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Add genetics to your health

Name: XXX
Medical Request No. xxxx

D.O.B:	dd/mm/2012	Referring physician:	Dr. XXX
Sex:	Male	Referring facility:	Street, City, Country
Subject ID:	8xxxxx	Email physician:	physician@email.com
Order ID:	2xxxxx	Report type:	Genetic diagnosis
Device/ Material ID:	arcxxxxxx	Date of report:	dd/mm/yyyy
Specimen type:	Dried Blood Spots	C.S.:	0.0
Specimen arrival date:	dd/mm/yyyy		

Requested Test: myLifeGenome™
Indication for test: Hypertrophic cardiomyopathy, Left ventricular hypertrophy, Palpitations

Suspected disease(s): None
Consanguineous parents: No
Consent for evaluation: Primary findings: Yes
Incidental findings: Yes

SUMMARY OF GENETIC FINDINGS

PRIMARY	INCIDENTAL	CARRIER STATUS	PHARMACOGENOMICS
Positive	Positive	Positive	Positive

Primary Findings

ⓘ Primary findings describe genetic variants that are relevant to the indication for which sequencing was ordered.

Results: A heteroplasmic pathogenic mitochondrial genetic variant (VAF: 67.39%) was identified in the MT-TL1 gene. This result is consistent with the genetic diagnosis of mitochondrial MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes).

Gene	Variant	Zygosity	Variant class*	Disease name	Disease MOI*
MT-TL1	chrM:3243A>G	Heteroplasmic	P	MELAS syndrome	Mitochondrial

Incidental Findings

ⓘ Incidental findings describe actionable variants in gene(s) that are unrelated to the indication for which sequencing was ordered. These findings are reported based on ACMG guidelines and ClinGen recommendations.

Results: A heterozygous likely pathogenic variant was identified in the TTN gene, A-band. This result is consistent with increased risk to develop autosomal dominant dilated cardiomyopathy type 1G.

Gene	Variant	Zygosity	Variant class*	Disease name	Disease MOI*
TTN	c.107641G>T; p.(Glu35881*)	Het	LP	Dilated cardiomyopathy type 1G (CMD1G)	AD

AD: autosomal dominant; AR: autosomal recessive; XL- X-linked, DG: digenic; Het: Heterozygous; Hom: Homozygous; Hem: Hemizygous; LP: Likely Pathogenic; P: Pathogenic; RF: risk factor VUS: Variant of Uncertain Significance.

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Carrier Status

Carrier Status includes pathogenic or likely pathogenic variants which have a direct impact on reproductive risk (heterozygous variants in a gene associated with a recessive or X-linked disorder).

Results: This proband is found to be a carrier for 2 genetic condition(s).

Gene	Variant	Zygosity	Variant class*	Disease name	Disease MOI*
MOCOS	c.1088_1089del; p.Leu363fs*16	Het	LP	Xanthinuria Type 2	AR
PAH	c.1066-11G>A; p.?	Het	P	Phenylketonuria	AR

Pharmacogenomic Associations

Pharmacogenomic (PGx) Associations are representations of the relationship between specific genes and drugs based on their drug metabolizing status defined according to publicly available data sets provided by Clinical Pharmacogenetics Implementation Consortium (CPIC) (mainly levels A/B or 1/2) using Pharmacogenomics Clinical Annotation Tool (PharmCAT).

Results: Genetic variants associated with drug use and dosing were identified.

See the Pharmacogenomic Associations section under Detailed Insights to understand the identified gene-drug pairs that could lead to treatment modifications based on the individual's genetic variants. See the Technical information section for the list of all genes and drugs supported by PharmCAT.

RECOMMENDATIONS

- Genetic counselling is recommended to further explain the implications of this test result and assess family health history, which may point to health information that merits additional consideration.
- The medical genetics field is continuously evolving, so updates related to your genetic results, medical recommendations, and potential treatments may be available over time.
- MELAS syndrome is caused by pathogenic variants in mtDNA and is transmitted by maternal inheritance. The father of a proband is not at risk of having the mtDNA pathogenic variant. The mother of a proband usually has the mtDNA pathogenic variant and may or may not have symptoms. A woman with a mtDNA pathogenic variant (whether symptomatic or asymptomatic) transmits the variant to all her offspring. Prenatal testing and preimplantation genetic testing for MELAS is possible if a mtDNA pathogenic variant has been detected in the mother. However, because the mutational load in embryonic and fetal tissues sampled (i.e., amniocytes and chorionic villi) may not correspond to that of all fetal tissues, and because the mutational load in tissues sampled prenatally may shift in utero or after birth because of random mitotic segregation, prediction of the phenotype from prenatal studies cannot be made with certainty.

Signatures

DETAILED INSIGHTS

Primary Findings

A heteroplasmic pathogenic mitochondrial DNA variant (VAF: 67.39%) was identified in the MT-TL1 gene. This result is consistent with the genetic diagnosis of mitochondrial MELAS syndrome.

Transcription termination of the mitochondrial genome requires binding of mitochondrial transcription termination factor to a 13-bp termination sequence (mitochondrial DNA nucleotides 3237 to 3249) located within the tRNA-leu(UUR) gene. Using gel filtration and PCR for repeated selection of bound sequences from a random pool of double-stranded DNA, Nam and Kang found that MTERF bound a 16-bp consensus sequence containing the 13-bp termination sequence within tRNA-leu(UUR). MTERF bound single-stranded DNA containing this sequence from the mitochondrial light strand, but not the heavy strand. Nam and Kang hypothesized that preferential binding of MTERF to the light strand may explain its orientation-dependent termination activity (PMID: 16336784)

	Gene/OMIM	*MT-TL1*/ N/A
	Genomic coordinate (GRCh38)	chrM:3243A>G
	ID Transcript	ENST00000386347.1
	HGVS nomenclature	N/A
	Protein change	N/A
	Location	Mitochondrial
	Zygosity	Heteroplasmic
	Function	Missense
	Impact	High
	ClinVar	Pathogenic, Likely Pathogenic
Allele Frequency	Local Database	N/A
	gnomAD	0.00019
In silico Predictors	REVEL	N/A
	CADD (PHRED)	N/A
	Splice-AI	N/A
	Clinical significance	Pathogenic
	ACMG Criteria	PM5, PS4, PM2_SUP, PP3, PP1-Mod

HGVS= Human Genome Variation Society; gnomAD= Genome Aggregation Database; ACMG= American College of Medical Genetics and Genomics; REVEL score (combination from 13 individual tools; rages from 0 to 1)= higher scores reflect greater likelihood that variant is disease- causing; CADD (PHRED)= Combined Annotation Dependent Depletion scoring, ranging from 1 to 99, Splice-AI= deep neural network that accurately predicts splice junctions from an pre-mRNA transcript (using 0.8 as high-precision cut-off).
**: The ACMG criteria are described under Methods /Variant interpretation section.*

Disease description: MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) is a multisystem disorder with protean manifestations. Most affected individuals develop signs and symptoms of MELAS between the ages of two and 40 years, but usually occur before 20 years. Common clinical manifestations include stroke-like episodes, encephalopathy with seizures and/or dementia, muscle weakness and exercise intolerance, normal early psychomotor development, recurrent headaches, recurrent vomiting, hearing impairment, peripheral neuropathy, learning disability, and short stature.

Lactic acidemia is very common and muscle biopsies typically show ragged red fibers. Diagnostic laboratory findings include demonstration of lactic acidosis, brain imaging during stroke not conforming to the vascular territory, muscle biopsy showing ragged red fibers, and respiratory chain analysis showing multiple partial defects (ORPHA:550, PMID: 20301411). Treatment for MELAS is generally supportive. Ptosis, cardiomyopathy, cardiac conduction defects, nephropathy, and migraine headache are treated in the standard manner.

Affected individuals may participate in the clinical trials:
https://clinicaltrials.gov/ct2/results?cond=MELAS&term=&cntry=&state=&city=&dist=
https://www.clinicaltrialsregister.eu/ctr-search/search?query=MELAS

Variant description: The m.3243A>G variant (rs199474657) disrupts the mitochondrial tRNA for leucine (UUR), and is one of the most common pathogenic variants in the mitochondrial genome. The variant is present in gnomAD (allele frequency: 0.00019) and is absent from the local database. This variant is listed in ClinVar as pathogenic and likely pathogenic (Accession ID: 9589). This variant is classified as pathogenic based on ACMG recommendations.

Carrier Status Findings

Carrier status determines the proband's risk for passing inherited genetic condition(s) to the children. Carriers are typically healthy/ asymptomatic. When an individual is found to be a carrier of a genetic condition, his or her relatives are at risk of carrying the same mutation. The patient should be encouraged to inform his or her relatives of the risk and the availability of carrier screening. If an individual is found to be a carrier of a specific condition, the patient's reproductive partner should be offered testing to receive informed genetic counseling about potential reproductive outcomes. If both partners are found to be carriers of the same genetic condition, genetic counseling should be offered.

This proband is found to be a carrier for 2 genetic condition(s).

Gene	Variant details	Zygosity	Annotations	Related disease (OMIM)- MOI Clinical assessment	Clinical significance (ACMG criteria*)
MOCOS	chr18:36205140CCT>C NM_017947.4 c.1088_1089del p.Leu363fs*16 Exon/Intron rank: 6/15 Frameshift Impact:High VAF(%):51.85	Het	-ClinVar:Pathogenic, Likely Pathogenic -Mastermind ID:N/A -gnomAD Total: 0.0004812 -Internal DB:0.00019 -Total MAF:N/A -REVEL:N/A -CADD (PHRED):N/A -Splice-AI:0.25	Xanthinuria Type 2 AR Carrier	Likely pathogenic PVS1, PM2
PAH	chr12:102843790C>T NM_000277.3 c.1066-11G>A p.? Exon/Intron rank: 10/13 Intron Impact:Medium VAF(%):44.44	Het	-ClinVar:Pathogenic -Mastermind ID:N/A -gnomAD Total: 0.0005990 -Internal DB:0.00075 -Total MAF:N/A -REVEL:N/A -CADD (PHRED):23.5 -Splice-AI:0.98	Phenylketonuria AR Carrier	Pathogenic PS3, PS4, PM2, PP3, PP4

Pharmacogenomic Associations

This test identified the following variants associated with drug use and dosing generated based on PharmCAT v2.8.3 (according to CPIC Guidelines (https://cpicpgx.org/guidelines). Pharmacogenomics tests, along with other information about patients and their disease or condition, can play an important role in drug therapy. When a health care provider is considering prescribing a drug, knowledge of a patient's genotype may be used to aid in determining a therapeutic strategy, determining an appropriate dosage, or assessing the likelihood of benefit or toxicity.

Genetic variants associated with drug use and dosing were identified.

Drugs	PGx Phenotype	Genes / Genotype	CPIC recommendations
Acenocoumarol	Not assigned	VKORC1: rs9923231 reference (C)/ rs9923231 variant (T)	No CPIC recommendations available for this drug-gene interaction.
Allopurinol	Normal Function	ABCG2: rs2231142 reference (G)/ rs2231142 reference (G)	No CPIC recommendations available for this drug-gene interaction.
Amitriptyline	Normal Metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended starting dose.
Atazanavir	Normal Metabolizer	UGT1A1:*1/*1	There is no need to avoid prescribing of atazanavir based on UGT1A1 genetic test result. Inform the patient that some patients stop atazanavir because of jaundice (yellow eyes and skin), but that this patient's genotype makes this unlikely (less than about a 1 in 20 chance of stopping atazanavir because of jaundice).
Atorvastatin	Decreased Function	SLCO1B1:*15/*20	Prescribe ≤40mg as a starting dose and adjust doses of atorvastatin based on disease-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for 40mg dose. If dose >40mg needed for desired efficacy, consider combination therapy (i.e., atorvastatin plus non-statin guideline directed medical therapy) (PMID: 30423391).
Azathioprine	Normal Metabolizer	NUDT15:*1/*1 TPMT:*1/*1	Start with normal starting dose (e.g., 2-3 mg/kg/day) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady-state after each dose adjustment (PMID 20354201, 11302950, 15606506).
Capecitabine	Not assigned	DPYD:Reference/ Reference	Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration.
Celecoxib	Normal Metabolizer	CYP2C9:*1/*1	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.
Citalopram	Normal Metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended starting dose
Clomipramine	Normal Metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended starting dose.
Clopidogrel	Normal Metabolizer	CYP2C19:*1/*1	If considering clopidogrel, use at standard dose (75 mg/day)
Dapsone	Normal	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status
Desflurane	Indeterminate	CACNA1S:Reference/ Reference RYR1:Reference/ Reference	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.
Dexlansoprazole	Normal Metabolizer	CYP2C19:*1/*1	Initiate standard starting daily dose. Consider increasing dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.
Doxepin	Normal Metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended starting dose.

Efavirenz	Normal Metabolizer	CYP2B6:*2/*5	Initiate efavirenz with standard dosing (600 mg/day)
Enflurane	Indeterminate	CACNA1S:Reference/ Reference RYR1:Reference/ Reference	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.
Escitalopram	Normal Metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended starting dose
Flucytosine	Not assigned	DPYD:Reference/ Reference	No CPIC recommendations available for this drug-gene interaction.
Fluorouracil	Not assigned	DPYD:Reference/ Reference	Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration.
Flurbiprofen	Normal Metabolizer	CYP2C9:*1/*1	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.
Fluvastatin	CYP2C9: Normal Metabolizer SLCO1B1: Decreased Function	CYP2C9:*1/*1 SLCO1B1:*15/*20	Prescribe desired starting dose and adjust doses of fluvastatin based on disease-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for doses >40mg per day.
Fosphenytoin	Normal Metabolizer	CYP2C9:*1/*1	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug monitoring, response, and side effects. An HLA-B*15:02 negative test does not eliminate the risk of phenytoin-induced SJS/TEN and patients should be carefully monitored according to a usual standard.
Halothane	Indeterminate	CACNA1S:Reference/ Reference RYR1:Reference/ Reference	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.
Ibuprofen	Normal Metabolizer	CYP2C9:*1/*1	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.
Imipramine	Normal Metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended starting dose.
Irinotecan	Normal Metabolizer	UGT1A1:*1/*1	No CPIC recommendations available for this drug-gene interaction.
Isoflurane	Indeterminate	CACNA1S:Reference/ Reference RYR1:Reference/ Reference	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.
Ivacaftor	ivacaftor non-responsive in CF patients	CFTR:Reference/ Reference	Ivacaftor is not recommended
Lansoprazole	Normal Metabolizer	CYP2C19:*1/*1	Initiate standard starting daily dose. Consider increasing dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.
Lornoxicam	Normal Metabolizer	CYP2C9:*1/*1	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.
Lovastatin	Decreased Function	SLCO1B1:*15/*20	Prescribe an alternative statin depending on the desired potency (see Figure 1 of PMID: 35152405 for recommendations for alternative statins). If lovastatin therapy is warranted, limit dose to ≤20mg/day.
Meloxicam	Normal Metabolizer	CYP2C9:*1/*1	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.
Mercaptopurine	Normal Metabolizer	NUDT15:*1/*1 TPMT:*1/*1	Start with normal starting dose (e.g., 75 mg/m2/day or 1.5 mg/kg/day) and adjust doses of mercaptopurine (and of any other myelosuppressive therapy) without any special emphasis on mercaptopurine compared to other agents.

			Allow at least 2 weeks to reach steady-state after each dose adjustment (PMID 20354201, 16401827, 11302950).
Methoxyflurane	Indeterminate	CACNA1S:Reference/ Reference RYR1:Reference/ Reference	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.
Methylene blue	Normal	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status
Nitrofurantoin	Normal	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status
Omeprazole	Normal Metabolizer	CYP2C19:*1/*1	Initiate standard starting daily dose. Consider increasing dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.
Pantoprazole	Normal Metabolizer	CYP2C19:*1/*1	Initiate standard starting daily dose. Consider increasing dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.
Peginterferon alfa-2a	Not assigned	IFNL3:rs12979860 reference (C)/rs12979860 variant (T)	CPIC provides no genotype-based recommendations for the following genotype, after evaluating the evidence.
Peginterferon alfa-2b	Not assigned	IFNL3:rs12979860 reference (C)/rs12979860 variant (T)	CPIC provides no genotype-based recommendations for the following genotype, after evaluating the evidence.
Pegloticase	Normal	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status
Phenprocoumon	Not assigned	VKORC1: rs9923231 reference (C)/ rs9923231 variant (T)	No CPIC recommendations available for this drug-gene interaction.
Phenytoin	Normal Metabolizer	CYP2C9:*1/*1	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug monitoring, response, and side effects. An HLA-B*15:02 negative test does not eliminate the risk of phenytoin-induced SJS/TEN and patients should be carefully monitored according to a usual standard.
Piroxicam	Normal Metabolizer	CYP2C9:*1/*1	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.
Pitavastatin	Decreased Function	SLCO1B1:*15/*20	Prescribe ≤ 2mg as a starting dose and adjust doses of pitavastatin based on disease-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for doses >1mg. If dose >2mg needed for desired efficacy, consider an alternative statin (see Figure 1 of PMID: 35152405 for recommendations for alternative statins) or combination therapy (i.e. pitavastatin plus non-statin guideline directed medical therapy) (PMID: 30423391).
Pravastatin	Decreased Function	SLCO1B1:*15/*20	Prescribe desired starting dose and adjust doses of pravastatin based on disease-specific guidelines. Prescriber should be aware of possible increased risk for myopathy with pravastatin especially with doses >40mg per day.
Primaquine	Normal	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status
Quetiapine	Normal Metabolizer	CYP3A4:*1/*1	No CPIC recommendations available for this drug-gene interaction.
Rasburicase	Normal	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status
Ribavirin	Not assigned	IFNL3:rs12979860 reference (C)/rs12979860 variant (T)	CPIC provides no genotype-based recommendations for the following genotype, after evaluating the evidence.
Rosuvastatin	ABCG2: Normal Function	ABCG2: rs2231142 reference (G)/ rs2231142 reference	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and specific population guidelines. Prescriber should be aware of possible increased risk for myopathy especially for doses >20mg.

	SLCO1B1: Decreased Function	(G) SLCO1B1:*15/*20	
Sertraline	Normal Metabolizer	CYP2B6:*2/*5 CYP2C19:*1/*1	Initiate therapy with recommended starting dose.
Sevoflurane	Indeterminate	CACNA1S:Reference/ Reference RYR1:Reference/ Reference	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.
Simvastatin	Decreased Function	SLCO1B1:*15/*20	Prescribe an alternative statin depending on the desired potency (see Figure 1 of PMID: 35152405 for recommendations for alternative statins). If simvastatin therapy is warranted, limit dose to 20mg/day.
Siponimod	Normal Metabolizer	CYP2C9:*1/*1	No CPIC recommendations available for this drug-gene interaction.
Succinylcholine	Indeterminate	CACNA1S:Reference/ Reference RYR1:Reference/ Reference	Clinical findings, family history, further genetic testing and other laboratory data should guide use of halogenated volatile anesthetics or depolarizing muscle relaxants.
Tacrolimus	Poor Metabolizer	CYP3A5:*3/*3	Initiate therapy with standard recommended dose. Use therapeutic drug monitoring to guide dose adjustments.
Tafenoquine	Normal	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status
Tegafur	Not assigned	DPYD:Reference/ Reference	No CPIC recommendations available for this drug-gene interaction.
Tenoxicam	Normal Metabolizer	CYP2C9:*1/*1	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.
Thioguanine	Normal Metabolizer	NUDT15:*1/*1 TPMT:*1/*1	Start with normal starting dose (e.g., 40-60 mg/m2/day) and adjust doses of thioguanine and of other myelosuppressive therapy without any special emphasis on thioguanine. Allow 2 weeks to reach steady-state after each dose adjustment (PMID 20354201, 11037857).
Toluidine blue	Normal	G6PD:B (reference)/ B (reference)	No reason to avoid based on G6PD status
Trimipramine	Normal Metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended starting dose.
Voriconazole	Normal Metabolizer	CYP2C19:*1/*1	Initiate therapy with recommended standard of care dosing
Warfarin	CYP2C9: Normal Metabolizer CYP4F2: Not assigned VKORC1: Not assigned	CYP2C9:*1/*1 CYP4F2:*1/*3 VKORC1: rs9923231 reference (C)/ rs9923231 variant (T) rs12777823:G/G	The updated guideline for pharmacogenetics-guided warfarin dosing is published by the *Clinical Pharmacogenetics Implementation Consortium*. The recommendations for dosing are for adult and pediatric patients that are specific to continental ancestry, and are based on genotypes from *CYP2C9, VKORC1, CYP4F2*, and rs12777823. For more information please visit: https://www.pharmgkb.org/guidelineAnnotation/PA166104949

TECHNICAL INFORMATION

Methods	**Whole genome sequencing and data analysis.** DNA was extracted from a biological sample at Cegat (https://cegat.com/) and TruSeq Nano DNA High Throughput Library Prep Kit (Illumina®) was used to prepare libraries, which were sequenced using the 150nt pair-end protocol on an Illumina platform to yield an average coverage depth of 30x for the nuclear genome and at least 1000x for the mitochondrial genome. Bacterial contamination of a sample may impact the depth of coverage. Raw read alignment to reference genome GRCh38 and variant calling, including single nucleotide substitutions (SNVs), small insertions/deletions (Indels) and structural variants (SVs) with default parameters were performed using DRAGEN (version 4.2.4, Illumina). Variant annotation was performed by Geneyx (https://geneyx.com). For the mitochondrial genome, variants with frequencies/heteroplasmy level ≥5% are detected. Genetic variants are described following the Human Genome Variation Society (HGVS) recommendations (www.hgvs.org). In case of complex DNA changes both International System for Human Cytogenomic Nomenclature (ISCN; https://iscn.karger.com/) and complex HGVS/ISCN recommendations (https://hgvs-nomenclature.org/stable/recommendations/ DNA/ complex/) are indicated.
	Incidental genes: The gene panel is based on the ACMG (American College of Medical Genetics and Genomics) SF v.3.2 recommendations (https://www.gimjournal.org/article/S1098-3600(23)00879-1/fulltext). ACTA2, ACTC1, ACVRL1, APC, APOB, ATP7B, BAG3, BMPR1A, BRCA1, BRCA2, BTD, CACNA1S, CALM1, CALM2, CALM3, CASQ2, COL3A1, DES, DSC2, DSG2, DSP, ENG, FBN1, FLNC, GAA, GLA, HFE, HNF1A, KCNH2, KCNQ1, LDLR, LMNA, MAX, MEN1, MLH1, MSH2, MSH6, MUTYH, MYBPC3, MYH11, MYH7, MYL2, MYL3, NF2, OTC, PALB2, PCSK9, PKP2, PMS2, PRKAG2, PTEN, RB1, RBM20, RET, RPE65, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TMEM127, TMEM43, TNNC1, TNNI3, TNNT2, TP53, TPM1, TRDN, TSC1, TSC2, TTN, TTR, VHL, WT1.
	Variant interpretation: All candidate variants were evaluated with respect to their pathogenicity and causality significance, which are categorized following ACMG guidelines (PMID: 25741868) and ClinGen recommendations (https://www.clinicalgenome.org). Only those variants with evidence for causing or contributing to disease are reported as primary findings. All variants are visually inspected in IGV prior to reporting. The variants are classified following the 5-tier classes: pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely benign and benign. Likely benign and benign variants are not reported. VUSs are classified as "strong variants of unclear significance" when there is limited supporting evidence of pathogenicity (e.g., rare or absent from general population databases BUT in silico tools predict a deleterious effect on the protein consistent with the mechanism of disease; AND the gene has already been confirmed to be associated with the patient's observed phenotype). Incidental findings that do not correlate with the provided phenotype(s) are reported according to ACMG recommendations for reporting of incidental findings in using clinical exome and genome sequencing (PMID: 37347242), if consented. Only variants classified as pathogenic, likely pathogenic or uncertain (variants of unknown significance or VUS) according to the ACMG guidelines and associated with the patient's phenotype are listed among the primary findings. Variants of uncertain significance are categorized as strong candidates when they are extremely rare or absent in external and internal databases, are predicted to be deleterious, and the respective gene matches patient's phenotype (i.e. insufficient evidence available). Variants like risk factors (or risk alleles) and genetic modifiers, impacting the disease severity are reported ONLY when extensive scientific and clinical evidence is established. **ACMG criteria for classifying SNV/ Indels pathogenic variants:** PVS1- Null variant (nonsense, frameshift, canonical +/−1 or 2 splice sites, initiation codon, single or multi-exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease; PS1- Same amino acid change as a previously established pathogenic variant regardless of nucleotide change; PS2- De novo (both maternity and paternity confirmed) in a patient with the disease and no family history; PS3- Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product; PS4- The prevalence of the variant in affected individuals is significantly increased compared to the prevalence in controls; PM1- Located in a mutational hot spot and/or critical and well-established functional domain (e.g. active site of an enzyme) without benign variation; PM2- Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes, ExAC or gnomAD databases; PM3- For recessive disorders, detected in trans with a pathogenic variant; PM4-Protein length changes due to in-frame deletions/insertions in a non-repeat region or stop-loss variants; PM5- Novel missense change at an amino acid residue where a different missense change determined to be pathogenic has been seen before at the acid/protein level; PM6- Assumed de novo, but without confirmation of paternity and maternity; PP1- Co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease; PP2- Missense variant in a gene that has a low rate of benign missense variation and where missense variants are a common mechanism of disease; PP3- Multiple lines of computational evidence support a deleterious effect on the gene or gene product (conservation, evolutionary, splicing impact, etc); PP4- Patient's phenotype or family history is highly specific for a disease with a single genetic etiology.

	ACMG criteria for classifying benign variants: BA1- Allele frequency is above 5% in Exome Sequencing Project, 1000 Genomes, ExAC or gnomAD databases; BS1- Allele frequency is greater than expected for the disorder; BS2- Observed in a healthy adult individual for a recessive (homozygous), dominant (heterozygous), or X-linked (hemizygous) disorder with full penetrance expected at an early age; BS3- Well-established in vitro or in vivo functional studies shows no damaging effect on protein function or splicing; BS4- Lack of segregation in affected members of a family; BP1- Missense variant in a gene for which primarily truncating variants are known to cause disease; BP2- Observed in trans with a pathogenic variant for a fully penetrant dominant gene/disorder; or observed in cis with a pathogenic variant in any inheritance pattern; BP3- In-frame deletions/insertions in a repetitive region without a known function; BP4- Multiple lines of computational evidence suggest no impact on gene or gene product (conservation, evolutionary, splicing impact, etc); BP5- Variant found in a case with an alternate molecular basis for disease; BP7- A synonymous (silent) variant for which splicing prediction algorithms predict no impact to the splice consensus sequence nor the creation of a new splice site AND the nucleotide is not highly conserved. **ACMG criteria for classifying CNV/ SV pathogenic variants: LOSS** 1A. Contains protein-coding or other known functionally important elements; 1B. Does NOT contain protein-coding or any known functionally important elements; 2A. Complete overlap of an established HI gene/genomic region; 2B. Partial overlap of an established HI genomic region; 2C. Partial overlap with the 5' end of an established HI gene (3' end of the gene not involved); 2D. Partial overlap with the 3' end of an established HI gene (5' end of the gene not involved); 2E. Both breakpoints are within the same gene (intragenic CNV; gene-level sequence variant); 2F. Completely contained within an established benign CNV region; 2G. Overlaps an established benign CNV but includes additional genomic material; 2H. Two or more HI predictors suggest that AT LEAST ONE gene in the interval is haploinsufficient (HI); 3A. Number of protein-coding RefSeq genes wholly or partially included in the copy number loss (0-24 genes); 3B. Number of protein-coding RefSeq genes wholly or partially included in the copy number loss (25-34 genes); 3C. Number of protein-coding RefSeq genes wholly or partially included in the copy number loss (35+ genes); 4A-4C. Individual case evidence – de novo occurrences; 4D. Individual case evidence – inconsistent phenotype; 4E. Individual case evidence – unknown inheritance; 4F-4H. Individual case evidence – segregation among similarly affected family members; 4I-4K. Individual case evidence - Non-Segregations; 4L-4O. Case-control and population evidence; 5A. Observed copy number loss is DE NOVO; 5B-5D. Observed copy number loss is INHERITED; 5E. Observed copy number loss – NON-SEGREGATIONS; 5F-5H Other. **GAIN**: 1A. Contains protein-coding or other known functionally important elements; 1B. Does NOT contain protein-coding or any known functionally important elements; 2A. Complete overlap; the TS gene or minimal critical region is fully contained within the observed copy number gain; 2B. Partial overlap of an established TS region; 2C. Identical in gene content to the established benign copy number gain; 2D. Smaller than established benign copy number gain, breakpoint(s) does not interrupt protein-coding genes; 2E. Smaller than established benign copy number gain, breakpoint(s) potentially interrupts protein-coding gene; 2F. Larger than known benign copy number gain, does not include additional protein-coding genes; 2G. Overlaps a benign copy number gain but includes additional genomic material; 2H. HI gene fully contained within observed copy number gain; 2I. Both breakpoints are within the same gene (gene-level sequence variant, possibly resulting in loss of function (LOF)); 2J. One breakpoint is within an established HI gene, patient's phenotype is either inconsistent with what is expected for LOF of that gene OR unknown; 2K. One breakpoint is within an established HI gene, patient's phenotype is highly specific and consistent with what is expected for LOF of that gene; 2L. One or both breakpoints are within gene(s) of no established clinical significance; 3A. Number of protein-coding RefSeq genes wholly or partially included in the copy number gain (0-34 genes); 3B. Number of protein-coding RefSeq genes wholly or partially included in the copy number gain (35-49 genes); 3C. Number of protein-coding RefSeq genes wholly or partially included in the copy number gain (50+ genes); 4A-4C. Individual case evidence – de novo occurrences; 4D. Individual case evidence – inconsistent phenotype; 4E. Individual case evidence – unknown inheritance; 4F-4H. Individual case evidence – segregation among similarly affected family members; 4I-4K. Individual case evidence - Non-Segregations; 4L-4O. Case-control and population evidence; 5A. Observed copy number loss is DE NOVO; 5B-5D. Observed copy number loss is INHERITED; 5E. Observed copy number loss – NON-SEGREGATIONS; 5F-5H Other. Point- based scoring framework: Pathogenic for 0.99 or more points; Likely pathogenic for 0.90 to 0.98 points; Variant of Uncertain Significance for scores between -0.89 to 0.89 points; Likely benign for scores between -0.90 to - 0.98; Benign for -0.99 or fewer points. **Consanguinity score (CS):** this score is obtained from the DRAGEN's region of homozygosity calculation that considers homozygous single nucleotide variants on the autosomes. The higher the score, the closer the biological relationship of subjects´ parents. A score above two (2) suggests consanguinity.
Pharmacogenomic variants	The design of the pharmacogenomics panel is based on PharmCAT v2.8.3 (https://pharmcat.org/) and CPIC v1.30.0 (https://cpicpgx.org/guidelines/). The list of genes and drugs covered by PharmCAT is provided under: https://pharmcat.org/Genes-Drugs The covered drugs based on Anatomical Therapeutic Chemical (ATC) classification by PharmCAT v2.8.3 are:

	i. Anti-cancer and immune response: Azathioprine, Capecitabine, Fluorouracil, Irinotecan, Mercaptopurine, Peginterferon alfa-2a, Peginterferon alfa-2b, Rasburicase, Siponimod, Tacrolimus, Tegafur, Thioguanine ii. Blood and cardiovascular system: Acenocoumarol, Atorvastatin, Clopidogrel, Fluvastatin, Lovastatin, Methylene blue, Phenprocoumon, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin, Warfarin iii. Digestive system: Dexlansoprazole, Lansoprazole, Omeprazole, Pantoprazole iv. Infection control: Atazanavir, Dapsone, Efavirenz, Flucytosine, Nitrofurantoin, Primaquine, Ribavirin, Tafenoquine, Voriconazole v. Musculo-skeletal system: Allopurinol, Celecoxib, Flurbiprofen, Ibuprofen, Lornoxicam, Meloxicam, Pegloticase, Piroxicam, Succinylcholine, Tenoxicam vi. Nervous system: Amitriptyline, Citalopram, Clomipramine, Desflurane, Doxepin, Enflurane, Escitalopram, Fosphenytoin, Halothane, Imipramine, Isoflurane, Methoxyflurane, Phenytoin, Quetiapine, Sertraline, Sevoflurane, Trimipramine vii. Respiratory system: Ivacaftor viii. Other: Toluidine blue The covered genes by PharmCAT v2.8.3 are: ABCG2, CACNA1S, CFTR, CYP2B6, CYP2C19, CYP2C9, CYP3A4, CYP3A5, CYP4F2, DPYD, G6PD, IFNL3, NUDT15, RYR1, SLCO1B1, TPMT, UGT1A1, VKORC1 PharmCAT is only able to generate recommendations based on the information provided to the software. The gene and variant information for all reported sections are interpreted directly from Arcensus-supplied data. Reported genotype calls are displayed with respect to the reference genome. Variants indicated as homozygous or heterozygous differ from the GRCh38/hg38 reference sequence (wild type). For all genes, variation reported in the VCF file but NOT included in the gene definition table will not be considered during allele assignment. There is a possibility that any such variation results in a reduced or no activity allele which could lead to inaccurate phenotype and CPIC recommendation. Structural variation star alleles that cannot be detected using VCF file data: CYP2B7-CYP2B6 hybrids: CYP2B6*29, CYP2B6*30; Partial and whole gene deletions: CYP2C19*36, CYP2C19*37, CYP4F2*16, SLCO1B1*48, SLCO1B1*49. This test does not report polymorphisms other than those specifically listed, and mutations in other genes associated with drug metabolism will not be reported. All content is sourced from the CPIC database.
Limitations	myLifeGenome is NOT indicated for somatic variant analysis of tumor samples, Alzheimer's risk assessment, prenatal testing, partial UPD (uniparental disomy), epigenetic modifications like methlyation (known to cause Prader-Willi, Russell Silver or Beckwith-Wiedemann syndromes), gene conversions (GBA/GBAP1, CYP21A2, NCF1 or VWF), D4Z4 repeat expansion (known to cause facioscapulohumeral muscular dystrophy), or low level of mosaicims (VAF10%). Pathogenic repeat expansions within the following genes can be determined. Repeat expansion in genes outside the list (for e.g. but not limited to ATN1, ATXN1, ATXN10, ATXN2, ATXN3, ATXN7, C9orf72, CACNA1A, CNBP, CSTB, FMR1, FXN, HTT, PABPN1, PHOX2B, PPP2R2B, PRNP, TBP) may not be reliably detected. Variants within low-complexity and repeat sequence such as CFH, HLA, MUC5B, NOTCH2, NCL, PKD1 or RPGR genes might be detected, but recommendations to be confirmed by an orthogonal method provided. The genetic result's interpretation is strongly dependent on the clarity of provided clinical information and family history. Misinterpretation may occur if this data is provided incorrectly or incompletely. Variant frequencies are subjected to changes due to growing variant databases and may result in reclassification of previously reported variants. The variants detected with this assay cover the whole genome, within (intragenic) and beyond (intergenic) genes. The detectable variant types include nucleotide substitution, small insertions/deletions, copy number variants (CNVs), inversions, translocations, and complex rearrangements. Variants may not be detected in low complexity genomic regions due to high sequence homology, pseudogenes, or highly repetitive sequences. This methodology detects events of mosaicism of single nucleotide variants (SNVs) with an minor allele fraction of at least 10%. It is possible that a particular genetic variant may not be recognized as the underlying cause of the genetic disorder due to incomplete scientific knowledge about the biological function of the gene and/or the impact of the variant on the expression and/or function of the gene.

Test Performance

Total number of reads: 715,710,64 Percentage of reads mapping to hg38: 98.34% Median coverage: 35.91x

Annotation Datasets:

1kGenome:2019-02	ACMG:2024-12	AcmgSv:2024-12	AlphaMissense:v2-t113	CADD:1.6
CamouflagedGenes:v1	ClinGen:2024-12	ClinVar:2024-12	CoLoRSdb:v1.0.0	Cytogenetic:2022-10
DarkGenes:v1	DbNsfp:4.4a	DbscSNV:1.1	DbSnp:1405	DGVGold:v107_2020-03-02
DGVSV:v107_2020-02-25	ESP6500:2	GeneEnhancerSv:v6.1	GeneYX Version :v6.1	GeneyxRepeats:v1.1
Gerp:2010	gnomAD-exomes:2.1.1	gnomAD-genomes:3.1.2	gnomAD-mit:2.1.1	GnomADSV:v2.1
GnomADv4-exomes:4.1.0	GnomADv4-genomes:4.1.0	LitVar2:2024-12	MANE:v1.4	MasterMind:2024-07
MitoMap:2021-10	OMIM:2024-12	Phylop:2015-05	Revel:2016-03	Rmsk:2022-10
SnpEff:v5.2-2024-12	SpliceAI:1.3			

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