This information is for health professionals. It is not essential that you read this section.

Subject information	Order Information
Name: John Doe	**Type of Test:** *myLifeHeart*™
Sex: Male	**Sample Type:** Buccal swab
D.O.B: dd.mm.yyyy	**Internal ID:**xxxx
Age: 18 years old	**Order date:** 27.09.2021
Box ID: arxxxxxxx	**Sample collection date:** 12.08.2021
Payment ID: DNA-xxxxxxxxxx	**Sample arrival date: 18**.08.2021
E-mail: john.doe@email.com	**Date of report: 18.09.2021**

Requested test: *myLifeHeart*™

Consent for the evaluation of incidental findings was given by the subject.

Medical summary

- Family History: unremarkable.
- Physical Information: not provided.
- Clinical manifestations: Fatigue and weakness, Shortness of breath

Summary of the genetic results

Primary Finding

A heterozygous pathogenic variant was identified in the ***SCN5A* gene**. The genetic diagnosis of **autosomal dominant Bragada syndrome type 1** is confirmed.

Incidental Finding

We did not detect any class 1 and 2 variants in the genes for which incidental findings are reported based on the ACMG guidelines.

Recommendation

- Clinical correlation is advised.
- Familiar genetic testing is advised to stablish whether the pathogenic variant ***SCN5A*** variant is inherited in close relatives at risk.
- Genetic counselling is recommended.

John Doe
D.O.B. dd.mm.yyyy
Box ID: arxxxxxxxx

Interpretation of primary finding

By Whole Genome Sequencing (WGS), we have identified a heterozygous genetic variant in alpha subunit of the main cardiac sodium channel $Na_v1.5$ (*SCN5A*) gene. This gene encodes is known to be responsible for maintaining the normal function of inward sodium current (INa). INa current is the main component in fast depolarization phase after which the excitation–contraction coupling cascade and proper conduction of the electrical impulse is subsequently initiated within the heart (Aronsen et al., 2013). Since 1995, SCN5A variants have been found to be causatively associated with Brugada syndrome, long QT syndrome, cardiac conduction system dysfunction and dilated cardiomyopathy.

Gene/OMIM		***SCN5A*/ 600163**
Genomic coordinate (GRCh38)		Chr3: 38550782
ID Transcript		NM_001099404.2
HGVS[1] nomenclature		c.5587G>T
Protein change		p.(Glu1864*)
Location		Exon 28 of 28
Zygosity		**Heterozygous**
Function		Nonsense variant
Impact		HIGH
ClinVar		Pathogenic
Allele Frequency	*Local Database*	-
	gnomAD[2]	-
In silico Predictors	MetaLR	-
	MetaSVM	-
	DANN	Pathogenic
	Mutation Taster	Disease causing
Clinical significance		**Pathogenic (class 1)**
ACMG[3] Criteria		PVS1 very strong; PM2 strong

[1]HGVS= Human Genome Variation Society; [2]gnomAD= Genome Aggregation Database; [3]ACMG= American College of Medical Genetics and Genomics; Class 1: Pathogenic; Class 2: Likely Pathogenic; Class 3: Variant of uncertain significance (VUS); Class 4: Likely benign; Class 5: Benign.

***SCN5A*; c. c.5587G>T p.(Glu1864*)**

This sequence change results in a premature translational stop signal in the SCN5A gene (p.Glu1864*). While this is not anticipated to result in nonsense mediated decay, it is expected to disrupt the last 153 amino acids of the SCN5A protein. This variant is not present in population databases (gnomAD no frequency) and classified as pathogenic in ClinVar database (variation ID406418). More than 700 SCN5A variation locations are shown to be associated with cardiac disorders (Li et al., 2018) and about 90% variants account for non-synonymous variants, while the rest are due to deletion and duplication. This variant is classified as pathogenic (class 1) based on ACMG guidelines.

PVS1: Null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease.

PM2: Absent from controls (or at extremely low frequency if recessive) in gnomAD.

Disease name/ OMIM	MOI	Genotype	Clinical statement
Brugada syndrome 1 / 601144	AD	Heterozygote	Affected

MOI: Mode of inheritance; AD: autosomal dominant, AR: autosomal recessive; XL: X-linked

Brugada Syndrome (BS)

Brugada Syndrome (BS) is an autosomal dominant channelopathy, caused by pathogenic variants in the *SCN5A* gene located on chromosome 3p22. Genetic changes in transmembrane ion channels creates action potentials, in this case, leading to an increased risk of cardiac arrhythmia (PMID: 19889341).

Clinical Manifestations

Brugada syndrome is characterized by a distinctive electrocardiographic (ECG) pattern of sinus tachycardia (ST) segment elevation in the V1-V3 leads in the absence of gross structural heart abnormalities. Patients might present a high risk for ventricular arrhythmias (VA), which can result in syncope or sudden cardiac death (SCD). Clinical presentations may also include the sudden unexpected nocturnal death syndrome (SUNDS). Other conduction defects can include intraventricular conduction delay, first-degree atrioventricular (AV) block, right bundle branch block, and sick sinus syndrome. Electrical storms, multiple episodes of VA over a short period of time, are malignant but rare in patients. Symptoms include nocturnal agonal respiration, palpitations and chest discomfort, which often occur during rest, sleep, during a febrile state, or with vagotonic conditions, but rarely during exercise (GeneReviews®, NBK1517).

BS presents primarily during adulthood, with syncope as the most common presenting feature. Age at diagnosis may present during late adulthood. The mean age of SCD is approximately 40 years. Both sexes are at a high risk for VA and SCD, though the vast majority of those affected are male. Patients who have easily induced sustained VA, a spontaneous type 1 ECG pattern (compared to pharmacologically-induced), and a history of syncope have a worse prognosis (PMID: 21823372, PMID: 23916535). Available prevalence estimates 1/3,300-1/10,000 in Europe and the United States (PMID: 29908370).

Surveillance and treatment

The primary goal of treatment is to establish extent of disease and individual needs after initial diagnosis, patients are recommended to undergo an ECG, induction with sodium channel blockers, and medical genetics consultation. In case of asymptomatic patients, or those with only inducible type 1 ECG pattern, clinical observation without therapy is recommended. Implantation of an ICD in an asymptomatic patient without a spontaneous type 1 ECG pattern has not been shown to confer any benefit (GeneReviews®, NBK1517). Surveillance in individuals with a pathogenic variant should undergo ECG monitoring every one to two years (PMID: 29097320). BS Patients should avoid certain antiarrhythmic, psychotropic, and anesthetic drugs that can induce or aggravate cardiac arrhythmias. Other agents to avoid include acetylcholine, alcohol toxicity, cocaine, cannabis, and ergonovine (PMID: 26320108).

Clinical Trials

Clinical trials are essential for the development of new treatments. When considering a clinical trial, a person should try to gather as much information as they can and then do what they feel is best in their own mind. Those who decide to volunteer may be contributing directly to the undersanding of diseases and how to treat them. To get further information about clinical trials for Brugada syndrome, please visit:
https://clinicaltrials.gov/ct2/show/NCT02014961

Technical information- Methods

Library preparation and whole genome sequencing has been performed at Cegat (https:\\www.cegat.de), using TruSeq Nano DNA Throughput Library Prep Kit from Illumina®. The libraries are paired end sequenced on an Illumina platform to yield an average coverage depth of ~30x. Raw sequencing data were transformed into FASTQ format and transferred to Varvis® service (Limbus Medical Technologies GmbH; https://www.limbus-medtec.com/).

Computational and data analysis: Sequence reads of each sample were mapped to the human reference genome (hg38). Varvis® version 1.18 has been used for bioinformatics pipeline, including read alignment, variant calling, annotation, variant filtering and analysis. Genetic variants are described following the Human Genome Variation Society (HGVS) recommendations (www.hgvs.org)

myLifeHeart™ was developed and assessed for accuracy and precision by arcensus. The design of the virtual panel is property of arcensus and includes the following 450 genes related to heart medical conditions:

AARS2, ABCA1, ABCC6, ABCC9, ABCG5, ABCG8, ABL1, ACAD9, ACADVL, ACTA1, ACTA2, ACTC1, ACTG1, ACTN2, ACVRL1, ADAMTS10, ADAMTS17, AFF4, AGK, AGL, AGPAT2, AGT, AKAP9, AKT3, ALDH18A1, ALMS1, ALPK3, AMMECR1, ANGPTL3, ANK2, APOA1, APOA5, APOB, APOC2, APOC3, ARHGAP31, ARID1A, ARID1B, ATP7A, ATPAF2, B3GAT3, BAG3, BCOR, BGN, BMPR2, BRAF, CACNA1C, CACNB2, CALM1, CALM2, CALM3, CALR3, CASQ2, CAV1, CAV3, CAVIN4, CBL, CBS, CDC42, CDH2, CDK13, CFC1, CHD4, CHD7, CHKB, CITED2, COA5, COA6, COL1A1, COL1A2, COL2A1, COL3A1, COL4A1, COL4A5, COL5A1, COLGALT1, COX15, CPT2, CREB3L3, CREBBP, CRELD1, CRYAB, CSRP3, CTC1, TNNA3, DBH, DES, DHCR7, DLL4, DMD, DNAJC19, DOLK, DPM3, DPP6, DSC2, DSG2, DSP, DTNA, EFEMP2, EFTUD2, EHMT1, EIF2AK4, ELAC2, ELN, EMD, ENG, ENPP1, EOGT, EPG5, EPHB4, EVC, EVC2, EYA4, FAH, FBLN5, FBN1, FBN2, FBXL4, FHL1, FKBP14, FKRP, FKTN, FLNA, FLNC, FOXC1, FOXE3, FOXF1, FOXRED1, FTO, FXN, GAA, GATA4, GATA5, GATA6, GATAD1, GATC, GBE1, GDF1, GDF2, GJA1, GJA5, GLA, GLB1, GMPPB, GNAI2, GNB5, GPC3, GPD1L, GTPBP3, GUSB, HADHA, HCCS, HCN4, HFE, HNRNPK, HOXA1, HRAS, HTRA1, IDUA, JAG1, JPH2, JUP,KAT6B, KCNA5, KCND3, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ2, KCNJ5, CNJ8, KCNK3, KCNQ1, KDM6A, KMT2D, KRAS, KYNU, LAMA4, LAMP2, LDB3, LDLR, LEMD2, LIMS2, LIPC, LMNA, LOX, LRRC10, LTBP2, LZTR1, MED12, MED13L, MEF2A, MEIS2, MFAP5, MIB1, MIPEP, MLXIPL, MLYCD, MMAB, MMP21, MMP3, MRAS, MRPL3, MRPL44, MRPS22, MT-ATP6, MT-ATP8, MT-CO1, MT-CO2, MT-CO3, MT-CYB, MTHFR, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND4L, MTND5, MTND6, MTO1, MT-RNR1, MT-RNR2, MT-TA,MT-TC, MT-TD, MT-TE, MT-TF, MTTG, MTTH, MTTI, MTTK, MTTL1, MTTL2, MTTM, MT-TN, MTTP, MTTQ, MT-TR, MTTS1, MTTS2, MT-TT, MT-TV, MT-TW, MT-TY, MURC, MYBPC3, MYBPHL, MYCN, MYH11, MYH6, MYH7, MYL2, MYL3, MYL4, MYLK, MYLK2, MYO18B, MYO6, MYOT, MYOZ2, MYPN, MYRF, NAA15, NCAN, NDUFAF2, NDUFB11, NDUFV2, NEB, NEBL, NEXN, NF1, NF2, NFATC1, NFU1, NIPBL, NKX2-5, NKX2-6, NODAL, NONO, NOS1AP, NOS3, NOTCH1, NOTCH2, NOTCH3, NPPA, NR2F2, NRAP, NRAS, NSD1, NSUN2, NUP155, PARS2, PCCA, PCCB, PCSK1, PCSK9, PDLIM3, PIK3CA, PIK3R2, PITX2, PKD1L1, PKD2, PKP2, PLD1, PLEC, PLEKHM2, PLN, PLOD1, PNPLA2, POMT1, POMT2, PON1, PPA2, PPARG, PPCS, PPP1CB, PRDM16, PRDM6, PRKAG2, PRKAR1A, PRKD1, PRKG1, PSEN1, PSEN2, PTPN11, PUF60, QRSL1, RAB23, RAF1, RANGRF, RASA1, RASA2, RBCK1,RBFOX2, RBM10, RBM20, RERE,RIT1, RMND1, ROBO1, RRAS, RYR1, RYR2, SALL1, SALL4, SARS2, SASH1, SCN10A, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SCNN1B, SCNN1G, SCO1, SCO2, SDHA, SELENON, SEMA3A, SGCA, SGCB, SGCD, SGCG, SHOC2, SKI, SLC12A3, SLC22A5, SLC25A20, SMC1A, SMC3, SMCHD1, SNTA1, SOD2, SORT1, SOS1, SOS2, SOX17, SOX2, SPEG, SPRED1, SREBF2, STAG2, STAMBP, STRA6, SUGP1, SYNE1, SYNE2, SYNGAP1, TAB2, TAZ, TBX1, TBX20, TBX3, TBX4, TBX5, TCAP, TECRL, TFAP2B, TGDS, TGFB2, TGFB3, TGFBR1, TGFBR2, TK2, TLL1, TMEM43, TMEM70, TMEM94, TMPO, TNNC1, TNNI3, TNNI3K, TNNT2, TOR1AIP1, TPM1, TRDN, TREX1, TRIB1, TRIM32, TRIM63, TRPM4, TRPM6, TSFM, TTN, TTR, TXNRD2, VARS2, VCL, VCP, VPS13A, XK, ZBTB17, ZDHHC9, ZEB2, ZFPM2, ZHX3, ZIC3.

Incidental genes: The design of the panel is based on the ACMG (American College of Medical Genetics and Genomics) SF v.3.0 recommendations (https://www.nature.com/articles/s41436-021-01172-3).

ACTA2, ACTC1, ACVRL1, APC, APOB, ATP7B, BMPR1A, BRCA1, BRCA2, BTD, CACNA1S, CASQ2, COL3A1, 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, RET, RPE65, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TMEM127, TMEM43, TNNI3, TNNT2, TP53, TPM1, TRDN, TSC1, TSC2, TTN, VHL, WT1.

Variant interpretation: All candidate variants were evaluated with respect to their pathogenicity and causality, and these are categorized following ACMG guidelines (PMID: 25741868). 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. Incidental findings that do not correlate with the provided phenotype(s) are reported according to ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing (PMID: 23788249), if consented.

Limitations

The genetic result's interpretation is strongly dependent on the clinical information (preferably based on HPO) and family history. Misinterpretation may occur if this data not provided correctly or completely. The knowledge about the frequency of variants is growing and databases are updating, therefore the reclassification of variants is expected.

Variants in the intronic, UTR and promoter regions are not intended to be detected by this assay. This test does not detect complex inversions, gene conversions, balanced translocations, repeat expansion. Therefore, it is possible that the gene region where pathogenic variant is located, could not be sequenced using the current technology of this test and therefore was not detected.

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 all genes in the human genome and the impact of variants in those genes.

Signatures

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