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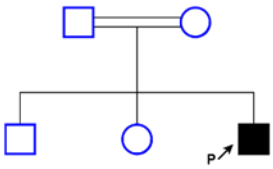
Name: John Doe
Medical Request No. 1234567

D.O.B:	dd/mm/yyyy	Referring physician:	Dr. Doctor name
Sex:	Male	Referring facility:	Medical Center, Country
Subject ID:	8xxxx	Email physician:	doctorname@email.com
Order ID:	2xxxxx	Report type:	Re-analysis myLifeGenome
Device/ Material ID:	ARCxxxxxx	Date of report:	11/12/2023
Specimen type:	Buccal swab		
Specimen arrival date:	dd/mm/2022		

Requested Test: myLifeGenome™
Indication for test: Infertility



Consanguineous parents: Yes

Consent for evaluation: Primary findings: Yes
Incidental findings: Yes

About this test: Re-analysis of the whole genome sequencing (WGS) data is initiated at regular intervals. Re-analysis includes a re-examination of the existing genomic data, the annotation of the variants with appropriate meta-data, re-assessment of the clinical picture of the patient, of the variant interpretation, and of the novel gene-disease associations

ADDITIONAL VARIANT / CHANGE IDENTIFIED

PRIMARY	INCIDENTAL	CARRIER RISK	PHARMACOGENOMICS
☒	☐	☐	☐

Primary Findings

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

Results: A homozygous pathogenic variant was identified in the CFAP61 gene. Mutations in this gene have been meanwhile associated with autosomal recessive spermatogenic failure type 84 (Hu et al., 2023; OMIM May 2023 update).

Gene	Variant	Zygosity	Variant class*	Disease name	Disease MOI*
CFAP61	c.847C>T; p.Arg283*	Hom	P	Spermatogenic Failure type 84	AR

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: No change under incidental finding detected.

AD: autosomal dominant, AR: autosomal recessive, Het: Heterozygous; Hom: Homozygous; LP: Likely Pathogenic; P: Pathogenic; RF: risk factor VUS: Variant of Uncertain Significance.

Arcensus GmbH
Goethestrasse 20, 18055 Rostock
www.arcensus-diagnostics.com

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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: No change under carrier finding detected.

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: No change under pharmacogenomic associations identified.

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.
- Spermatogenic failure type 84 is inherited in an autosomal recessive manner. For infertile males, assisted reproductive technologies such as intracytoplasmic sperm injection are likely to be an effective fertility option. Spermatogenic failure-84 (SPGF84) is characterized by male infertility due to multiple morphologic abnormalities of the sperm flagella (MMAF), including irregular-caliber, bent, coiled, absent, or short tails, resulting in severely reduced motility. Some patients also have a reduced sperm count (Hu et al., 2023). Transmission electron microscopy of sperm from F1 revealed that over 97% of cross-sections of sperm flagella exhibited abnormal characteristics, including the absence of the central pair (9+0 configuration), disorganization of the 9+2 structure, and absence of microtubule doublets. Probands underwent intracytoplasmic sperm injection (ICSI) with fertilization rates of 100%.

Signatures

Medical Advisor | Lab Director | Clinical Genomics Scientist

DETAILED INSIGHTS

Primary Findings

A homozygous pathogenic variant was identified in the CFAP61 gene. This result is consistent with the genetic diagnosis of autosomal recessive spermatogenic failure type 84.

CFAP61 (Cilia and Flagella Associated Protein 61) is a Protein Coding gene. Predicted to be involved in cilium movement and cilium organization. Predicted to be located in axoneme and motile cilium. Predicted to colocalize with radial spoke stalk.

	Gene/OMIM	*CFAP61/620381*
	Genomic coordinate (GRCh38)	chr20:20098802C>T
	ID Transcript	NM_015585.4
	HGVS nomenclature	c.847C>T
	Protein change	p.Arg283*
	Location	exon 8/27
	Zygosity	Hom
	Function	stop_gained
	Impact	High
	ClinVar	Pathogenic
Allele Frequency	Local Database	0.0011
	gnomAD	0.0002
In silico Predictors	REVEL	N/A
	CADD (PHRED)	33.0
	Splice-AI	0.14
	Clinical significance	Pathogenic
	ACMG Criteria	PVS1, PS4, PM2

HGVS= Human Genome Variation Society; gnomAD= Genome Aggregation Database; ACMG= American College of Medical Genetics and Genomics; REVEL score (combination from 13 individual tools; ranges 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: Spermatogenic failure-84 (SPGF84) is characterized by male infertility due to multiple morphologic abnormalities of the sperm flagella (MMAF), including irregular-caliber, bent, coiled, absent, or short tails, resulting in severely reduced motility. Some patients also have a reduced sperm count (Liu et al., 2021; Hu et al., 2023).
For infertile males, assisted reproductive technologies such as intracytoplasmic sperm injection are likely to be an effective fertility option.
To attend in clinical trial, see the following link: https://clinicaltrials.gov/search?cond=SPERMATOGENIC%20FAILURE

Variant description: This variant creates a premature stop codon at position 283. It is expected to result in a truncated or disrupted protein. The variant is present in gnomAD (allele frequency: 0.0002) and is absent from the local database (allele frequency: 0.0011). This variant is listed in ClinVar as pathogenic (Accession ID: 2504102) in June 2023. This variant is classified as pathogenic based on ACMG recommendations.

TECHNICAL INFORMATION

Methods	**Whole genome sequencing and data analysis.** DNA was extracted from a biological sample 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). SNV and Indel variant annotation was performed by Geneyx (https://geneyx.com). Structural variants were annotated with ANNOTSV3.1 and in- house structural variant database to obtain allele frequencies. 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).
	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, and these are categorized following ACMG guidelines (PMID: 25741868) and ClinGen recommendations (https://www.clinicalgenome.org). All variants are verified to have good quality, and only those variants with evidence for causing or contributing to disease are reported as primary findings. 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 for 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 extremely are very 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 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 show 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. **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	The genetic result's interpretation is strongly dependent on the 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 (SVN) with an minor allele fraction of minimum 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.

GeneYX Version set 45

1kGenome:2019-02	ACMG:2023-10	CADD:1.6	ClinGen:2023-10	ClinVar:2023-10
Cytogenetic:2022-12	DbNsfp:4.4a	DbscSNV:1.1	DbSnp:1405	DGVGold:v107_2016-05-15
DGVSV:v107_2020-02-25	ESP6500:2	GeneEnhancerSv:v5.15	GeneyxRepeats:v1.1	Gerp:2010
gnomAD-exomes:2.1.1	gnomAD-genomes:3.1.2	gnomAD-mit:2.1.1	GnomADSV:v2.1	LitVar2:2023-10
MANE:v1.1				

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