAL SIGNIFICANCE	ACCESSION
• Trimethylaminuria, mild • Trimethylaminuria	• Pathogenic • Likely pathogenic	• RCV000017711 • RCV000201276

Main finding: Variant Identified in **FGFR4**

Details about G388R (NM_002011.4) [Dominant HET] - Relevance: Medium - Likely Pathogenic

- The heterozygote G->A substitution at chr5:176520243 is predicted to result in abnormal protein translation of the FGFR4 protein at amino acid position 388.
- Predicted effect(s) on the protein: Missense
- The quality and reliability of the variant calling is High and the severity of the impact on the protein is Med.
- The maximal allele frequency of this specific variant in healthy control population was found in the Converge (Han Chinese) and is 4.23e-1.
- This variant is annotated in ClinVar as: Pathogenic.

Variant Note:

Clinical correlation is indicated. Doesn\'t seem to fit the phenotype presentation. Confirmation of signed and symptoms is advised.

CONDITION	CLINICAL SIGNIFICANCE	ACCESSION
• Cancer progression and tumor cell motility	• Pathogenic	• RCV000017723

Main finding: Variant Identified in CCDC170

Details about V604I (NM_025059.3) [Dominant HET] - Relevance: Medium - Likely Pathogenic

- The heterozygote G->A substitution at chr6:151936677 is predicted to result in abnormal protein translation of the CCDC170 protein at amino acid position 604.
- Predicted effect(s) on the protein: Missense
- The quality and reliability of the variant calling is High and the severity of the impact on the protein is Med.
- The maximal allele frequency of this specific variant in healthy control population was found in the ESP (African Americans) and is 4.95e-1.
- This variant is annotated in ClinVar as: Likely pathogenic.

Variant Note:

Clinical correlation is indicated. Further evaluation is advised for estrogen resistance. The function of this gene and its encoded protein is not known. Several genome-wide association studies have implicated the region around this gene to be involved in breast cancer and bone mineral density, but no link to this specific gene has been found. [provided by RefSeq, May 2010]

CONDITION	CLINICAL SIGNIFICANCE	ACCESSION
• Estrogen resistance	• Likely pathogenic	• RCV000143990

Clinical Significance of ACSF3

ACSF3 Indications

COMBINED MALONIC AND METHYLMALONIC ACIDURIA; CMAMMA [MIM:14265 (\"https://omim.org/entry/14265\")]

Gregg et al. (1998) reported a patient with combined malonic and methylmalonic aciduria who excreted much larger amounts of methylmalonic acid (MMA) than malonic acid (MA). He had normal malonyl-CoA decarboxylase activity. The patient, 6 years old at the time of the report, was born at 34 weeks\' gestation to nonconsanguineous parents. At 2 months he was hospitalized for diarrhea, vomiting, and dehydration and had recurrent similar episodes throughout the first year, necessitating placement of a gastric tube for failure to thrive. He had apnea and pneumonia at 2 months of age; he had episodes of tachypnea at 2 years. He was hospitalized for clonic seizures at age 2, at which time a routine urine organic acid analysis revealed CMAMMA.

References:

1. Gregg, A. R., Warman, A. W., Thorburn, D. R., O\'Brien, W. E. Combined malonic and methylmalonic aciduria with normal malonyl-coenzyme A decarboxylase activity: a case supporting multiple aetiologies. J. Inherit. Metab. Dis. 21: 382-390, 1998. [PMID: 9700595 (\"https://www.ncbi.nlm.nih.gov/pubmed/9700595\")]

ACSF3 FUNCTIONS

Direct Disease Association: - Combined Malonic and Methylmalonic Aciduria

Symptoms: Diarrhea

Summary: Combined Malonic and Methylmalonic Aciduria, also known as cmamma, is related to adenine phosphoribosyltransferase deficiency, and has symptoms including vomiting, diarrhea and failure to thrive. An important gene associated with Combined Malonic and Methylmalonic Aciduria is ACSF3 (Acyl-CoA Synthetase Family Member 3).

Phenotype Association: - HP:0002014:

Summary: Diarrhea; Diarrhea; Watery stool

Phenotype Association: - HP:0002017:

Summary: Nausea and Vomiting

Clinical Significance of SERPINA1

SERPINA1 Indications

ALPHA-1-ANTITRYPSIN DEFICIENCY; A1ATD [MIM:613490 (\"https://omim.org/entry/613490\")]

Alpha-1-antitrypsin deficiency is an autosomal recessive disorder. The most common manifestation is emphysema, which becomes evident by the third to fourth decade. A less common manifestation of the deficiency is liver disease, which occurs in children and adults, and may result in cirrhosis and liver failure. Environmental factors, particularly cigarette smoking, greatly increase the risk of emphysema at an earlier age (Crystal, 19901).

References:

1. Alpha-1-antitrypsin deficiency, emphysema, and liver disease: genetic basis and strategies for therapy. [PMID: 2185272 (\"https://www.ncbi.nlm.nih.gov/pubmed/2185272\")]

SERPINA1 FUNCTIONS

Direct Disease Association: - Emphysema Due to Aat Deficiency

Symptoms: Varies

Summary: alpha-1 antitrypsin deficiency (aatd) is a disorder that causes a deficiency or absence of the alpha-1 antitrypsin (aat) protein in the blood. aat is made in the liver and sent through the bloodstream to the lungs, to protect the lungs from damage. having low levels of att (or no att) can allow the lungs to become damaged, making breathing hard. age of onset and severity of aatd can vary based on how much att an affected person is missing. in adults, symptoms may include shortness of breath; reduced ability to exercise; wheezing; respiratory infections; fatigue; vision problems; and weight loss. some people have chronic obstructive pulmonary disease (copd) or asthma. liver disease (cirrhosis) may occur in affected children or adults. rarely, aatd can cause a skin condition called panniculitis. aatd is caused by mutations in the serpina1 gene and is inherited in a codominant manner. treatment is based on each person\'s symptoms and may include bronchodilators; antibiotics for upper respiratory tract infections; intravenous therapy of aat; and/or lung transplantation in severe cases. last updated: 4/6/2016

Indirect Disease Association: - Wegener Granulomatosis

Symptoms: Fatigue; Nausea and Vomiting; Autoimmunity

Summary: Wegener Granulomatosis, also known as granulomatosis with polyangiitis, is related to labyrinthitis and choroiditis, and has symptoms including arthralgia, fatigue and myalgia. An important gene associated with Wegener Granulomatosis is WG (Wegener Granulomatosis), and among its related pathways/superpathways are Innate Immune System and Allograft rejection. The drugs alemtuzumab and Azathioprine have been mentioned in the context of this disorder. Affiliated tissues include lung, kidney and skin, and related phenotypes are hematopoietic system and cardiovascular system

Indirect Disease Association: - Hemochromatosis

Symptoms: Constipation; Fatigue; Diarrhea; Nausea and Vomiting

Summary: Hemochromatosis, also known as hereditary hemochromatosis, is related to hemochromatosis, type 4 and hemochromatosis, type 3, and has symptoms including arthralgia, fatigue and vertigo. An important gene associated with Hemochromatosis is HFE (Hemochromatosis), and among its related pathways/superpathways are Transport of glucose and other sugars, bile salts and organic acids, metal ions and amine compounds and Insulin receptor recycling. The drugs Iron and Omeprazole have been mentioned in the context of this disorder. Affiliated tissues include liver, heart and pancreas, and related phenotypes are hematopoietic system and homeostasis/metabolism

Indirect Disease Association: - Fructose Intolerance

Symptoms: Nausea; Hypoglycemia

Summary: Fructose Intolerance, also known as hereditary fructose intolerance, is related to acquired fructose intolerance and fructose-1,6-bisphosphatase deficiency, and has symptoms including seizures, abdominal pain and nausea. An important gene associated with Fructose Intolerance is ALDOB (Aldolase, Fructose-Bisphosphate B), and among its related pathways/superpathways are Influenza A and WNT Signaling. The drugs Hydrocortisone and Pharmaceutical Solutions have been mentioned in the context of this disorder. Affiliated tissues include liver and testes, and related phenotypes are Decreased substrate adherent cell growth and homeostasis/metabolism

Indirect Disease Association: - Gastrointestinal System Disease

Symptoms: Constipation; Nausea; Diarrhea; Nausea and Vomiting

Summary: Gastrointestinal System Disease, also known as gastrointestinal diseases, is related to lymphocytic gastritis and celiac disease, and has symptoms including abdominal pain, constipation and diarrhea. An important gene associated with Gastrointestinal System Disease is TRPV1 (Transient Receptor Potential Cation Channel Subfamily V Member 1), and among its related pathways/superpathways are Peptide ligand-binding receptors and Allograft rejection. The drugs Ethanol and Heparin have been mentioned in the context of this disorder. Affiliated tissues include liver, pancreas and small intestine, and related phenotypes are digestive/alimentary and homeostasis/metabolism

Phenotype Association: - HP:0012115:

Summary: Liver inflammation;Inflammation of the liver.

Phenotype Association: - HP:0006510:

Summary: An anomaly that is characterized progressive airflow obstruction that is only partly reversible, inflammation in the airways, and systemic effects or comorbities.

Clinical Significance of MC1R

MC1R Indications

MELANOMA, CUTANEOUS MALIGNANT, SUSCEPTIBILITY TO, 5; CMM5 [MIM:613099 (\"https://omim.org/entry/613099\")]

Malignant melanoma is a neoplasm of pigment-producing cells called melanocytes that occurs most often in the skin, but may also occur in the eyes, ears, gastrointestinal tract, leptomeninges, and oral and genital mucous membranes (summary by Habif, 20101). For a discussion of genetic heterogeneity of malignant melanoma, see 155600.

INCREASED ANALGESIA FROM KAPPA-OPIOID RECEPTOR AGONIST, FEMALE-SPECIFIC [MIM:613098 (\"https://omim.org/entry/613098\")]

No description available.

References:

N/A

MC1R FUNCTIONS

Tip: Targeting melanocortin receptors as a novel strategy to control inflammation.

Clinical Significance of FMO3

FMO3 Indications

TRIMETHYLAMINURIA; TMAU [MIM:602079 (\"https://omim.org/entry/602079\")]

Trimethylaminuria results from the abnormal presence of large amounts of volatile and malodorous trimethylamine within the body. This chemical, a tertiary aliphatic amine, is excreted in the urine, sweat (ichthyohidrosis), and breath, which take on the offensive odor of decaying fish (Mitchell, 19961).

References:

1.The fish-odor syndrome. [PMID: 8753757 (\"https://www.ncbi.nlm.nih.gov/pubmed/8753757\")]

FMO3 FUNCTIONS

Phenotype Association: - HP:0000716:

Summary: A condition characterized by pervasive dysphoric mood, loss of interests, and inability to experience pleasure.

Phenotype Association: - HP:0002090:

Summary: Inflammation of any part of the lung parenchyma.

Clinical Significance of FGFR4

FGFR4 Indications

Tip: Effect of increased bile acid synthesis or fecal excretion in irritable bowel syndrome-diarrhea. (PMID: 25070056)

Tip: Characterizing Factors Associated With Differences in FGF19 Blood Levels and Synthesis in Patients With Primary Bile Acid Diarrhea. (PMID: 26856750)

References:

N/A

FGFR4 FUNCTIONS

N/A

Clinical Significance of **CCDC170**

CCDC170 Indications

N/A

References:

N/A

CCDC170 FUNCTIONS

N/A

Clinical Significance of **ADAMTS13**

ADAMTS13 Indications

THROMBOTIC THROMBOCYTOPENIC PURPURA, CONGENITAL; TTP [MIM:274150 (\"https://omim.org/entry/274150\")]

The classic pentad of TTP includes hemolytic anemia with fragmentation of erythrocytes, thrombocytopenia, diffuse and nonfocal neurologic findings, decreased renal function, and fever. Congenital TTP, also known as Schulman-Upshaw syndrome, is characterized by neonatal onset, response to fresh plasma infusion, and frequent relapses (Savasan et al., 20031; Kokame et al., 20022). Acquired TTP, which is usually sporadic, usually occurs in adults and is caused by an IgG inhibitor against the von Willebrand factor-cleaving protease.

References:

1. ADAMTS13 gene mutation in congenital thrombotic thrombocytopenic purpura with previously reported normal VWF cleaving protease activity.[PMID: 12576319 (\"https://www.ncbi.nlm.nih.gov/pubmed/12576319\")]

2. Mutations and common polymorphisms in ADAMTS13 gene responsible for von Willebrand factor-cleaving protease activity.[PMID: 12181489 (\"https://www.ncbi.nlm.nih.gov/pubmed/12181489\")]

ADAMTS13 FUNCTIONS

N/A

PowerXomeGS Test Performance

This test was designed to sequence the exons and canoncial splice sites (+/1,2) of the whole exome including extra coverage genes associated with medical disorders and treatment options. GeneSavvy has developed a highly advanced protocol for identifying gene regions of interest with the following technical specifications.

Mean depth of coverage:	Specificity:	Spensitivity:
50x (Across all exome basepairs)	>98%	>94%

GeneSavvy's Unmatched Customer Support

Turn Around Time:	8-10 weeks. We Sacrifice a little time to make sure we provide a better product.
Saliva Sample:	DNA for sequencing is reliably extracted from a single saliva sample. No blood draw or muscle biopsy required: however blood and muscle tissue are also accept- ed. No charge saliva Kits are provided, assisted collection kits are also available.
Insurance Assistance:	Genesavvy currently does not work with any insurers. However, we do provide any information we can find to help you self submit to your Insurance for potential reimbursement for our tests or services.
Online Portal:	Genesavvy provides an online portal to access your test results. We also allow you to share your results with your health team. Our online portal will also allow for constant result updates as new research comes out. You will be notified if your report gets updated due to new research.
Reports:	Our reports are built using our proprietary TrairKK bioinformatics pipeline, combined with manual curation to provide the most valuable and actionable results we can find. We utilize the the following databases to build actionable results for you:

Gene/Varinant Definitions:

BUILD - hg19
Refseq
UCSC
ENSEMBL
GENCODE
dbSNP

Population Frequency:

1000 Genomes Project
EXAC
NHLBI-ESP
gnomAD
Complete Genomic

Splice Site Predictions:

dbscSNV

Functional Variant Predictions:

SIFT
PolyPhen2CADD
LRTG ERP-+ +
MutationTasterDANN
Mutation/kssessorEigen
FATHMMGenotanyon
PROVEANfitcons
MetaSVMPhy|oP
MetaLRSiPhy
VESTspan>Revel
MitImpadIntervar
regSN P>RVIS-ESV
LoFtoo|CDI
Genesavvy DBTMC-SNPDBCDI

SIFTM-(AP
PolyPhen2CADD
LRTG ERP-+ +
MutationTasterDANN
Mutation/kssessorEigen
FATHMMGenotanyon
PROVEANfitcons
MetaSVMPhy|oP
MetaLRSiPhy
VESTspan>Revel
MitImpadIntervar
regSN P>RVIS-ESV
LoFtoo|CDI
Genesavvy DBTMC-SNPDBCDI

Disease Specific Databases:

clinVar
Cosmic
ICGC
NCI
OMIM

Ontologies:

Human Phenotype Ontology
Gene Ontology
MGI
Jensen

Pathway Associations:

KEGG
WikiPathways
Reactome

Data and DNA Security: Advanted IT solutions safeguard patient records and finantial information. Genesavvy de-identifies patient and test records and uses industry standards to keep your personal information safe.

FOR RESEARCH PURPOSE ONLY

PowerXomeGS DNA/RNA Testing Terminology and Tips

It is important to understand some of the genetic terminology used in this report. Please see the following common terms used in our reports and a few tips for reducing confusion.

Substitution	A nucleotide substitution is a sequence change where one nucleotide is replaced by one other nucleotide. Nucleotide substitutions are described using a ">"-character (indicating "changes to").
Deletion:	A nucleotide deletion is a sequence change where one or more nucleotides are removed. Deletions are described using "del" after an indication of the first and last nucleotide(s) deleted, separated by a "_" For all descriptions the most 3' position possible, is arbitrarily assigned to have been changed.
Duplicaton:	Duplications are designated by "dup" after an indication of the first and last nucleotide(s) duplicated. It should be noted that the description "dup" may by definition only be used when the sequence copy is directly 3'-flanking the original copy.
Insertion:	Insertions are designated by, "ins" after an indication of the nucleotides flanking the insertion site, followed by a description of the nucleotides inserted. Duplicating insertions should be described as duplications, not as insertion. For large insertions the number of inserted nucleotides should be mentioned, together with an accession version number referring to a sequence database file containing the complete inserted sequence.
Inversion:	Inversions are designated by "inv" after an indication of the first and last nucleotides affected by the inversion.
Conversion:	Conversions are designated by "con" a sequence change where, compared to a reference sequence, a range of nucleotides are replaced by a sequence from elsewhere in the genome.
Complex:	Sequence changes can be very complex, involving several changes at a specific location. A sequence change where, compared to a reference sequence, a range of changes occurs that cannot be described as one of the basic variant types (substitution, deletion, duplication, insertion, conversion, inversion, deletion-insertion, or repeated sequence).
Indels:	Insertions / Deletions
Repeats:	A frequently occuring sequence change is the variability of repeated sequences. Within this category we discriminate both small sequences (mono-, di-, tri-, etc nucleotide repeats) as well as the much larger ones. Such changes are described using the format "position-first-repeat-unit_[number]" (e.g. g.123_124[4]) where position-first-repeat-unit gives the location of the first unit of the variable sequence repeat and [number] the number of units present in the allele described.
Frameshift:	A sequence change between the translation initiation (start) and termination (stop) codon where, compared to a reference sequence, translation shifts to another reading frame.
Missense:	A variant in a protein sequence where compared to the reference sequence one amino acid is replaced by another amino acid.

Nonsense:	A variant in a protein sequence where compared to the reference sequence an amino acid is replaced by a translational stop codon (termination codon).
UTR:	UnTranslated Region (UTR), the segments of of a protein coding RNA molecule that is not translated. 5'UTR = UTR 5' of the tranlsation initiation codon (ATG start codon). 3'UTR = UTR 3' of the translation termination codon.
Homolog:	A gene related to a second gene by descent from a common ancestral DNA sequence. The term, homolog, may apply to the relationship between genes separated by the event of speciation (see ortholog) or to the relationship between genes separated by the event of genetic duplication (see paralog).
Ortholog:	Orthologs are genes in different species that evolved from a common ancestral gene by speciation. Normally, orthologs retain the same function in the course of evolution. Identification of orthologs is critical for reliable prediction of gene function in newly sequenced genomes. (See also Paralogs.).
Speciation:	Speciation is the origin of a new species capable of making a living in a new way from the species from which it arose. As part of this process it has also acquired some barrier to genetic exchange with the parent species.
Paralog:	Paralogs are genes related by duplication within a genome. Orthologs retain the same function in the course of evolution, whereas paralogs evolve new functions, even if these are related to the original one.
Pathogenicity Scoring of Variants:	Exome sequencing has increasingly been used to identify mutations that cause human diseases, especially rare Mendelian diseases. Among the analysis steps, functional prediction (of being deleterious) plays an important role in filtering or prioritizing nonsynonymous SNP (NS) for further analysis. It has been suggested that investigators should use predictions from multiple algorithms instead of relying on a single one. Prediction algorithm tools such as LRT, SIFT, PolyPhen-2, Mutation Taster and Mutation Assessor are functional prediction and annotation tools as part of dbNSFP and based on scores that consider the position of amino acids in highly conserved protein domains because they are likely to be important for protein function. These programs, when they agree, have 89% accuracy for predicting damaging protein effects.
Depth of Coverage:	Sequencing coverage describes the average number of reads that align to, or "cover," known reference bases. The next-generation sequencing (NGS) coverage level often determines whether variant discovery can be made with a certain degree of confidence at particular base positions. The "Mean" depth of coverage is the average coverage across all basepairs in the exome. The "Median" depth of coverage is the median depth of coverage across the extracted variants. The "Median" depth of coverages changes on a test-by-test basis.
Related Gene Pathways:	Deriving gene regulation networks or pathways, on the basis of expression data, is based on the general premise that coregulated genes function in the same pathway, or, in other words, functionally related genes are coregulated or coexpressed.
Direct and Indirect Genes Definition:	Genes that are directly or indirectly annotated relate to the presenting gene variant filtered and curated. Gene direct and indirect relationships are according to association with phenotype, ontology, metabolic pathway, disease, disorder, signs and symptoms, physiological, biochemical, hormonal / neurohormonal signaling and neurotransmitter connectivity / communication, paralog (are homologous genes that have evolved by duplication and code for protein with similar, but not identical functions) and domain.

HPI (History of Present Illness):	When assessing exome data it is essential that an HPI be taken carefully as phenotype expression and filtering of gene variants that are implicated in increased functional disease risk will be curated for analysis. Obtaining an accurate history is the critical first step in determining the etiology of a patient's problem. A large percentage of the time, you will actually be able to make a diagnosis based on the history alone. The value of the history, of course, will depend on your ability to elicit relevant information. Your sense of what constitutes important data will grow exponentially in the coming years as you gain a greater understanding of the pathophysiology of disease through increased exposure to patients and illness. However, you are already in possession of the tools that will enable you to obtain a good history. That is, an ability to listen and ask common-sense questions that help define the nature of a particular problem. It does not take a vast, sophisticated fund of knowledge to successfully interview a patient. In fact seasoned physicians often lose site of this important point, placing too much emphasis on the use of testing while failing to take the time to listen to their patients. Successful interviewing is for the most part dependent upon your already well-developed communication skills.
Interacting Genes:	Sometimes mutations in two genes produce a phenotype that is surprising in light of each mutation's individual effects. This phenomenon, which defines genetic interaction, can reveal functional relationships between genes and pathways.
Phenotype Terms:	The phenotype is a composite of observable characteristics and traits such as, symptoms, signs, physiological, biochemical, behavior and any functional or disease risk associations. It is essential that phenotypes are annotated in the identification gene variants associated with system functional disturbance and disease risk in order to filter and curate actionable gene variants. The Human Phenotype Ontology (HPO) aims to provide a standardized vocabulary of phenotypic abnormalities encountered in human disease. Each term in the HPO describes a phenotypic abnormality, such as atrial septal defect. The HPO is currently being developed using the medical literature, Orphanet, DECIPHER, and OMIM. HPO currently contains approximately 11,000 terms (still growing) and over 115,000 annotations to hereditary diseases. The HPO also provides a large set of HPO annotations to approximately 4000 common diseases.
Population Scoring:	DThe genes carried by the population thus have continuity from generation to generation, but the genotypes in which they appear do not. The genetic constitution of a population, referring to the genes it carries, is described by the array of gene frequencies that is by specification of the alleles present at every locu s and the numbers or proportions of the different alleles at each locus. Population genetics attempts to describe how the frequency of the alleles, which control the trait change over time. To study frequency changes, we analyze populations rather than individuals. Furthermore, because changes in gene frequencies are at the heart of evolution and speciation, population and evolutionary genetics are often studied together. For a population of individuals to succeed over evolutionary time, it must contain genetic variability. Because we do not know all the genetic variables that would predict evolutionary success, we study the variability of different phenotypes and genotypes to provide an overview of the population. The traits that are analyzed can be outward phenotypes that can be easily scored. More recently, biochemical and RFLP data has been used to assess population variability.
Report Overview:	The report overview is a summary of the specific gene variants based upon phenotype presentation, which may have associative indications and implications, which can directly and /or indirectly impact the integrity of functional proteins controlled by the curated genes and impact functional system balance of the human body.

Actionable Interpretation:	Description of the gene and its functional relationship and targeted action. This is crucial in developing specific treatment approaches and actions.
Gene Summary:	The gene summary briefly describes the gene, functional action with the protein it encodes, pathway control, and disease or disorder relationship and mutation association.
SNP (Single Nucleotide Polymorphism):	A SNP or single nucleotide polymorphism does imply that there is an implication how often this variation occurs. This means that there is an inherit implication when someone refers to a SNP that this variation is common (at least 1% of population). This means that it isn't just a fluke that we are seeing this variation, but is an observation seen more often than a few individuals. This implies there might be something important at that location. A SNP is population focused.
SNV (Single Nucleotide Variation):	A SNV stands for single nucleotide variation, which means at one base there is a difference. This definition does not imply how often this variation occurs, just that there is at this particular nucleotide a difference. For example: ATG -> CTG has a SNV at A -> C. A SNV is individual focused.
Gene-Disease Associations:	Deciphering gene–disease association is a crucial step in designing therapeutic strategies against diseases. The process has been directed by manually curated biomedical databases owing to the faith that is placed on expert knowledge and individual attention. The exponential rate at which biomedical databases grow is quickly rendering manual curation of biomedical databases unattainable. The big challenge now is that of obtaining gene–disease associations on a large scale while at the same time not compromising on the quality of the associations. In this section genes are selected through a combination of sophisticated bioinformatics and manual curation.
Tips:	• Do not use "mutation" use variant, disease-associated variant. • Do not use "polymorphism" use variant not disease-associated variant. • Do not use "pathogenic" use disease-associated variant.