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WARD, ALISON
12 SHORTS RD, COBURG NORTH. 3058
Phone: 93505306
Birthdate: 19/12/1955 **Sex:** F **Medicare Number:** 30612701631
Your Reference: **Lab Reference:** 25-33427154-FIC-0
Laboratory: DOREVITCH PATHOLOGY
Addressee: DR AVI CHARLTON **Referred by:** DR ROSS WALKER
Copy to:
DR AVI CHARLTON

Name of Test: FAMILIAL CHOLESTEROLAEMIA
Requested: 12/02/2025 **Collected:** 24/02/2025 **Reported:** 27/03/2025 16:45

GERMLINE VARIANT SCREENING FOR FAMILIAL HYPERCHOLESTEROLAEMIA

Clinical Details: Family history of vascular disease. Recent cholesterol results: Chol 16.7; TG 1.2, HDL 3.2; LDL 12.9.

Sample Type: Blood
Genes tested: ABCG5,ABCG8,APOB,APOE,CYP27A1,LDLR,LDLRAP1,LIPA,PCSK9

Summary: NO PATHOGENIC or LIKELY PATHOGENIC VARIANT DETECTED

Result:
Massively parallel DNA sequencing did not identify any reportable sequence variant in the genes tested. No LDLR copy number variant was detected.

This result excludes most variants in the tested genes that may contribute to familial hypercholesterolaemia (see limitations of assay below). However, it does not eliminate the risk of a genetic cause of hypercholesterolaemia in this patient or their family.

Recommendations:
This result should be communicated to the patient with appropriate genetic counselling.

Method:
Extracted DNA is screened for germline sequence variants in the listed genes and LDLR gene copy number variants (CNVs) using a custom massively parallel sequencing (MPS) assay (Agilent SureSelect XT HS2). LDLR gene CNVs are confirmed using MLPA (MRC Holland P062-D2). Regions of interest (ROIs) comprise all coding exons of the reference transcripts, plus 10 bases into the flanking introns and untranslated regions. ROIs are sequenced to a minimum coverage of 20x reads on a MiSeq sequencer (Illumina). Illumina Emedgene Analyze software is used to analyse and

annotate MPS data. Variants are interpreted using ACMG guidelines (PMID: 18414213) and current ClinGen Familial Hypercholesterolaemia Expert Panel Specifications (PMID: 34906454). Variants considered Benign (Class 1) or Likely Benign (Class 2) are not reported. The GRCh38/hg38 human reference genome is used for alignment and variant annotation. Variants are described according to current HGVS nomenclature.

Limitations of the assay:
The MPS assay has been shown in our laboratory to have a sensitivity and specificity of >99.9% for germline sequence variants within the ROIs, including single nucleotide variants (SNVs), small complex variants (such as indels). Large complex variants, structural variants, variants within repetitive sequences or highly duplicated regions, and mosaic/chimeric variants may not be detected by this analysis. Copy number changes in genes other than LDLR and variants in other genes associated with familial hypercholesterolaemia will not be detected. Genetic results from blood samples may be affected by haematological malignancy or following allogeneic bone marrow transplants.

Gene Transcript Reference Sequences:
ABCG5:NM_022436.3; ABCG8:NM_022437.3; APOB:NM_000384.3; APOE:NM_000041.4 ; CYP27A1:NM_000784.4; LDLR:NM_000527.4; LDLRAP1:NM_015627.2; LIPA :NM_000235.3; PCSK9:NM_174936.3.

Dr Abhijit Kulkarni MBBS, MD, FRCPath (UK), FRCPA
Genetic Pathologist, Genomic Diagnostics

END OF REPORT

Requested Tests : FIC

WARD, ALISON
12 SHORTS RD, COBURG NORTH. 3058
Phone: 93505306
Birthdate: 19/12/1955 **Sex:** F **Medicare Number:** 30612701631
Your Reference: **Lab Reference:** 25-35709035-HGE-0
Laboratory: DOREVITCH PATHOLOGY
Addressee: DR AVI CHARLTON **Referred by:** DR AVI CHARLTON

Name of Test: MTHF RED. C677T MUT. PCR
Requested: 17/03/2025 **Collected:** 19/03/2025 **Reported:** 27/03/2025 11:30

METHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) GENOTYPING

Specimen:
Blood

Result:
MTHFR C677T Mutation: DETECTED HETEROZYGOUS
MTHFR A1298C Mutation: Not Detected

Comments:
Hyperhomocysteinaemia is a risk factor for atherosclerotic arterial disease and venous thromboembolism. It is a multifactorial condition with genetic and environmental factors involved; the latter include vitamin deficiencies (B6, B12, folic acid).
Methylene tetrahydrofolate reductase (MTHFR) is an important enzyme in homocysteine metabolism for which homozygotes for the mutation C677T (Ala>Val) in MTHFR typically have elevated plasma homocysteine when folate deplete, although normal when folate replete.
Homocysteine levels in heterozygotes for the C677T mutation are

indistinguishable from the normal population.
The evidence for any effect of MTHFR polymorphism is not conclusive, and testing for these genetic variants has minimal clinical utility.
Current American College of Medical Genetics and Genomics guidelines (Hickey S.E et al, Genet Med 2013: 15 (2): 153-156) recommend that MTHFR polymorphisms genotyping should not be ordered in clinical evaluation of thrombophilia, recurrent pregnancy loss or in other family members.

Dr Abhijit Kulkarni MBBS, MD, FRCPath (UK), FRCPA

Genomic Diagnostics

Requested Tests : HGE, DDL