In summary

- MTHFR variants are very common in the general population
- MTHFR acts in association with a number of other genes as a threshold risk factor, and is not usually individually significant
- Folic acid supplementation has been shown to increase folate levels, regardless of MTHFR status, to that which is considered protective for neural tube defects
- MTHFR variants are unlikely to have any impact on health in the absence of low red blood cell folate or high homocysteine
- 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.

WHAT IS MTHFR?

The MTHFR gene encodes an enzyme in the methylation cycle (See Figure 1).

MTHFR (‘5,10-methylenetetrahydrofolate reductase’) converts 5,10-methylenetetrahydrofolate to L-Methylfolate and is an important cofactor in the biosynthesis of SAMe (S-adenosyl methionine), the primary methyl donor involved in regulating gene expression.

MTHFR VARIANTS

A number of variants have been identified in the MTHFR gene. The two most commonly reported variants are **C677T** and **A1298C**. These variants are common among the general population.

Having one or both of these variants may reduce a person’s ability to metabolise folate. This does not generally cause health problems if there is sufficient folate through diet or supplementation. Low folate is unlikely in countries such as Australia that have folic acid fortification programs. (See Table 2 for more details).

---

**Table 2** – Frequency of MTHFR variants as a percentage of the population

<table>
<thead>
<tr>
<th>C677T (rs1801131)</th>
<th>A1298C (rs1801133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-/-</td>
<td>-/-</td>
</tr>
<tr>
<td>-/+</td>
<td>+/-</td>
</tr>
<tr>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>C677T (%)</th>
<th>A1298C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>30-55</td>
<td>40-50</td>
</tr>
<tr>
<td>Black</td>
<td>78</td>
<td>20</td>
</tr>
<tr>
<td>Asian</td>
<td>30-60</td>
<td>35-50</td>
</tr>
</tbody>
</table>

---

Figure 1 – The Methylation Cycle: Taken from [http://www.currentpsychiatry.com/fileadmin/cp_archive/images/1201/1201CP_Ramsey-fig1.jpg](http://www.currentpsychiatry.com/fileadmin/cp_archive/images/1201/1201CP_Ramsey-fig1.jpg)
WHEN IS A MTHFR TEST PERFORMED?

There is insufficient evidence in the literature at this stage to determine the clinical utility of MTHFR testing. MTHFR gene variants, in combination with other factors, have been associated with an increased risk of developing a number of conditions, such as neural tube defects, cardiovascular disease, cancer, thrombophilia, infertility, autism.

Testing for MTHFR would be considered investigational only.

In summary:

1. MTHFR testing attracts a Medicare rebate only if there is a proved DVT/PE or a known mutation in a first degree relative.
2. MTHFR testing as part of an investigation for infertility or as a direct-to-consumer test currently occurs in some organisations in NSW.
3. There is some evidence to consider MTHFR in the event of:
   i. A stillbirth or baby born with cleft lip and/or palate, neural tube defect and congenital cardiac abnormalities.
   ii. If maternal fasting homocysteine is high following investigations of fetal death associated with fetal growth restriction, pre-eclampsia, maternal thrombosis and/or maternal family history of thrombosis.
   iii. Stroke with elevated homocysteine.

WHAT DOES IT MEAN IF A MTHFR VARIANT IS FOUND FOLLOWING A DNA TEST?

DNA testing may reveal that a person has either one or two MTHFR variants. There are currently no recommended changes in clinical management based on a MTHFR test result.

Some people that are homozygous for the MTHFR C677T variant may develop a mild to moderate increased blood homocysteine level or hyperhomocysteinaemia. This alone does not usually cause any symptoms or health problems, however further testing may be considered, such as B12, red blood cell folate and homocysteine.

Table 2 shows the potential MTHFR variant test results.

MTHFR AND NEURAL TUBE DEFECTS (NTDs)

NTDs are multifactorial conditions. Being homozygous for the C677T variant (TT) has been associated with low red blood cell folate and has been identified as a risk factor for neural tube defects. Folic acid supplementation, prior to, and during, early pregnancy, has been shown to increase folate status to that which is considered protective for neural tube defects, regardless of the mother’s MTHFR status.

It is recommended that for all women, regardless of their MTHFR genetic testing result, folic acid supplements (0.5mg per day) be taken 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.
Table 2 – Potential MTHFR variant test results
Remember some results will be completely normal – i.e. no variant found

<table>
<thead>
<tr>
<th>MTHFR Genetic test result</th>
<th>Expected outcome and possible further treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C677T heterozygote (CT)</strong></td>
<td>This means one copy (allele) of the MTHFR C677T variant gene has the normal C allele and the other copy is the variant T allele. C677T heterozygotes have approximately 50% enzyme activity however this does not usually cause any health concerns if dietary folate intake is adequate.</td>
</tr>
<tr>
<td><strong>A1298C heterozygote (AC)</strong></td>
<td>This means one copy (allele) of the MTHFR A1298C variant gene has the normal A allele and the other copy is the variant C allele. A1298C heterozygotes have approximately 60% enzyme activity. This has not been associated with any health concerns.</td>
</tr>
<tr>
<td><strong>C677T/A1298C compound heterozygote (CT/AC)</strong></td>
<td>This means one copy (allele) of the MTHFR C677T variant gene has the normal C allele and the other copy is the variant T allele and the MTHFR A1298C variant gene has the normal A allele and the other copy is the variant C allele. MTHFR compound heterozygotes have approximately 36% enzyme activity. This result does not usually cause any health concerns if dietary folate intake is adequate.</td>
</tr>
<tr>
<td><strong>A1298C homozygote (CC)</strong></td>
<td>This means both copies (alleles) of the MTHFR A1298C variant gene have the variant C allele. A1298 homozygotes have approximately 50% enzyme activity. This result does not usually cause any health concerns.</td>
</tr>
<tr>
<td><strong>C677T homozygote (TT)</strong></td>
<td>This means both copies (alleles) of the MTHFR C677T variant gene have the variant T allele. C677T homozygotes have approximately 22% enzyme activity. Some people with this result may develop a mild to moderate increased blood homocysteine level or hyperhomocysteinaemia, which is a risk factor for cardiovascular disease. The thrombophilic tendency is minimised by an adequacy of folate, riboflavin, B6 and B12. Some clinicians advocate that all pregnant women should ensure adequate intake of these vitamins. Further testing may be recommended, such as B12, RBC folate and homocysteine.</td>
</tr>
</tbody>
</table>

REFERENCES
8. RANZCOG (2014) Vitamin and mineral supplementation and pregnancy: C-Obs 25