MEDICOVER GENETICS

MOLECULAR GENETIC REPORT
GM19.12345

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Date: 21.04.2018

Report to:

Requesting Physician Name

Address

Contact Information

Order Number	**21 2018 1234**
Born	**01.01.1976**
Sex	M
Date test requested:	21.03.2018
Sample collected:	21.03.2018
Sample / Specimen:	DNA from EDTA blood

Order: Endocrine tumors panel
Additional Information /patient phenotype: Pheochromocytoma. Previous analysis of the genes NF1, RET and VHL identified no pathogenic variants.

RESULT SUMMARY:

SDHB: detection of a heterozygous pathogenic variant
In the analyzed portions of the genes SDHA, SDHAF2, SDHC and SDHD, no pathogenic/probably pathogenic variant was detected, as well as no deletion or duplication of a larger gene segment.

Result

The examination result confirms the suspicion of a hereditary pheochromocytoma. The variant c.268G>T was detected in the *SDHB* gene, which leads to the generation of a premature translation termination signal in codon 90. The variant occurs in the general population at a frequency of 0.0004% (only one carrier among >118,000 presumed non-tumor patients). In contrast, the variant has been repeatedly detected in the germline of patients with paraganglioma, pheochromocytoma and/or gastrointestinal stromal tumor (Jochmanaova et al. 2017, J Cancer Res Clin Oncol 143:1421; Elston et al. 2017, J clin Endocrinol Metab 102:1447; Hensen et al. 2012, Clin Genet 81:284). It has been shown that no SDHB protein could be synthesized and no SDH enzyme activity could be measured with the variant c.268G>T (Kim et al. 2015, Endocr Relat Cancer 22:387). According to the current guidelines for the classification of genetic variants, it is therefore to be considered pathogenic and causative. Carriers of pathogenic SDHB germline variants have an increased risk of pheochromocytoma and paraganglioma compared to the general population. More rarely, gastrointestinal stromal tumors, thyroid or renal cell carcinomas are also observed. SDHB variants are also associated with a high risk of malignant transformation compared to variants in other SDHx genes (Fishbein et Nathanson 2012, Cancer Genet 205:1)

Recommended action

- Carriers are recommended to participate in regular screening tests that include biochemical and imaging procedures
- Genetic testing of close relatives: 50% probability that the variant will be inherited by offspring. There is a risk that further blood relatives who also symptom-free, are also carriers of the variant detected here, as the penetrance may be incomplete. Healthy persons at risk can be specifically examined for the variant. They are also recommended to take part in preventive medical checkups as long as the presence of the variant known in the family has not been ruled out by molecular genetics.
- Genetic counseling

VARIANT DETAILS

Gene	HGVS description	Exon	Location on GRCh38	Zygosity
SDHB	NM_003000.2:c.268C>T	Exon 3	Chr1: 17033078 (on Assembly GRCh38)	heterozygous

OMIM-P	Consequence	Mode of inheritance	ACMG/AMP criteria (Richards et al.; Ellard et al.)	Classification
185470	p.Arg90Ter. Nonsense mutation	Autosomal dominant	PVS1	**pathogenic**

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

SDHA (NM_004168.4), *SDHAF2* (NM_017841.2), *SDHB* (NM_003000.2), *SDHC* (NM_003001.3), *SDHD* (NM_003002.4)

PERCENTAGE OF SEQUENCED BASES WITH COVERAGE >20X

100 %

LIST OF EXONS WITH COVERAGE <20X

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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 %

Report released by

John Doe