HerediGENE

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Scientific Director: George Nasioulas PhD

SAMPLE INFORMATION

Name :	XXX	**Date Received :**	XXX
Medical ID :	XXX	**Date of Report :**	XXX
Date of Birth :	XXX	**Req. Physician :**	XXX
Location :	XXX	**Barcode :**	XXX
Material :	XXX	**Sample acceptability :**	XXX

HerediGENE: ***Hereditary Cancer Panel by Next Generation Sequencing***

Result

PATHOGENIC VARIANT IDENTIFIED

Gene	Variant	Clinical Significance	Zygosity
BRCA1	NM_007294:c.4035del, p.(Glu1346Lysfs*20)	Pathogenic-Clinically significant variant	Heterozygous
FANCA	NM_000135:c.2402T>A, p.(Val801Glu)	Variant of Uncertain Significance (VUS)	Heterozygous

Note: "CLINICALLY SIGNIFICANT" as defined in this report, is a genetic change that is associated with the potential to alter medical intervention

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Variants Details

***BRCA1*, Exon 10, NM_007294:c.4035del, p.(Glu1346Lysfs*20)** ClinVar

This sequence change deletes one nucleotide in exon 10 of the BRCA1 mRNA (c.4035delA), causing a frameshift after codon 1346 and the creation of a premature translational stop signal 20 amino acid residues later - p.(Glu1346Lysfs*20). This is expected to result in an absent or disrupted protein product. This pathogenic variant is a known common cause of breast and ovarian cancer in individuals from Eastern Europe (PMID: 22032251 ,23199084). In addition, this variant has been described in mutation database ClinVar as pathogenic (Variation ID: 37560). This variant is also known as 4153delA and 4154delA in the literature using alternative nomenclature. For these reasons, this variant has been classified as Pathogenic. According to international guidelines it is recommended that relatives of the patient are tested for the above mutation.

The *BRCA1* gene is involved in the homologous recombination complex (HR), with pathogenic/likely pathogenic variants strongly associated with autosomal dominant hereditary breast and ovarian cancer (HBOC) syndrome. HBOC syndrome is characterized by an increased lifetime risk for breast cancer and contralateral breast cancer in females (>60%) and males (1.2%) and ovarian cancer (39%-58%). Pathogenic/likely pathogenic variants are also moderately associated with pancreatic ((PMID: 31429902, 12237281, 23628597, 28632866, 31378807, 26700119). The risk for contralateral breast cancer 20 years after the initial breast cancer diagnosis is 40% in these individuals (PMID: 28632866). Clinical management guidelines for HBOC syndrome can be found at www.nccn.org.

The patient must be referred for genetic counseling for adequate interpretation of the study and post-genetic support. Relatives of this individual have up to 50% risk of having the same mutation. Predictive testing of this mutation should be offered to all at-risk adult relatives after receiving genetic counseling.

Patients with germline mutations in HR genes may benefit from platinum-based therapies (PMID: 20406929) and treatment with PARP inhibitors (PMID: 31218365).

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***FANCA* ,Exon 26, NM_000135:c.2402T>A, p.(Val801Glu)** ClinVar

Gene	***FANCA***	OMIM
Variant	NM_000135:c.2402T>A, p.(Val801Glu)	
Zygosity	Heterozygous	
Type of variant	Missense	
Allele frequency (dbSNP)	<0.1%	rs772721300
Grantham score	121	
Protein position information	Highly conserved, in a domain of the protein that is not known to be functionally important	
ClinVar	Variation ID: 836880	
In silico analysis	Damaging	
Clinical Significance	Variant of Uncertain Significance (VUS)	

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Methodology

Genomic DNA was extracted from the sample under investigation and was analysed by a solution based capture approach using a custom target enrichment panel containing 52 genes involved in hereditary predisposition to cancer, of which 21 genes involved in the homologous recombination (HR) complex (KAPA HyperExplore Max 3Mb T1, NimbleGen, Roche) (see table). Sequencing was carried out using MGI technology. Reads were aligned to the reference sequence (GRCh37), and sequence changes were identified and interpreted in the context of a single clinically relevant transcript. All clinically significant observations were confirmed by Sanger Sequencing. All targeted regions within exons were sequenced with ≥20x depth. Unless otherwise stated, this assay targets all coding regions of the indicated transcripts and 20 base pairs of flanking intronic sequences. For the *HOXB13*, *POLE* and *POLD1* genes, distinct genomic regions have been associated with increased cancer risk. Consequently, the reported regions for the aforementioned genes are: *HOXB13* - rs138213197, *POLE* - Exons 1-14 (NM_006231), *POLD1*- Exons 8-13 (NM_001256849).

The presence of large genomic rearrangements (LGRs), was investigated using the commercial computational algorithm SeqPilot Version 4.4 Build 505 (JSI Medical System). In addition, the computational algorithm panelcn.MOPS (PMID: 28449315) was also used in the *BRCA1* and *BRCA2* genes. The presence of LGRs is verified by use the MLPA method (Multiplex Ligation-dependent Probe Amplification, MRC Holland; PMID: 10978226).

Notes:

Every molecular test has an internal 0,5-1% chance of failure. This is due to rare molecular events and factors related to the preparation and analysis of the samples.

The variants reported in *PMS2* gene are detected with coverage >25%. The method used cannot detect low-level mosaicism (with coverage <25%).

The method used achieves 99% sensitivity and specificity for single nucleotide variants and insertions and deletions <15bp. Sensitivity to detect genomic rearrangements larger than 15bp but smaller than a full exon may be reduced. Balanced genomic rearrangements cannot be detected.

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Details about non-pathogenic variants

All individuals carry DNA changes (i.e., variants), and most variants do not increase an individual's risk of cancer or other diseases. When identified, variants of uncertain significance (VUS) are reported. Benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause increased cancer risk. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by the personal and family history and any other clinically significant findings.

Genes Analyzed

Gene	Reference sequence	Gene	Reference sequence
APC	NM_000038	*MRE11* *1	NM_005591
ATM *1	NM_000051	*MSH2*2	NM_000251
ATR *1	NM_001184	*MSH3*	NM_002439
AXIN2	NM_004655	*MSH6*2	NM_000179
BAP1 *1	NM_004656	*MUTYH*2	NM_001128425
BARD1 *1	NM_000465	*NBN* *1	NM_002485
BLM *1	NM_000057	*NF1*	NM_000267
BMPR1A	NM_004329	*NTHL1*	NM_002528
*BRCA1*1,2*	NM_007294	*PALB2*1,2*	NM_024675
*BRCA2*1,2*	NM_000059	*PMS2*	NM_000535
BRIP1 *1	NM_032043	*POLD1 (Exons 8-13)*	NM_001256849
CDH1	NM_004360	*POLE (Exons 1-14)*	NM_006231
CDK4	NM_000075	*PPP2R2A*1*	NM_002717
CDKN2A (p14ARF, p16INK4a)	NM_000077, NM_058195	*PTEN*	NM_000314
*CHEK2*1,2*	NM_007194	*RAD50*1,2*	NM_005732
*EPCAM*2*	NM_002354	*RAD51B*1*	NM_133509
*FAM175A*1*	NM_139076	*RAD51C*1,2*	NM_058216
FANCA *1	NM_000135	*RAD51D*1,2*	NM_002878
*FANCL*1*	NM_001114636	*RET*	NM_020975
FANCM *1	NM_020937	*RNF43*	NM_017763
GALNT12	NM_024642	*RPS20*	NM_001023
*GEN1*1*	NM_001130009	*SMAD4*	NM_005359
HOXB13:c.251G>A p.(G84E)	NM_006361	*SMARCA4*	NM_001128849
MEN1	NM_000244	*STK11*	NM_000455
MITF	NM_001354604	*TP53*2*	NM_000546
*MLH1*2*	NM_000249	*VHL*	NM_000551

*1 Genes of the homologous recombination (HR) complex

*2 Unless otherwise noted analysis of large rearrangement was performed on the following genes:
BRCA1, BRCA2, CHEK2, EPCAM (Exons 8, 9), MLH1, MSH2, MSH6, MUTYH, PALB2, RAD50 (Exons 1, 2, 4, 10, 14, 21, 23 and 25), RAD51C, RAD51D, and TP53.

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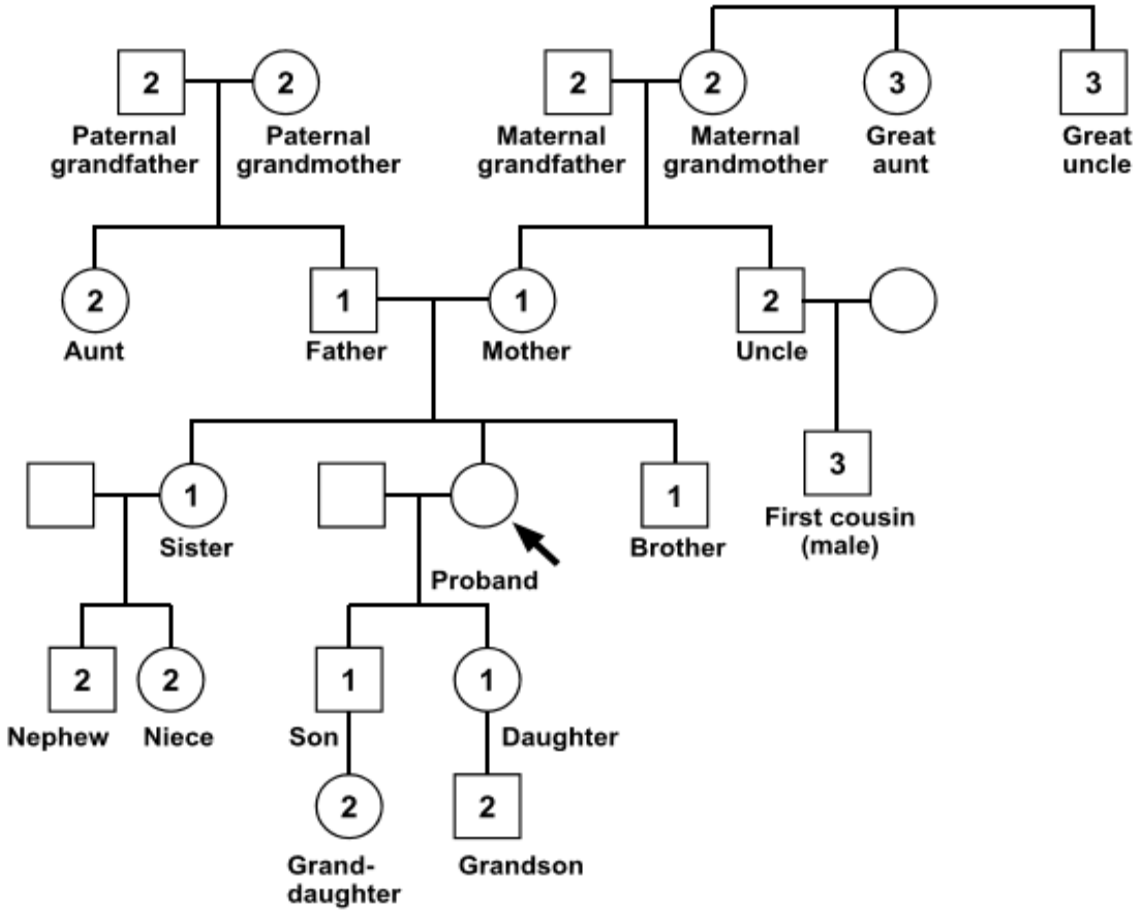
Family tree



Note: **The information shown on the family tree has been provided by the patient and not by medical records.**

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