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

In summary

- *MTHFR* gene variants are very common in the community.
- The *MTHFR* gene is involved in converting the vitamin folate 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, regardless of whether you have an *MTHFR* variant.

WHAT IS *MTHFR*?

MTHFR is a gene that codes for an enzyme. This enzyme changes the vitamin folate in to 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 become faulty or can have no impact at all. This is called a variant.

A number of variants have been identified in the *MTHFR* gene. The two most commonly reported variants are called **C677T** and **A1298C**. These variants are common among the general population. For example in White Caucasian and Asian populations, around 50% of people will have a copy of the C677T variant.

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 with a normal 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 sufficient MTHFR enzyme produced for the body to create methyl-folate from folate and the body will function as normal.

Some people will have a variant in both copies of the *MTHFR* gene. In these cases, the amount of MTHFR enzyme produced will be reduced (up to two-thirds less than normal), depending on the variants. Despite a reduction in the MTHFR enzyme, most people will still produce enough methyl-folate for the body to function as normal.

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

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

Having a variant in one or both of your *MTHFR* genes does not generally cause health problems if there is sufficient folate through diet or supplementation. In Australia we have access to a good diet and we also have a mandatory folic acid fortification program, where folic acid is added to wheat products such as bread. Because of this, most people have sufficient folate in their diet to reduce the effect of the *MTHFR* variant [1].

MTHFR variants have been associated with an increased risk of some conditions such as neural tube defects. It is important, however, to remember that most people with an *MTHFR* variant do not have a pregnancy affected by a neural tube defect. Changes in the *MTHFR* gene are only 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 **C677T** and **A1298C** 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 history. It is strongly recommended that you discuss the utility of testing with your GP before ordering the test.

The results are unlikely to change the way your GP manages your care.

MTHFR gene testing is not considered an appropriate referral to genetics services.

Outcomes of *MTHFR* testing – (refer to table on page 3).

SHOULD I TAKE FOLIC ACID?

It is important to have adequate folate in the diet. 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. Having a diet rich in folate has been shown to help reduce the effect of the *MTHFR* variant.[2]

Folic acid supplementation, prior to, and during, early pregnancy, has been shown to increase folate status to a level that protects against neural tube defects, regardless of the mother's *MTHFR* status [3].

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 3 three months of pregnancy.

Women who have had a previous child with a neural tube defect, have a family history of neural tube defect, or are C677T homozygotes may require a higher dose of folic acid when planning a pregnancy and should discuss this with their family doctor or health practitioner.

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

- Let your GP know that you have an *MTHFR* variant.
- Eat a well-balanced diet with foods high in B6, B12 and folate[4].
- Avoid or reduce lifestyle factors that can reduce folate metabolism e.g. smoking, coffee and alcohol consumption[4].
- If you are planning a pregnancy, take the usual recommended daily intake of 0.4mg/ day of folic acid.

References

1. Yang, Q., Bailey, L., Clarke, R., Flanders, W.D., Liu, T., Yesupriya, A., Khoury, M.J., and Friedman, J.M. (2012). Prospective study of methylenetetrahydrofolate reductase (*MTHFR*) variant C677T and risk of all-cause and cardiovascular disease mortality among 6000 US adults. The American Journal of Clinical Nutrition 95, 1245-1253.
2. Guenther, B.D., Sheppard, C.A., Tran, P., Rozen, R., Matthews, R.G., and Ludwig, M.L. (1999). The structure and properties of methylenetetrahydrofolate reductase from Escherichia coli suggest how folate ameliorates human hyperhomocysteinemia. Nat Struct Mol Biol 6, 359-365.
3. Crider, K.S., Zhu, J.-H., Hao, L., Yang, Q.-H., Yang, T.P., Gindler, J., Maneval, D.R., Quinlivan, E.P., Li, Z., Bailey, L.B., et al. (2011). *MTHFR* 677C→T genotype is associated with folate and homocysteine concentrations in a large, population-based, double-blind trial of folic acid supplementation. The American Journal of Clinical Nutrition 93, 1365-1372.
4. SA Maternal & Neonatal Clinical Network. (2004). South Australian Perinatal Practice Guidelines: Thrombophilia in pregnancy. In, D. Health, ed. (Government of South Australia.

MTHFR Testing Guide—Possible outcomes of testing

- *MTHFR* variants are very common in the general population
- *MTHFR* C677T is considered a strong determinant of folate status in women of reproductive age
- 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 folic acid supplementation at least 1 month prior to conception, as per general guidelines.

C677T heterozygote (CT)	A1298C heterozygote (AC)	C677T/A1298C compound Heterozygote (CT/AC)	A1298C homozygote (CC)	C677T homozygote (TT)
• One copy of the *MTHFR* 677T 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* A1298C 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* C677T gene has the normal C allele and the other copy has the variant T allele and the *MTHFR* A1298C variant gene has the normal A allele and the other copy is the variant C allele • Approx. 36% enzyme activity • Does not usually cause any health concerns if dietary folate intake is adequate	• Both copies of the *MTHFR* A1298C 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* C677T variant gene have the variant T allele • Approx. 22% enzyme activity • May be at slightly increased risk of increased blood homocysteine levels • Further testing of B12, red blood cell folate and homocysteine may be helpful.