

***Trust Logo***

**<GLH region name>**

**NHS Genomic Laboratory Hub**

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| ***Head of Department****Name* |  | *Local Genetics Service**Local Trust**Address**Address**Post Code**Web site address* |
| General Enquiries: *telephone contact*Email: *generic email address* |
|  |

**GENOMIC LABORATORY REPORT**

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| --- | --- | --- |
| Dr xxx | **Patient Name:** | **Jane DOE** |
| Consultant  | Gender: | Female |
| <<Hospital address>> | Date of Birth: | 14 Jan 1968 |
| NHS No: | 123 456 7890 |
| Hospital No: | NK |
| Your ref: | GC12345 |

**Reason for testing**

Diagnostic testing. <<Referral reason>>. Patient phenotype / HPO terms

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| --- |
| **Result summary** |
| **Genetic diagnosis of *<CHEK2/ATM>*-associated cancer susceptibility** |

**Result**

This individual is heterozygous for a germline pathogenic *ATM* missense variant (details below). This variant causes high-risk1 cancer susceptibility, particularly breast cancer in females (OMIM: 607585).

**Implications**

Each of their offspring would be at 50% risk of inheriting this variant and genetic predisposition to *ATM-*associated cancers. Other relatives are also at increased risk.

**Recommended action**

This individual is at high risk of developing further *ATM*-associated cancers and should be managed appropriately.

We recommend referral to Clinical Genetics where predictive and diagnostic testing for this variant in their relatives can be arranged.

Date issued: <AUTHORISEDDATE> Authoriser: Clinical Scientist

1. Moslemi et al (2021) PMID: 33402103

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**TECHNICAL INFORMATION**

**Variant details**

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| --- | --- | --- | --- | --- |
| Gene | Zygosity | HGVS description | Location: GRCh37 (hg19) | \*Classification |
| *ATM* | Heterozygous  | NM\_000051.4: c.7271T>G p.(Val2424Gly) | Chr11(GRCh37):g.108199929T>G | Pathogenic |

**Test methodology**

1. Genes screened in the panel: *BRCA1; BRCA2;* *PALB2, ATM, CHEK2* (all coding exons & exon-intron boundaries). **For *ATM* & *CHEK2* genes only clearly truncating variants (nonsense, frameshift, ±1/2 splice & CNVs) in these genes, plus the *ATM* c.7271T>G p.(Val2424Gly) pathogenic missense variant are reported.**
2. Methodology including sensitivity, CNV detection, Bioinformatics pipeline etc e.g. Enrichment method: Agilent SureSelect Custom Design and sequenced on the Illumina platform with a sensitivity of at least 95%.The target regions of selected transcripts is covered to a minimum read depth of 30x.
3. Screening for large deletions and duplications is performed using comparative depth of coverage of NGS data. Deletions/duplications are confirmed by Multiplex Ligation-Dependent Probe Amplification (MRC-Holland).
4. Limits of detection e.g.NGS technical sensitivity may be reduced for genes with pseudogenes or paralogs, and copy-number variation >xx nucleotides.
5. \*Variant classification – see Appendix 1 overleaf
6. Only clinically relevant results are shown; full details of methods and results, including benign/likely benign variants and variants of uncertain clinical significance with limited evidence, are stored on file and are available on request.

**Sample details**

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| Your lab ref: | 122001180 |  |  |
| Sample ID | 1234567 | Sample collected: | 05 Jun 2020 |
| Sample type | DNA from peripheral blood | Sample received | 05 Jun 2020 |

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| --- | --- | --- |
| Dr xxx | **Patient Name:** | **Jane DOE** |
| Consultant  | Gender: | Female |
| <<Hospital address>> | Date of Birth: | 14 Jan 1968 |
| NHS No: | 123 456 7890 |
| Hospital No: | NK |
| Your ref: | GC12345 |

**Appendix 1: Variant classification**

**Variant details**

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| --- | --- | --- | --- | --- |
| Gene | Zygosity | HGVS description | Location: GRCh37 (hg19) | \*Classification |
| *ATM* | Heterozygous  | NM\_000051.4: c.7271T>G p.(Val2424Gly) | Chr11(GRCh37):g.108199929T>G | Pathogenic |
| Gene-Disease Association | Hereditary cancer susceptibility OMIM 607585 |
| Inheritance | Autosomal Dominant  |
| **Evidence for variant classification using ACMG/AMP guidelines\***:  | Evidence points^ |
| PS4\_strPM3\_strPS3\_modPP3\_sup | Moslemi et al 2021 (PMID: 33402103) Meta-analysis of adjusted case-control studies shows OR: 8.94; %95 CI: 4.28-18.67 for c.7271T>GFound in compound heterozygous or homozygous state in patients with autosomal recessive Ataxia Telangectasia (PMIDs: 9463314, 18575927, 27528516, 30549301)Functional characterisation shows effect on kinase activity and radiosensitivity (PMIDs: 18634022, 19431188)REVEL: 0.855 | 4421 |
| Total: 11 |

^Evidence point ranges: VUS: 0-5 (10-90% posterior probability pathogenicity); Likely pathogenic: 6-9 (90-99% posterior probability); Pathogenic: >10 (>99% posterior probability). Points awarded per evidence weighting: sup (supporting) = 1, mod (moderate) = 2, str (strong) = 4, vstr (very strong) = 8 (Tavtigian et al 2020 PMID: [32720330](https://pubmed.ncbi.nlm.nih.gov/32720330/); Garrett et al 2020 PMID: [33208383](https://pubmed.ncbi.nlm.nih.gov/33208383/); [ACGS 2020 variant guidelines](http://www.acgs.uk.com/quality/best-practice-guidelines))

\*Variant classification according to ClinGen Hereditary Breast, Ovarian and Pancreatic Cancer Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ATM Version 1.1 Expert Panel Page: <https://www.clinicalgenome.org/affiliation/50039>;

<https://clinicalgenome.org/site/assets/files/7451/clingen_hbop_acmg_specifications_atm_v1_1.pdf>