VCGS
leaders in genetic health

MTHFR testing fact sheet

Genetic testing of the *MTHFR* gene

What is the *MTHFR* gene?

MTHFR stands for methylenetetrahydrofolate reductase, which is the name of an enzyme. The MTHFR enzyme helps our bodies to process two chemicals called folate and homocysteine. Like all other enzymes, the MTHFR enzyme is made by a gene, in this case the *MTHFR* gene. We all have two copies of the *MTHFR* gene; one inherited from our mother and one inherited from our father.

Everyone's genes are different

Although we all usually have the same number of genes, and the same types of genes, each person's genes are slightly different. So, the *MTHFR* gene in one person may be slightly different to the *MTHFR* gene in another person. There are two types of gene changes: gene variants and gene polymorphisms.

Gene variants (or mutations)

Gene variants are changes that can disrupt the way a gene works. For example, an *MTHFR* gene with a certain variant may make no MTHFR enzyme, or makes a faulty version of the MTHFR enzyme.

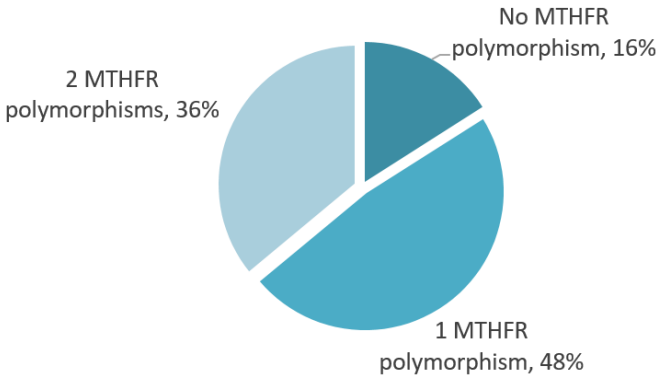
Gene variants can have very serious health consequences. Variants in the *MTHFR* gene which cause severe MTHFR deficiency are extremely rare (<200 reported cases worldwide). Babies born with two severe MTHFR variants suffer from major birth abnormalities and have a very poor outlook.

Gene polymorphisms

Poly means many; morphisms means forms. Polymorphism is the word used for common gene changes that are considered harmless to our health. There are two polymorphisms that are commonly found in the *MTHFR* gene. They are:

C677T (also referred to as c.665C→T or p.Ala222Val)
A1298C (also referred to as c.1286A→C or p.Glu429Ala)

These MTHFR polymorphisms are so common that there are more people who have MTHFR polymorphisms than there are people who don't have them (only 16% of people have no MTHFR polymorphisms: that's less than one fifth of the population).



MTHFR polymorphisms do not cause health problems

Neither of the common MTHFR polymorphisms disrupt the making of the MTHFR enzyme. Having one or two copies of these polymorphisms may slightly reduce the efficiency of the MTHFR enzyme, but the effect is so small that even people who have two MTHFR polymorphisms are unlikely to develop significant health problems as a result.

Why does MTHFR gene testing exist?

Low levels of the MTHFR enzyme may be one of many factors that can contribute to elevated levels of the chemical homocysteine in the blood. Previously, it was thought that MTHFR polymorphisms might be responsible for a number of different health problems linked to homocysteine levels, such as blood clotting problems. However more recent research has revealed that MTHFR polymorphisms are not the cause of any significant health problems.

MTHFR testing is not recommended

Testing is not recommended because knowing about MTHFR polymorphisms does not provide information that is useful for a person's health.

What if I've already had the test?

For people who have just one MTHFR polymorphism (either one copy of C677T or one copy of A1298C) and for people who have two different MTHFR polymorphisms (say, for example, one copy of the C677T polymorphism and one copy of the A1298C polymorphism) there is no evidence to suggest any increased risk of any health problems at all.

For people who have two copies of the C677T polymorphism, evidence shows the following:

1. A very small increase in the risk of having a stroke. This increase is so small that no special measures are recommended, but people in this category should avoid factors which have a much bigger effect on the risk of stroke, such as smoking and being overweight.
2. Women who have two copies of the C677T polymorphism have a slightly higher risk of having a baby with a neural tube defect such as spina bifida, however this effect disappears if the woman takes folate supplements. It is recommended that all women, regardless of their MTHFR status, take folate supplements (0.5mg per day) for a least 1 month prior to falling pregnant and for the first 3 months of pregnancy.
3. A person who has two copies of the C677T polymorphism has no greater risk of getting cancer than any other person in the general population. However a person with two copies of the C677T polymorphism may react differently to certain chemotherapy drugs such as methotrexate.

Should my relatives be tested?

Because MTHFR polymorphism testing is unlikely to provide any useful clinical information, we do not recommend genetic testing for family members.

Further information

The Royal College of Pathologists Australia (RCPA): Position statement, MTHFR genetic tests [https://www.rcpa.edu.au/Library/College-Policies/Position-Statements/MTHFR-Genetic-Tests]

The Royal Australian College of General Practitioners (RACGP): MTHFR gene testing [https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics-in-general-practice/mthfr-gene-testing]

American College of Medical Genetics (ACMG) Practice Guideline: Lack of evidence for MTHFR polymorphism testing [https://www.nature.com/articles/gim2012165]

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