

Female Health Genetic Report

Table of Contents

Understanding Your Results	5
Oestrogen	6
Oestrogen Metabolism Diagram	7
Oestrogen Synthesis	8
Oestrogen Synthesis Genetic Results	9
Oestrogen - Phase I Detoxification	10
Phase I Detoxification Genetic Results	11 - 12
Oestrogen Receptors	13
Oestrogen Receptor Genetic Results	14
Oestrogen - Phase II Detoxification	15
Phase II Detoxification Genetic Results	16 - 18
Other Important Genetic Factors	19 - 20
Genetic Results	21 - 25
Nutrition & Lifestyle Advice	26 - 27

Gene Contents

APOE2	1
BHMT2	2
COMT16	5
CYP1A11	1
CYP1B112	2
CYP3A412	2
CYP17A19	
CYP19A19	
ESR114	1
ESR212	1
Factor V Leiden20	0

GSTM1	16
GSTP1	16
MAOA	19
MTHFR	17
PEMT	21
SOD2	21
SULT1A1	17
UGT1A1	18
UGT1A6	18
VDR	22

Your Female Health Genetic Report

Welcome to your unique DNA-based female health report. The contents of this report will highlight potential genetic strengths and weaknesses in your oestrogen pathway starting from the creation of oestrogen to its detoxification, as well as other genetic factors that affect female health and wellbeing. This information can be viewed on its own but is highly recommended together with a hormone test in order to provide the most complete picture of current and future health.

Please be assured that your genes are **NOT** your destiny. Many health concerns can be reversed and/or avoided by assessing risk factors and implementing appropriate diet and lifestyle measures.

In this report we examine your personal genetic profile within the context of: Oestrogen Synthesis (creation), Oestrogen Receptors, and Oestrogen Detoxification (elimination) from the body. We also examine additional genes that impact female health at all ages.

Our advice and recommendations are based on your specific genotype in each of these areas.

We invite you to come along on this journey to reaching optimal hormone health - one **YOU** can be in control of.



Let's get started!

Understanding your report

What is DNA?

DNA is your body's instruction manual, controlling every single function from when you were only made up of a few cells, until now. It looks like a twisted ladder, made up of two halves.

Each "rung" of the ladder contains two "letters" of DNA code called *nucleotides* which bond together in pairs: A (adenine) and T (thymine) bond together, as do C (cytosine) and G (guanine).

Genes are portions of the ladder containing combinations of the nucleotide code which are "read" as instructions to perform a specific function.

SNPs

Over time, due to environmental and lifestyle factors, minor changes called **single nucleotide polymorphisms (SNPs)** occur within the DNA code and are passed down from parent to child, from generation to generation. Remember the nucleotides? Well, a C might be replaced by a T, changing the instructions.

Some SNPs are positive, making us stronger and more resilient (like being able to digest milk after infancy), some are negative (like being likely to store more fat as a result of past famine or food shortage) and some make no difference at all. SNPs can be passed down from just one parent, or from both, enhancing the effect. SNPs are generally what we are looking for when we test your DNA.

Results

Your results are shown by a combination of the letters **ATCG** along with a traffic light system to indicate if your result is good, neutral or potentially detrimental.

Identical letters (e.g. GG or AA) mean you are either what is called the **wild type** with no genetic variants (SNPs) OR you have **both** genetic variants (from both parents). A combination of letters (e.g. AG) means you have one inherited genetic variant.

- A green result indicates either no variants or a positive variant impact
- An amber result usually indicates one genetic variant present and / or a mildly negative impact
- A red result indicates a negative impact either due to both variants being present or a wild type result that is not as beneficial as the variant

Example of your genetic results

GENE	RESULT	IMPACT & ADVICE
GENE CODE - Gene Function Explanation of the role the gene plays and what effect genetic variants might have, symptoms, other contributing factors etc.	GG	An explanation of your result, how you might be affected along with specific diet and lifestyle advice
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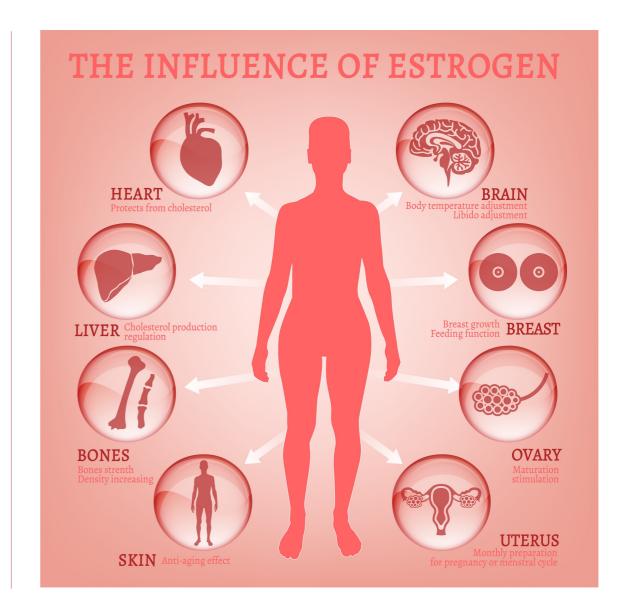
Oestrogen

Oestrogen is one of two major female steroidal sex hormones, the other being **progesterone**. The main source of oestrogen in females prior to menopause is the **ovaries**, after which the main source becomes the **adrenal glands** and **fat tissue**. Oestrogen is also produced by the placenta during pregnancy. Oestrogen levels fluctuate throughout life, naturally increasing during puberty and pregnancy, and falling after menopause. During the menstrual cycle, oestrogen levels peak during ovulation dropping off if pregnancy doesn't occur.

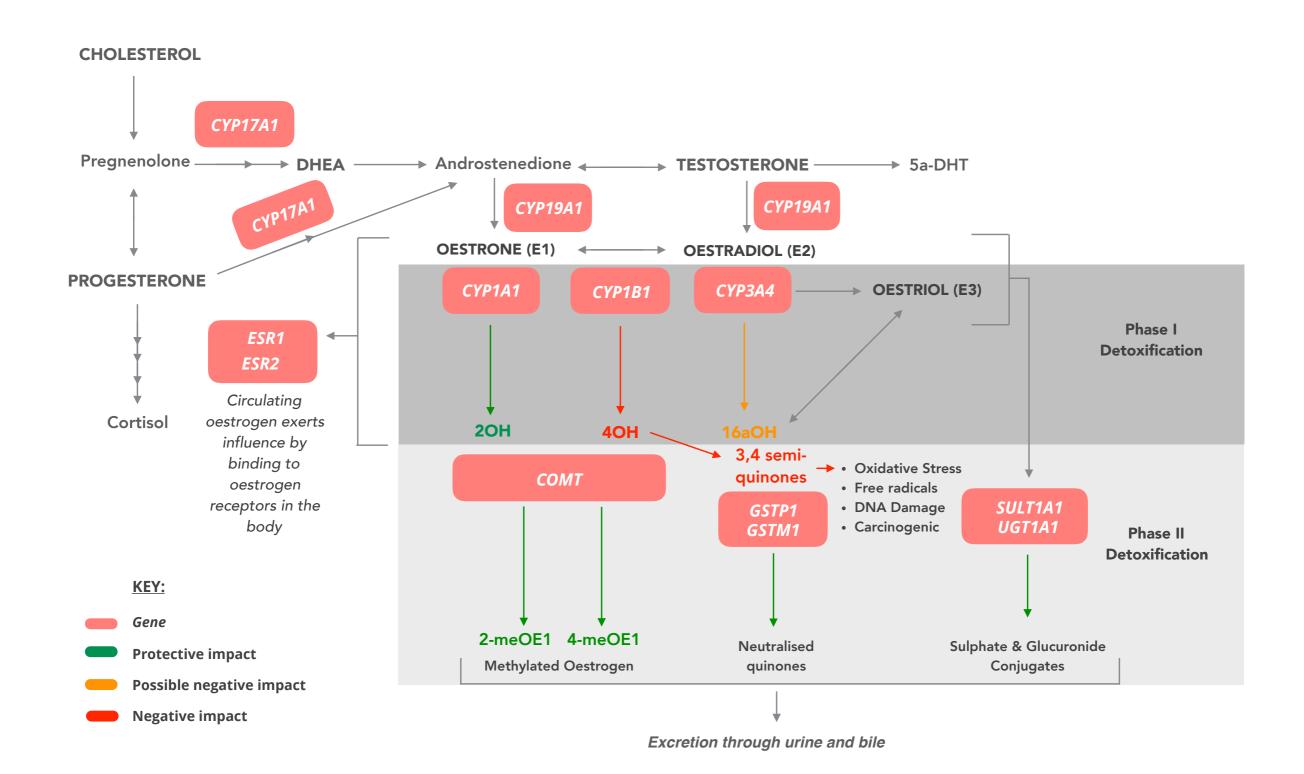
The main roles of oestrogen in the body are to increase the growth and production of cells, the development and regulation of the female reproductive system and secondary sex characteristics - breasts, pubic hair etc. Oestrogen is also involved in maintaining bone density, plays a role in blood clotting and affects skin, hair, mucous membranes and the pelvic muscles.

The body produces 3 different types of oestrogen:

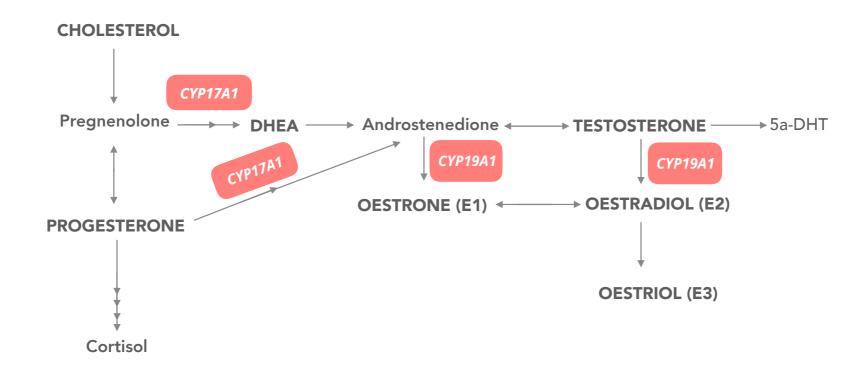
- E1 Oestrone: medium strength, predominant after menopause (adrenal glands)
- E2 Oestradiol: strongest form, predominant during childbearing age (ovaries & adrenal glands)
- E3 Oestriol: weakest form, predominant during pregnancy (placenta & liver)



Oestrogen Metabolism



Oestrogen Synthesis (production)



E1 and **E2** are produced directly from the androgens **androstenedione** and **testosterone** respectively. **E3** is produced from E2 according to the body's needs. Although androgens are considered male hormones, they play an important part in female physiology since all oestrogens are made from androgens. In every tissue where oestrogen is produced, it is made from an androgen.

The **CYP17A1** enzyme initiates the first step in oestrogen production by converting pregnenolone and progesterone into oestrogen precursors, including DHEA. The **CYP19A1** enzyme is responsible for controlling the rate at which androstenedione and testosterone are converted to oestrogen.

Women with low oestrogen may have reduced activity in one or both of these enzymes. Women with high oestrogen may have increased activity in one or both of these enzymes. This is important information clinically since these enzymes can be influenced through diet and lifestyle measures. Check page 9 to see whether your production might be too fast or too slow.

GENE	RESULT	IMPACT & ADVICE
CYP17A1 - Oestrogen Precursors CYP17A1 belongs to the cytochrome P450 (CYP450) superfamily of enzymes responsible for the production, activation and detoxification of a large number of substances in the body including pharmaceutical drugs, hormones (e.g. oestrogen and testosterone), corticoids and lipids. CYP17A1 is found in many tissues, including the adrenal glands, gonads, ovaries, heart, kidneys and fat tissue. In the oestrogen pathway, CYP17A1 is responsible for the conversion of pregnenolone and progesterone into oestrogen precursors including DHEA. Variants on this gene have been associated with increased enzyme activity leading to higher production of oestrogen precursors and also with postmenopausal depression and anxiety.	AA	The A result is associated with normal (not increased) CYP17A1 activity leading to normal conversion of androgens to oestrogen precursors. Chronic stress, alcohol and excess adipose (fat) tissue will increase CYP17A1 activity regardless of genotype. Ensure regular physical activity, drink alcohol in moderation and practise stress management techniques such as meditation and/ or yoga.
CYP19A1 - Androgen to Oestrogen Conversion CYP19A1 is another member of the CYP450 superfamily of enzymes. Mainly found in the gonads, brain, adipose (fat) tissue, placenta, blood vessels, skin and bones. It is also found in endometrial tissue and uterine fibroids. This enzyme regulates the final step in the production of oestrogen, converting androgens to oestrogen. Variants on the CYP19A1 gene are linked to both increased and decreased enzyme activity and may influence oestrogen:testosterone ratio.	AG	The A result is not associated with lower natural oestrogen levels. This may be considered negative since higher oestrogen levels can be harmful over time and can cause unpleasant symptoms such as PMS, heavy menstrual bleeding, weight gain, mood disorders, worsening of menopausal symptoms and is linked to certain cancers. Other factors such as excess body fat, high insulin levels, inflammation and stress increase CYP19A1 activity. Maintaining a healthy weight, balancing blood sugar, reducing inflammation and stress will help maintain hormonal balance. DIM, green tea and zinc have been shown to naturally reduce CYP19A1 activity.

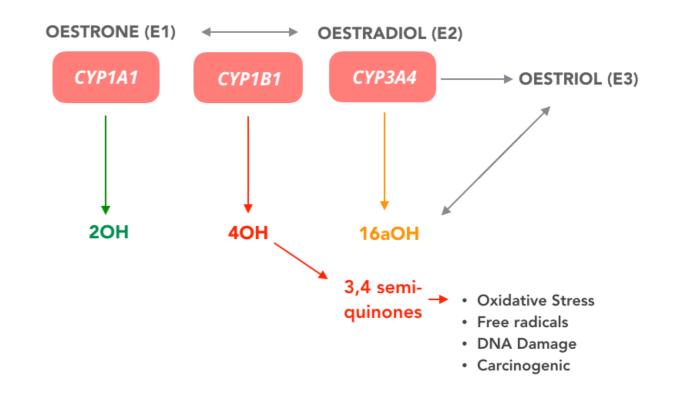
Oestrogen - Phase I Detoxification

Once produced, circulating oestrogen is converted via phase I detoxification enzymes:

CYP1A1: produces **20H oestrogen** which is 'weak' in action and thought to be neutral or even beneficial in the body. This is the most favourable pathway in terms of oestrogen metabolism.

CYP1B1: produces 4OH oestrogen and generates harmful free radicals in the process. 4OH oestrogen has stronger oestrogenic properties than 2OH oestrogen and has been associated with undesirable oestrogen-linked conditions and to DNA damage. As a result, this is the least favourable pathway of oestrogen metabolism.

CYP3A4: produces **16OH oestrogen**, thought to be stronger than 2OH and potentially harmful, although further research needs to be done. As a result, this is thought to be a less favourable pathway.

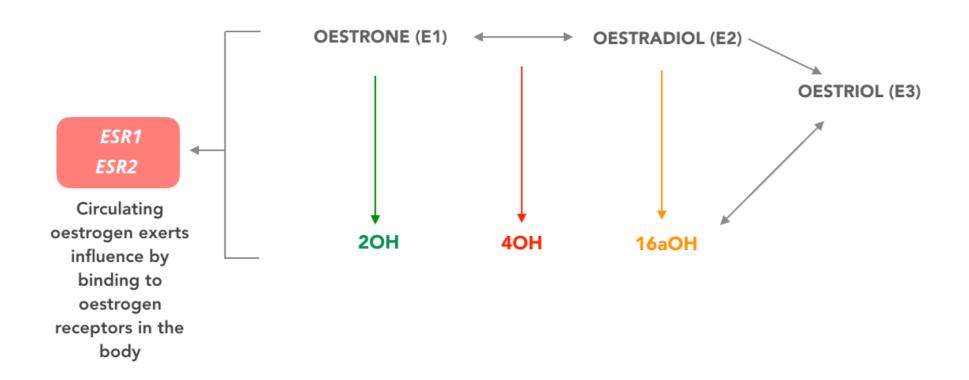


Knowing which phase I pathway/s your body favours is useful since it gives a clue as to which forms of oestrogen might be dominant in circulation and the diet and lifestyle measures you should take care to implement or avoid in order to maintain a healthy balance. Check pages 11 & 12 to see which pathway/s your body is most likely to favour.

GENE	RESULT	IMPACT & ADVICE
CYP1A1 - Production of 2OH Oestrogen CYP1A1 is another one of the CYP450 superfamily of enzymes. CYP1A1 is a primary phase I detoxification gene involved in (among other things) oestrogen metabolism, particularly the production of 2OH oestrogen, which is thought to be neutral or even beneficial in the body. Variants in the CYP1A1 gene are associated with increased enzyme activity - desirable for oestrogen metabolism but also linked to Polycystic Ovary Syndrome (PCOS) and increased free radical production due to high enzyme activity. Here we look at two different variants known to impact CYP1A1 activity.	CC	Likely to have increased CYP1A1 enzyme activity and increased production of 2OH oestrogen. This is positive since 2OH oestrogen is thought to be neutral or even beneficial in the body, however, increased activity also increases the production of harmful free radicals. Improving phase II detoxification pathways (see pages xx below) and increasing antioxidants will help to decrease free radical damage.
	AG	Likely to have increased CYP1A1 activity. This is both positive and negative since increased activity leads to higher 2OH oestrogen which is beneficial, however, this particular genotype is also associated with increased susceptibility to PCOS. Increased (phase I) activity also increases the production of harmful free radicals. Improving phase II detoxification pathways and increasing antioxidants will help to decrease free radical damage - see page xx for tips.

GENE	RESULT	IMPACT & ADVICE
CYP1B1 - Production of 4OH Oestrogen CYP1B1 is another primary phase I detoxification gene (and member of the CYP450 superfamily) involved in oestrogen metabolism, particularly the production of 4OH oestrogen, a potent form of oestrogen that can be harmful in the body. 4OH oestrogen binds strongly to oestrogen receptors, and is therefore longer and potently active. Variants in this gene are associated with increased activity which creates the harmful free radicals, quinones, and increased circulating 4OH oestrogen. CYP1B1 activity is further activated by high oestrogen levels.	GG	Associated with up to 3x higher CYP1B1 activity. This is unfavourable since 4OH is a potent form of oestrogen and increased CYP1B1 activity has been shown to promote the synthesis of the harmful free radicals which damage DNA. Diet and lifestyle factors such as smoking, stress and eating charred foods increase CYP1B1 activity further and should be avoided. Support phase II detoxification (see pages xx) and increase antioxidants to prevent free radical damage. Grapefruit has been shown to powerfully reduce CYP1B1 activity. Consult your doctor if you are on medication since grapefruit is known to interact with certain medications.
CYP3A4 - Production of 16aOH Oestrogen CYP3A4 is a phase I detoxification gene (and member of the CYP450 superfamily) involved in oestrogen metabolism, particularly the production of 16aOH oestrogen, which is thought to be harmful in the body. A large number of medications are metabolised through the CYP3A4 pathway such as codeine, acetaminophen (paracetamol), diazepam, the oral contraceptive pill (OCP) and statins. CYP3A4 also converts E2 to E3. Variants in this gene are associated with increased activity, undesirable for oestrogen metabolism, and affecting drug metabolism.	TC	Possible increased CYP3A4 activity. This is unfavourable since 16aOH oestrogen has been associated with oestrogen excess conditions. CYP3A4 enzyme activity can increase due to diet and lifestyle factors such as obesity, excess alcohol consumption, stress, certain medications and toxic chemical exposure. Regular physical exercise, moderate alcohol consumption and increased antioxidant intake would be beneficial. Grapefruit is a potent inhibitor of this pathway, consult your doctor if you are on medication since you may be affected.

Oestrogen Receptors



Once produced, oestrogen moves through the blood and exerts its influence in the body by binding to oestrogen receptors (ERs). ERs are important since they are also known to bind to DNA and control gene expression.

There are two types of oestrogen receptors encoded by two separate genes:

- ER alpha (ESR1) found in highest concentration in the endometrium, ovaries and hypothalamus (in the brain). ESR1 increases the action of the attached oestrogen
- ER beta (ESR2) found in highest concentration in the ovaries, kidneys, brain, bone, heart, lungs, intestinal mucosa and endothelial cells. ESR2 weakens the action of the attached oestrogen

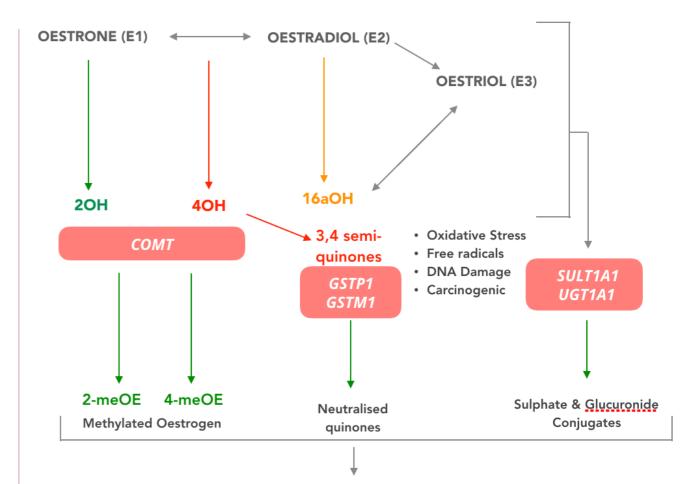
GENE	RESULT	IMPACT & ADVICE
ESR1 - Oestrogen Receptor 1 The ESR1 gene regulates oestrogen receptor alpha activity which is involved in hormone binding and activation, and also regulates gene transcription. ESR1 is thought to enhance the effect of oestrogen that attaches to it. This is necessary for oestrogen to perform its functions in the body but can be negative if high amounts of very strong forms of oestrogen (e.g. E2 and 4OH) are dominant in circulation. Variants in ESR1 are associated with enhanced receptor activity. Here we look at two variants known to affect ESR1 activity.	CC	Normal (not increased) ESR1 activity. High oestrogen levels will increase risk of oestrogen-linked conditions regardless of genotype. Optimising phase II oestrogen elimination via methylation (COMT), sulphation (SULT) and glucuronidation (UGT) pathways will support healthy oestrogen levels. Encouraging CYP1A1 activity over CYP1B1 and CYP3A4 will also ensure that 'weaker' 2OH is dominant in circulation over the 'stronger' 4OH and 16aOH forms.
	TC	Moderately increased ESR1 activity. This genotype increases risk of oestrogen-linked conditions particularly if 4OH and 16OH oestrogen are dominant in circulation. Care should be taken to reduce circulating oestrogen by improving phase II inactivation pathways - methylation (COMT), sulphation (SULT) and glucuronidation (UGT), encouraging phase I CYP1A1 activity over CYP1B1 and CYP3A4 to ensure that 'weaker' 2OH oestrogen is dominant in circulation.
ESR2 - Oestrogen Receptor 2 The ESR2 gene regulates oestrogen receptor beta activity which is involved in the hormone binding and activation, and also regulating gene transcription. ESR2 is thought in some cases to reduce the effect of oestrogen that binds to it. Since oestrogen is protective against heart disease, ESR2 has been linked to cardiovascular health. During the development of a tumour (tumourigenesis) an increase in ESR1 and decrease in ESR2 is observed. Variants	TT	Needs work - research the below Natural and synthetic oestrogens, phytoestrogens (coumestrol, daidzein, genistein and miroestrol), and selective oestrogen modulators (tamoxifen, clomifene and ralozifene) serve as agonists. Antioestrogens block the actions

Oestrogen - Phase II Detoxification

After phase I conversion, oestrogen metabolites pass through phase II detoxification where they are neutralised and prepared for excretion via urine and bile.

The 4 main oestrogen detoxification enzymes are:

- COMT (Methylation): the COMT enzyme turns 20H and 40H into the neutral compounds, 2-meOH and 4-meOH respectively via a process called methylation. Methylation is a major mechanism for preventing the potentially harmful effects of oestrogen in the body.
- **GSTs** (**Glutathione Transferases**): the **GSTs** are vital phase II detoxification enzymes responsible for providing protection against toxins by neutralising free radicals in the body with the help of the powerful antioxidant, **glutathione**.
- **SULT (Sulphation):** oestrogen metabolites are also deactivated via sulphotransferase enzymes
- **UGT** (**Glucuronidation**): the **UGT** enzymes render oestrogen more water-soluble and ready for excretion via the bile to the small intestine



Excretion through urine and bile

Knowing which of your phase II pathways might be sluggish or in need of extra support is important. Learn to optimise these pathways through diet and lifestyle measures to ensure healthy elimination of unwanted oestrogen (and other nasties like toxins and medication). Check pages 16 - 18 to see which ones are more likely to affect you.

GENE	RESULT	IMPACT & ADVICE
COMT - Oestrogen Methylation COMT is an important phase II detoxification enzyme responsible for inactivating many compounds including dopamine, adrenalin and oestrogen via methylation. COMT methylates 20H and 40H oestrogen to 2-me and 4-me oestrogen respectively, making them inactive and ready for excretion. Variants in this gene lead to reduced enzyme function and slower detoxification of oestrogen (and other compounds) via this pathway. High oestrogen levels reduce COMT activity.	GG	Normal (fast) COMT activity leading to efficient inactivation of circulating oestrogen (and other compounds) via methylation. Review your MTHFR result on the next page to see whether you might be a 'poor methylator' which will impede COMT activity due to lack of vital co-factors. A diet rich in B vitamins may help to improve your methylation ability. Magnesium and ellagic acid, found in red berries, support COMT activity.
GSTM1 is one of the GST superfamily of enzymes. It is present in virtually all tissue but is most highly active in the liver, kidneys and intestines. It is responsible for neutralising compounds such as free radicals, environmental toxins, carcinogens and pharmaceutical drugs via the powerful antioxidant Glutathione. It is also involved in preventing cellular mutations. Variants in this gene are very common with approximately 50% of the population having only one copy or no copies of the gene at all, increasing susceptibility to environmental toxins and free radical damage.	AG	One copy of the GSTM1 gene leading to reduced ability to neutralise free radicals (oxidative stress), environmental toxins and other carcinogens. Increase antioxidants (particularly glutathione) and reduce inflammation and oxidative stress which are known to deplete glutathione levels and increase free radicals. This is particularly important if you have the high activity CYP1B1 genotype. Diet and lifestyle factors like smoking, high alcohol intake, frequent consumption of grilled meats and exposure to chemicals in detergents or cosmetics should be avoided as much as possible to reduce toxic load. A diet rich in cruciferous vegetables will support this pathway.
GSTP1 - Neutralising Free Radicals GSTP1 is another member of the GST superfamily of enzymes highly expressed in the liver, kidneys, oesophagus, thyroid and intestines. It's main role is protection of cells against toxins and carcinogens such as pollution, heavy metals, cigarette smoke, pesticides and UV exposure via the powerful antioxidant Glutathione.	GG	Associated with impaired GSTP1 activity and reduced ability to neutralise free radicals. High levels of oxidative stress due to stress, smoking, high alcohol consumption and low glutathione levels will slow GST activity further. Reducing stress and inflammation and increasing antioxidants including glutathione is recommended. A diet rich in cruciferous vegetables will help to support this pathway.

GENE	RESULT	IMPACT & ADVICE
MTHFR - Methylation & Oestrogen Detoxification The MTHFR gene is responsible for converting folate (vitamin B9) into its active form. Active folate is an important component of methylation, a biochemical reaction involved in many processes in the body including detoxification, DNA synthesis and repair (vital for healthy cell division), gene expression, foetal development, and the metabolism of neurotransmitters, especially dopamine and serotonin. Variants in MTHFR lead to low activity and therefore low production of active folate. Here we look at two variants on the MTHFR gene (C677T and A1298C) known to impact its function.	GG	The 'G' result is associated with healthy (not reduced) MTHFR activity supporting the methylation and detoxification of oestrogen via the COMT enzyme. Methylation can be affected by diet and lifestyle factors regardless of genotype. A diet rich in green leafy vegetables (B vitamins and magnesium) and low in alcohol is recommended to ensure support of a healthy methylation cycle.
	TG	The 'G' result is associated with decreased MTHFR activity leading to low conversion of folate to active folate (methylfolate) and therefore poor methylation ability. As a result you may be at increased risk of mood disorders, have a reduced ability to eliminate oestrogen (especially if you have variants in COMT). A diet rich in green leafy vegetables (B vitamins and magnesium) and low in alcohol is recommended. Consult a qualified practitioner about supplementing methylfolate (not folic acid).
SULT1A1 - Sulphation SULT1A1 is highly expressed in the liver, small intestine, kidney, uterus, adrenal glands and breast tissue. It is one of the enzymes involved in deactivating oestrogen and other hormones, neurotransmitters and medications in the body. Variants in SULT1A1 cause reduced activity and therefore reduced deactivation of substrates - including oestrogen.	GG	The 'T' result is associated with poor sulphation (detoxification) of oestrogen and its metabolites. A diet rich in sulphur-containing foods such as garlic, onion, Brussels sprouts, broccoli and kale, will support this pathway.

GENE	RESULT	IMPACT & ADVICE
UGT1A1 - Glucuronidation UGT1A1 encodes an enzyme expressed largely in the liver, kidney, gut, prostate, ovary and breast tissue. It is responsible for the inactivation of molecules such as oestrogen and other steroid hormones, thyroxine and common drugs such as morphine and acetaminophen (paracetamol), and bilirubin, preparing them for excretion via urine and bile. Variants in UGT1A1 can cause low enzyme function. Due to the bacterial production of an enzyme called beta-glucuronidase, intestinal dysbiosis can cause inactivated (conjugated) compounds to become reactivated (unconjugated) and re-released into circulation.	GG	Normal (not slow) UGT1A1 enzyme activity and healthy glucuronidation (detoxification) of oestrogen and other compounds. Intestinal dysbiosis will affect this pathway regardless of genotype. Foods that support this pathway include apples, oranges and cruciferous vegetables (all of which naturally contain calcium-D-glucarate, a compound shown to inhibit beta-glucuronidase released by gut bacteria), and watercress.
UGT1A6 - Glucuronidation UGT1A6 encodes an enzyme that prepares molecules such as steroids, hormones (oestrogen & thyroxine) and drugs (morphine & acetaminophen), and bilirubin, for excretion via urine and bile. Glucuronidation turns lipophilic compounds into water-soluble compounds which are easily excreted in the urine and bile. Variants on UGT1A6 can cause low enzyme activity. Due to the bacterial production of an enzyme called beta-glucuronidase, intestinal dysbiosis can cause inactivated (conjugated) compounds to become reactivated (unconjugated) and re-released into circulation.	AG	The 'G' result is associated with reduced UGT1A6 activity and reduced inactivation and elimination of oestrogen, thyroxine and other substances detoxified by this pathway. It is also linked to increased risk of gallstones. Intestinal dysbiosis will impede this pathway further. Foods that support this pathway include apples, oranges and cruciferous vegetables (all of which naturally contain calcium-D-glucarate, a compound shown to inhibit beta-glucuronidase released by gut bacteria), and watercress.



Other Important Factors Affected by Genetics



GENE	RESULT	IMPACT & ADVICE
APOE - Fat and Cholesterol Metabolism APOE is highly expressed in the liver, kidneys and brain and produces apolipoprotein E, a protein that binds and transports fats in the body. It is responsible for removing cholesterol, particularly (bad) LDL and VLDL cholesterol from the bloodstream. Variants in APOE are associated with increased total cholesterol, particularly LDL and triglycerides (a type of fat), and decreased clearance of LDL and VLDL cholesterol. As a result, APOE variants have been linked to cardiovascular disease and also with cognitive decline. High LDL cholesterol and triglycerides are often a sign or predictor of other conditions too e.g. obesity, high blood pressure, high blood sugar, low thyroid function and stroke. Here we look at two variants (rs429358 & rs7412) in the APOE gene which are known to have an impact on function, particularly when inherited together.	TC	The 'TC' result for this SNP (rs429358) is associated with moderately elevated LDL cholesterol and triglyceride levels, leading to risk of cardiovascular disease and other related conditions such as obesity, high blood pressure, high blood sugar, low thyroid function and stroke. A 'C' result for the below variant increases risk. It is important that you maintain a healthy weight by exercising regularly and being careful about intake of dietary fats, refined sugar and alcohol. Fish oils lower triglycerides. dietary fats, refined sugar and alcohol. Fish oils lower triglycerides.
	СТ	The 'C' result for this SNP (rs7412) is associated with increased LDL cholesterol and higher post-meal triglycerides than the 'T' result for this SNP increasing risk of plaque buildup in arteries. This risk increases in combination with a 'C' result for rs429358 above.

GENE	RESULT	IMPACT & ADVICE
VDR - Vitamin D Receptivity The VDR gene is located on chromosome 12 and regulates the body's receptivity to vitamin D3, the active form of vitamin D. This vitamin can be acquired from certain foods but is mostly manufactured in the body following exposure to sunlight. Vitamin D serves many important functions in the body: it aids the absorption of calcium and phosphate - keeping bones and teeth healthy; it mediates the production of dopamine (one of the body's 'feel good' chemicals) this is one of the reasons why lack of sunlight is associated with low mood; it is also crucial for cell growth and differentiation, and supports a healthy immune system. Over 30% of the population carries a variant which may lead to low vitamin D receptivity. Here we look at two variants on the VDR gene which affect vitamin D receptivity.	CC	The CC genotype is associated with healthy receptivity to vitamin D. This means that provided you have adequate exposure to daily sunlight (without tanning or burning your skin), or take a good quality vitamin D supplement, you are less likely to be at risk of low vitamin D levels and low bone density, low mood and poor immunity as a result.



Nutrition & Lifestyle Advice



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