MEDICOVER GENETICS

MOLECULAR GENETIC REPORT
GM19.12345

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Date: 16.03.2020

Report to:

Requesting Physician Name

Address

Contact Information

Order Number	**20 2009 1234**
Born	**01.01.1976**
Sex	M
Date test requested:	27.02.2020
Sample collected:	27.02.2020
Sample / Specimen:	DNA from EDTA blood

Order: BRCA1/BRCA2 sequencing analysis
Additional Information /patient phenotype: suspected hereditary breast/ovarian cancer syndrome

RESULT SUMMARY:

BRCA1 – pathogenic variant identified
BRCA2 – no pathogenic/likely pathogenic or variant of uncertain significant was identified

Result

The sequencing analysis revealed a pathogenic variant c.1193C>G within exon 10 of the *BRCA1* gene. This variant replaces the amino acid serine with a translation termination codon at codon 398 (p.Ser398*). The substitution is predicted to generate a shortened and/or non-functional BRCA1 protein, or the mRNA might be decayed immediately. The variant c.1193C>G has been detected before in other patients with hereditary breast and/or ovarian cancer (e.g. Harter et al. 2017, PLoS One 12:e0186043). The databases HGMD®, ClinVar and BRCA Exchange list the variant unanimously as pathogenic and causative for hereditary breast and ovarian cancer

Recommended action

- Persons carrying a pathogenic *BRCA1* variant are recommended to participate in intensive surveillance programs. Prophylactic measures might be considered. There is a 50% chance for the variant to be passed down to children. Also, other blood relatives might be at risk and can be tested for the variant
- Genetic counselling

VARIANT DETAILS

Gene	**HGVS description**	**Exon**	**Location on GRCh38**	**Zygosity**
BRCA1	NM_007294.3:c.1193C>G	10	Chr17: 43094338	Heterozygous
OMIM-P	**Consequence**	**Mode of inheritance**	**ACMG/AMP criteria** (Richards et al.; Ellard et al.)	**Classification**
604370	p.Ser398Ter. Nonsense mutation	Autosomal dominant	PVS1_strong, PS4_moderate, PM2	**pathogenic**

Report released by

John Doe 16.3.2020

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TEST METHODOLOGY

Sequencing	Enrichment	SNV and CNV Data analysis	data evaluation	Reference genome
Next Generation Sequencing (Illumina)	Twist Human Core Exome plus RefSeq SpikeIn	Illumina Dragen Bio-IT Platform	VarSeq by GoldenHelix	hg38, NCBI GR38
Quality criteria	**SNV detection sensitivity**	**Classification of variants**	**in silico algorithms**	**Databases**
>30 (precision >99,9%) in min. 75% of bases	99.92 - 99.93 %; confirmation of reported SNV with Sanger sequencing, data analysis with SeqPilot	Richards et al. 2015, Genet Med 17:405; Ellard et al. "ACGS Best Practice Guidelines for Variant Classification 2020“	MaxEntScan, SpliceSiteFinder-like, REVEL	HGMD Professional release, ClinVar, gnomAD

ANALYZED GENES

BRCA1 (NM_007294.3), *BRCA2* (NM_000059.3)

PERCENTAGE OF SEQUENCED BASES WITH COVERAGE >20X

100 %

LIST OF EXONS WITH COVERAGE <20X

-

TECHNICAL LIMITATIONS

mosaics (<20%); indels >21bp; repeat expansions; variants in: homopolymeric regions or regions of high sequence homology, unenriched regions (untranslated regions, introns, promoter and enhancer regions) or enriched but insufficiently covered regions; determination of the phase of multiple variants in one gene; balanced genomic rearrangements

CLASSES OF VARIANTS

Class 5: pathogenic variant – are reported, posterior probability >99 %
Class 4: likely pathogenic variant – are reported, posterior probability >90 %
Class 3: uncertain significance – only be listed in the report if they have potential to be upgraded to class 4, posterior probability >50 %
Class 2: likely benign – not reported, posterior probability <10 %
Class 1: benign – not reported, posterior probability <0,1 %

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