Booked on	14/08/2018	**Patient Id**	011808110309	**Printed on**	01/09/2018
Name	Ms. Meenakshi B Gera	**Age**	28 Years	**Sex**	F
Referred by	bookmytestonline				

MTHFR gene analysis (Exons 5 & 8)

Sample Information

Sample Type: Blood

Clinical Indications

Not provided.

Test Details

MTHFR gene exons 5 and 8 were assessed for any key and incidental findings using PCR amplification and Sanger sequencing.

Results

A variant p.Ala222Val has been identified in exon 5 of *MTHFR* gene.

Gene strand	Variation	Zygosity	Exon No.	Clinical significance
MTHFR (-)	# chr1:11856378 G>A *c.665C>T *p.Ala222Val	Heterozygous	5	Clinically relevant[1-3]

Interpretation

A heterozygous missense variation (chr1:11856378G>A; c.665C>T) leading to an amino acid substitution from Alanine to Valine at codon 222 (p.Ala222Val) was detected in the exon 5 of *MTHFR* gene in this subject. Homocystinuria due to MTHFR deficiency (OMIM236250) is caused by homozygous and compound heterozygous variations in *MTHFR* gene (OMIM*607093). This variation (also known as C677T) leads to the production of a thermolabile MTHFR enzyme which is less active at higher temperatures. This variation is the most common genetic cause of elevated plasma homocysteine level[1] and is reported to be associated with mild hyperhomocystenemia with low folate levels[2]. Patients who are homozygous for this variation with elevated homocysteine levels are reported to have mildly increased risk for venous thromboembolism and recurrent pregnancy loss[3]. **Based on the above evidences this variation is clinically relevant and has to be carefully correlated with the clinical symptoms observed.**

Recommendations

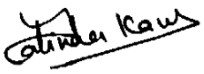
Genetic counseling is recommended.

References

1. Schwahn B1, Rozen R. Polymorphisms in the methylenetetrahydrofolate reductase gene: clinical consequences. Am J Pharmacogenomics. 2001;1(3):189-201.
2. Yamada K1, Chen Z, Rozen R, Matthews RG. Effects of common polymorphisms on the properties of recombinant human methylenetetrahydrofolate reductase. Proc Natl Acad Sci U S A. 2001 Dec 18;98(26):14853-8.
3. Hickey SE1, Curry CJ, Toriello HV. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. Genet Med. 2013 Feb;15(2):153-6. doi: 10.1038/gim.2012.165.

******End of the report******

Report Released by:



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Appendix

Methodology

Methylenetetrahydrofolate reductase (MTHFR) encoded by *MTHFR* gene is key enzyme in folate and homocysteine metabolism. MTHFR converts 5,10-Methylenetetrahydrofolate to 5-Methyltetrahydrofolate which provides the methyl group for methylation of homocysteine to methionine by the enzyme methionine synthase. Ala222Val and Glu429Ala in exons 5 and 8 are the most common variations reported in *MTHFR* gene. Ala222Val produces a thermolabile enzyme variant which is associated with high levels of homocysteine in the blood that causes neural tube defects (NTD), hyperhomocysteinemia, cardiovascular disease (CVD) etc. On the other hand, Glu429Ala variation also leads to decreased MTHFR activity but does not result in thermolabile protein.

Methodology

The exons 5 and 8 of *MTHFR* gene were PCR-amplified and the products were sequenced using Sanger sequencing. The sequence was aligned to genomic reference sequence, NG_013351.1 in the NCBI GenBank database to detect variations using multiple variant analysis software programs.

Variant	A change in a gene. This could be disease causing (pathogenic) or not disease causing (benign).
Pathogenic	A disease-causing variation in a gene which can explain the patients' symptoms has been detected. This usually means that a suspected disorder for which testing had been requested has been confirmed.
Likely Pathogenic	A variant which is very likely to contribute to the development of disease however, the scientific evidence is currently insufficient to prove this conclusively. Additional evidence is expected to confirm this assertion of pathogenicity
Benign	A variant which is known not to be responsible for disease has been detected. Generally, no further action is warranted on such variants when detected.
Likely Benign	A variant is not expected to have a major effect on disease however, the scientific evidence is currently insufficient to prove this conclusively. Additional evidence is expected to confirm this assertion.
Variant of Uncertain Significance	A variant has been detected, but it is difficult to classify it as either pathogenic (disease causing) or benign (non-disease causing) based on current available scientific evidence. Further testing of the patient or family members as recommended by your clinician may be needed. It is probable that their significance can be assessed only with time, subject to availability of scientific evidence

***Genetic test results are reported based on the recommendations of American College of Medical Genetics** *(Richards CS et al., Genet Med, 2015).*

Annotation is performed against GRCh37/hg19 version of human gene.

Mutation analysis is based on the MTHFR reference sequence nomenclature NG_013351.1 (REGION: 5001...25374) in the NCBI GenBank (*http://www.ncbi.nlm.nih.gov/nuccore/NG_013351.1?from=5001&to=25374&report=genbank*) database.

*cDNA base is reverse complement of genomic base in case on negative strand. The cDNA-based allele calls (c.) for the mutations and the corresponding amino acid change is based on MTHFR Ref Seq sequence EST00000376590.

***Clinical relevance, if any, is reported from previously published reports. Relevant references will be indicated for each known clinically relevant mutation.

Disclaimer

- This is not a medical report. It has laboratory test findings that need to be correlated with clinical symptoms and discussed with the referring clinician for any further management.
- The classification of variants of uncertain significance can change over time. Please contact MolQ Laboratory at a later date for any change.
- Large deletions or copy number variations / rearrangements cannot be assessed using this method.

Note

- The sequencing results (including the chromatograms and image of sequence alignment to the reference sequence) can be provided upon request from the referring physician.
- Clinical relevance, if any, is reported from previously published reports. Relevant references will be indicated for each known clinically relevant variation.

Note: *The test was performed at the reference laboratory.*