Fact sheet **64**

MTHFR GENE TESTING

This fact sheet talks about *MTHFR* gene testing and what the results can mean.

IN SUMMARY

- *MTHFR* gene variants are common in the community
- The *MTHFR* gene is involved in converting the vitamin folate (vitamin B9) into a form the body can use (methyl-folate)
- *MTHFR* variants do not usually cause any health problems
- If you are planning a pregnancy, it is recommended that you take 0.4mg/day of folic acid (vitamin B9), regardless of whether you have a *MTHFR* variant or not
- This fact sheet does not talk about very rare, severe health problems caused by the *MTHFR* gene not working properly. They are caused by rare types of changes in the gene, different to those talked about here.

WHAT IS *MTHFR*?

MTHFR is a **gene** that codes for an enzyme (type of **protein**). This enzyme changes the vitamin folate (vitamin B9) into a form that the body can use (methyl-folate). Methyl-folate is important for a number of functions in the body, including regulating other genes through a process called methylation. *MTHFR* stands for a gene 5,10-*methylenetetrahydrofolate reductase.*

WHAT IS *MTHFR* TESTING?

MTHFR testing looks for variations in the *MTHFR* gene. Sometimes, a gene may have a variation in its code (the instructions) that can make the gene work less efficiently or can have no impact at all. This is called a **variant**.

A number of variants have been identified in the *MTHFR* gene. One of the more commonly found variants is **665C>T** (historically called C677T or 677C>T). In other words, at position 665 in the gene, a 'C' chemical is changed to a 'T'. The other most common variant is **1286A>C** (historically called A1298C or 1298A>C). This is where chemical 'A' is changed to a 'C' at position 1286. These variants are common in the general population.

WHAT IS AN *MTHFR* VARIANT?

We all have two copies of the *MTHFR* gene. One copy is inherited from our mother and the other copy is inherited from our father.

Some people will have a variant in one copy of the *MTHFR* gene and a working copy. These people will have a reduction in the amount of *MTHFR* enzyme produced (up to 50% less than normal). Usually, however, there is enough *MTHFR* enzyme and methyl-folate made and the body will work as normal.

The majority of people who have one or two variants in the *MTHFR* gene do not develop health problems.

When people have a variant in both copies of the *MTHFR* gene, the amount of *MTHFR* enzyme produced will be reduced (up to two-thirds less than normal), depending on the variant type. Even though less *MTHFR* enzyme is made by the body, most people will still make enough methyl-folate for the body to work in the usual way. A severe health condition caused by *MTHFR* deficiency (<20% enzyme activity) is a genetic condition where there may be symptoms from childhood or adulthood including significant neurological and psychiatric problems. This is not caused by the 1286A>C or the 665C>T *MTHFR* variants.

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WHAT IS THE EFFECT OF HAVING A *MTHFR* VARIANT?

Having a variant in one or both of your *MTHFR* genes does not generally cause health problems if there is enough folate through diet or supplements. In Australia there is a mandatory folic acid fortification program in addition to access to folate in our diet. This is where folic acid is added to wheat products such as bread. Because of this, most people have enough folate in their diet to reduce the effect of the *MTHFR* variant.

MTHFR variants have been weakly linked with an increased chance of some conditions in pregnancy, for example neural tube defects such as spina bifida in the baby. It is important, however, to remember that most people with a *MTHFR* variant do not have a pregnancy with a neural tube defect. There is not strong evidence linking certain types of mental illness and the *MTHFR* variants mentioned in this fact sheet. Testing for *MTHFR* variants are not useful for managing pregnancy, blood clotting conditions or heart disease. Changes in the *MTHFR* gene may only be one of many genetic and environmental factors that lead to these **complex conditions**.

IS THERE ANY TESTING AVAILABLE FOR *MTHFR*?

MTHFR testing usually involves a blood test that looks for the two common variants **665C>T** and **1286A>C** in the *MTHFR* gene. However, the results may be difficult to interpret and need to be considered in the context of your medical and **family health history**. It is strongly recommended that you discuss how useful this test is with your family doctor or health care provider before ordering the test. Testing in Australia is subsidised by Medicare as part of a genetic screen for causes of blood clotting conditions. There is currently not enough evidence to say that *MTHFR* genetic testing should be included on genetic screening for clotting conditions. When having a gene test for *MTHFR*, it is important to first have an opportunity to talk to your health care provider about the clinical reason for testing.

The results are unlikely to change the way your health care provider manages your care

MTHFR gene testing is not considered an appropriate referral to genetics services. It may be helpful to discuss this further with your health care provider.

SHOULD I TAKE FOLATE?

It is important to have enough folate in our diets. This can come from dietary sources such as lentils and dark green leafy vegetables, or in the form of a supplement such as folic acid. No harmful effects have been associated with amounts of dietary folate usually found in foods or fortified foods.

Folic acid supplementation, prior to, and during early pregnancy, has been shown to protect against neural tube defects in a pregnancy, and may also reduce the risk of cleft lip and palate, regardless of the mother's *MTHFR* status.

It is recommended that all women who are planning a pregnancy take folic acid supplements (0.4mg per day) for a least 1 month prior to possible conception and continued at that level for the first three months of pregnancy.

Women who have had a previous child with a neural tube defect, or have a family history of neural tube defect, may require a higher dose of folic acid when planning a pregnancy and should discuss this with their family doctor or health care provider.

WHAT SHOULD I DO IF I HAVE A *MTHFR* VARIANT?

- Let your family doctor know that you have a *MTHFR* variant
- Eat a well-balanced diet with foods high in vitamins B6, B12 and folate (B9)
- Avoid or reduce lifestyle factors that can reduce folate metabolism e.g. smoking, coffee and alcohol consumption
- If you are planning a pregnancy, take the usual recommended daily intake of 0.4mg/day of folic acid (vitamin B9).

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MTHFR Testing Guide—Possible outcomes of testing

- *MTHFR* variants are common in the general population
- The *MTHFR* gene acts in association with other genes as a 'threshold risk factor', and is usually not clinically significant on its own
- *MTHFR* status does not change the recommendation for women to take 0.4mg/day of folate supplementation at least 1 month prior to conception, as per general guidelines.

665C>T heterozygote (CT)	1286A>C heterozygote (AC)	665C>T /1286A>C compound Heterozygote (CT/AC)	1286A>C homozygote (CC)	665C>T homozygote (TT)
• One copy of the *MTHFR* 665C>T variant gene has the normal C allele and the other copy is the variant T allele • Approx. 50% enzyme activity • Does not usually cause any health concerns if dietary folate intake is adequate	• One copy of the *MTHFR* 1286A>C variant gene has the normal A allele and the other copy is the variant C allele • Approx. 60% enzyme activity • Not associated with any health concerns	• One copy of the *MTHFR* 665C>T gene has the normal C allele and the other copy has the variant T allele and the *MTHFR* 1286A>C variant gene has the normal A allele and the other copy is the variant C allele • More than 30% enzyme activity • Does not usually cause any health concerns if dietary folate intake is adequate	• Both copies of the *MTHFR* 1286A>C variant gene have the variant C allele • Approx. 50% enzyme activity • This result does not usually cause any health concerns	• Both copies of the *MTHFR* 665C>T variant gene have the variant T allele • More than 20% enzyme activity • May be at slightly increased chance of increased blood homocysteine levels • Further testing of B12, red blood cell folate and homocysteine may be helpful