



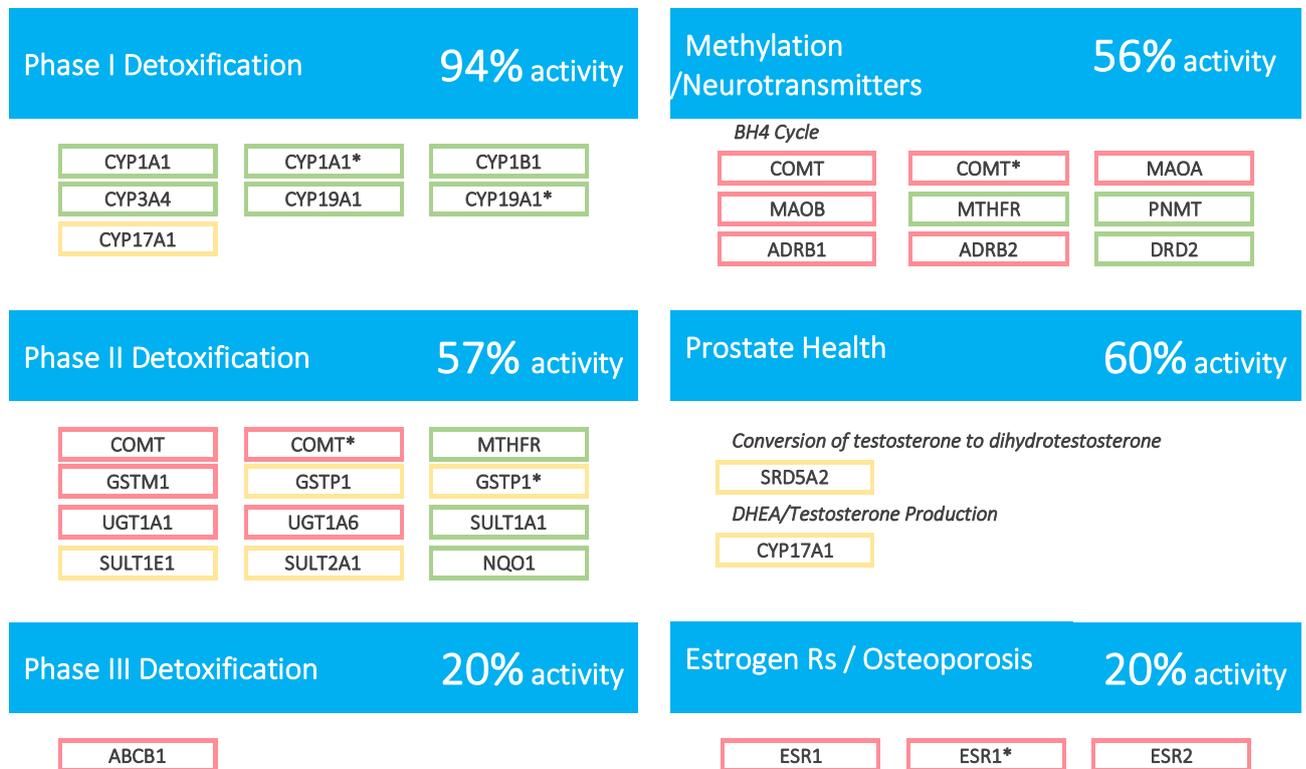
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## GENETIC REPORT OF MAN'S HORMONAL HEALTH - SAMPLE

The Man's Hormonal Health genetic testing investigates the patient's methylation, detoxification and neurotransmitters status. The most salient step that can be taken to prevent health imbalances is to prevent expression of gene mutations, or to limit their influence. This protocol investigates several areas: cardio health, prostate health, muscle degradation and osteoporosis, chronic fatigue and burnout, and energy restoration.



CYP1A1	CYP1A1*	CYP1B1
CYP3A4	CYP19A1	CYP19A1*
CYP17A1		

*BH4 Cycle*

COMT	COMT*	MAOA
MAOB	MTHFR	PNMT
ADRB1	ADRB2	DRD2

COMT	COMT*	MTHFR
GSTM1	GSTP1	GSTP1*
UGT1A1	UGT1A6	SULT1A1
SULT1E1	SULT2A1	NQO1

*Conversion of testosterone to dihydrotestosterone*

SRD5A2
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*DHEA/Testosterone Production*

CYP17A1
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ABCB1
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ESR1	ESR1*	ESR2
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**Color Key**

- Beneficial properties:
- Moderate risk:
- High risk:

\*2 Rs of the same gene

# Brief Explanation of the Functions of the Studied Genes

## Estrogen / Phase I, Phase II, Phase III Detoxification

Genetic variants in the estrogen metabolism pathways are known to impact the risk prostate cancer.

In a man's body, estrogen plays a vital role in several systems, including stabilizing the nervous system, maintaining and building muscle mass and bone strength, and preventing osteoporosis.

Men with **low estrogen** levels have shown to have a higher risk of cardiovascular diseases, diabetes, bone fractures and loss of muscle mass.

Mutations in the ESR1, ESR2 gene encoding the estradiol receptor may lead to increased sensitivity of cells to estradiol. Even with normal level of blood estradiol patients may exhibit symptoms of hypoestrogenemia.

Men with **high estrogen** have been shown to have a higher risk of gynecomastia, sexual dysfunction, fatigue, depression, anxiety, and prostate cancer.

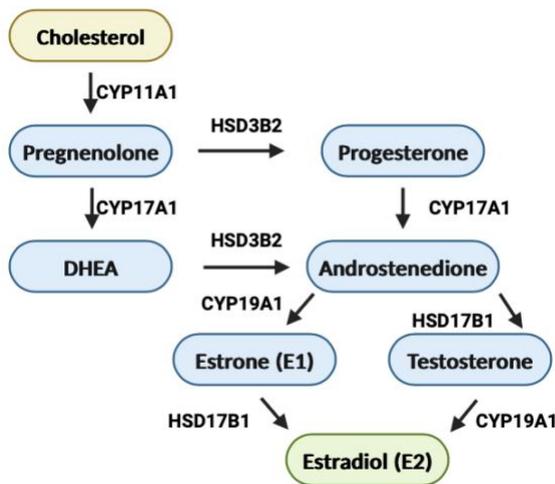
Genes that belong to the cytochromes class are known to encode the enzymes 17-alpha-hydroxylase and aromatase. 17-alpha-hydroxylase is involved in the synthesis of all sex hormones (androgens and estrogens). Mutations in corresponding genes can lead to increased hormone synthesis, i.e. hyperandrogenism and hyperestrogenism. Aromatase converts testosterone into estradiol. If aromatase activity is enhanced, this leads to increased synthesis of estradiol and hyperestrogenism.

Men with **estrogen metabolites imbalance** are known to have a higher risk of prostate cancer.

Prostate cancer risk has been shown to increase with 4-HOE1(E2) and 16 $\alpha$ -OHE metabolites. At the same time, it has been demonstrated that higher amounts of 2-OHE1(E2) decrease prostate cancer risk.

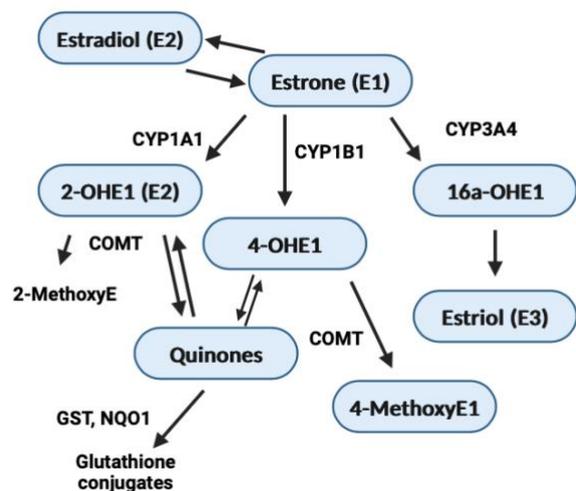
Estrogen metabolism and active forms of estrogen in balance depends on the function of Phase II Detoxification genes (COMT, MTHFR, GSTM1, GSTP1, UGT1A1, UGT1A6, SULT1A1, SULT1E1, SULT2E1, NQO1).

## Estrogen Biosynthesis

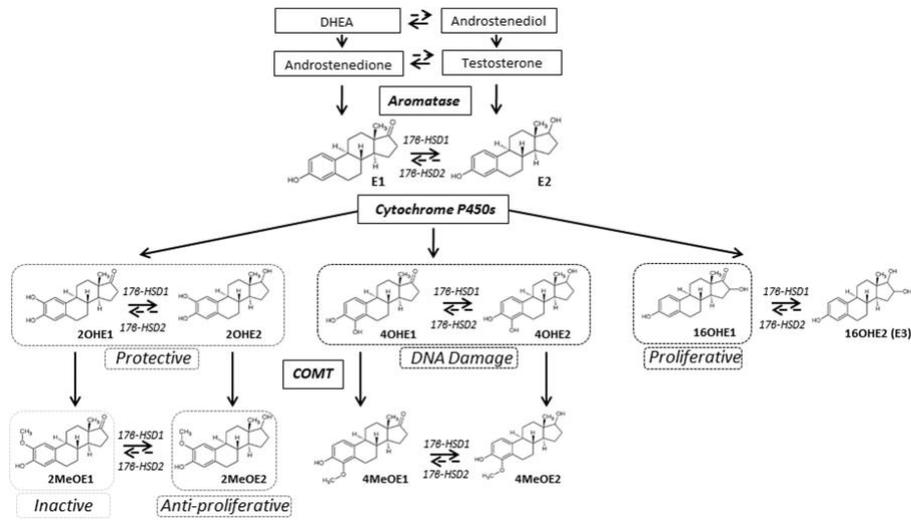


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## Estrogen Elimination



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\* Nina Denver, Shazia Khan, Natalie Z.M. Homer, Margaret R. MacLean, Ruth Andrew, Current strategies for quantification of estrogens in clinical research, The Journal of Steroid Biochemistry and Molecular Biology, Volume 192, 2019, 105373, ISSN 0960-0760, <https://doi.org/10.1016/j.jsbmb.2019.04.022>.

### Methylation / Neurotransmitters Metabolism

Methylation is a biochemical process that plays a very important role in gene expression and repair. Imbalances in the methylation cycle can affect levels and activity of neurotransmitters like serotonin and dopamine, which can contribute to depression and other mental health disorders.

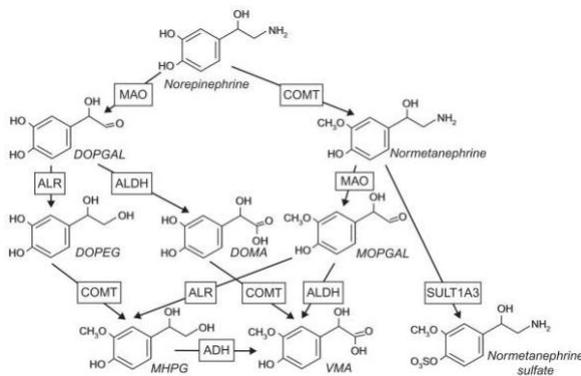
Methylation is a biological regulator that controls numerous reactions in the body. During this reaction a methyl group consisting of four atoms (one carbon atom and three hydrogen atoms) is added to DNA, proteins or other molecules. Methionine acts as a donor of methyl groups to the body.

Because of the methyl groups, gene expression occurs in a strictly defined order.

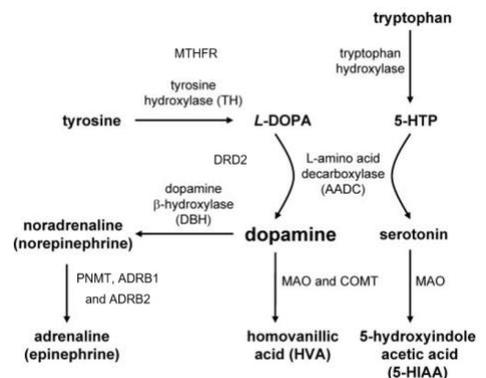
In addition to DNA expression (the process during which genetic information of a gene is converted into a functional product - RNA or protein), methylation is also responsible for a wide range of biological functions, including production of neurotransmitters (dopamine, serotonin, adrenaline, etc.); detoxification; and hormonal regulation.

Methylation impacts **stress response** and **energy levels**. Methylation helps produce neurotransmitters such as serotonin, dopamine, adrenaline, noradrenaline, and melatonin through COMT, MAOA, MAOB, MTHFR, PNMT, ADRB1, ADRB2, DRD2 gene function. This happens in several ways: methylation converts tryptophan into 5-hydroxytryptophan; it also ensures the transportation of dopamine, noradrenaline, and adrenaline; as well as converts noradrenaline into adrenaline. Moreover, methylation is responsible for the conversion of serotonin into melatonin.

Methylation impacts **hormonal regulation**. Men react to stress differently depending on their testosterone and estrogen levels. High and low testosterone levels as well as high and low estrogen levels influence methylation and breakdown of neurotransmitters.



Estrogen and testosterone both influence methylation and breakdown of neurotransmitters



Neurotransmitters Synthesis

\* Bortolato M, Shih JC. Behavioral outcomes of monoamine oxidase deficiency: preclinical and clinical evidence. Int Rev Neurobiol. 2011;100:13-42. doi: 10.1016/B978-0-12-386467-3.00002-9. PMID: 21971001; PMCID: PMC3371272.

\* Rubi, Blanca & Maechler, Pierre. (2010). Minireview: New Roles for Peripheral Dopamine on Metabolic Control and Tumor Growth: Let's Seek the Balance. Endocrinology. 151. 5570-81. 10.1210/en.2010.0745.

## Prostate Health

### DHEA, Testosterone Production / CYP17A1

CYP17A1 is involved in the steroidogenesis.

The CYP17A1 enzyme is involved in the conversion of pregnenolone into 17-hydroxypregnenolone and progesterone into 17-hydroxyprogesterone, by regulating 17 alpha ( $\alpha$ )-hydroxylase activity. These hormone precursors are then further processed to produce glucocorticoids and sex hormones. Additionally, CYP17A1 possesses 17,20-lyase activity, which converts 17-hydroxypregnenolone into dehydroepiandrosterone (DHEA), a critical reaction in the production of sex hormones.

Polymorphism in the CYP17A1 gene promoter has been related to a rise in testosterone levels.

### Conversion of testosterone to dihydrotestosterone / SRD5A2

The SRD5A2 gene encodes the enzyme steroid 5-alpha reductase 2, which plays a key role in processing androgens, the hormones that guide male sexual development. This enzyme specifically catalyzes the conversion of testosterone into a more potent androgen, dihydrotestosterone (DHT), within male reproductive tissues.

Mutations in this gene can increase the activity of steroid 5-alpha reductase 2, potentially elevating DHT levels in prostate tissue. Research has shown that androgens such as DHT can stimulate prostate cancer growth.

Deviations from the normal range of active forms of androgens/estrogens can cause many pathological conditions. These include an increased amount of dihydrotestosterone, one of the most active androgens, formed from testosterone directly in the "target organs" with the participation of a special enzyme (5-alpha-reductase). By controlling the activity of SRD5A2, many diseases can be avoided.

### GENETIC ANALYSIS RESULTS of Phase I enzymes

**Role:** Phase I detoxification involves the modification of toxins through chemical reactions, such as oxidation, reduction, and hydrolysis. These reactions introduce or expose a functional group (such as a hydroxyl group) on the toxin, making it more reactive.

**Key Enzymes:** Cytochrome P450 enzymes (CYPs):

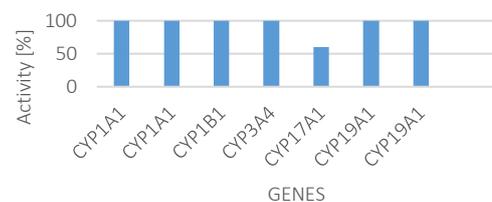
These are the most important Phase I enzymes. They are a large family of enzymes that catalyze the oxidation of organic substances. CYP enzymes, such as CYP1A1, CYP1B1, CYP3A4, CYP17A1, and CYP19A1 play a major role in drug metabolism and the detoxification of various toxins.

Genotypes and activity of Phase I enzymes

GENES	Genomic Coordinates	Genotype	Zygosity	Enzyme activity
CYP1A1	Chr15: 74720644	TT	Homozygous	100
CYP1A1	Chr15: 74719300	AA	Homozygous	100
CYP1B1	Chr2: 38071060	CC	Homozygous	100
CYP3A4	Chr7: 99784473	TT	Homozygous	100
CYP17A1	Chr10: 102837395	GT	Heterozygous	60
CYP19A1	Chr15: 51242350	TT	Homozygous	100
CYP19A1	Chr15: 51210789	GG	Homozygous	100

Global activity: 94%

Phase I Enzyme activity



### GENETIC ANALYSIS RESULTS of Phase II enzymes

**Role:** Phase II detoxification involves Sulphation, Conjugation with glutathione, Glucuronidation, Acetylation, Amino-Acid Conjugation, Methylation to form more stable and water-soluble compounds that can be easily excreted.

**Key Enzymes:** The UGT1A1 gene encodes UDP-glucuronyl transferase, the main enzyme responsible for the glucuronidation of bilirubin and some other compounds. The UGT1A1 gene is expressed mainly in the liver. Certain genetic variants affecting the production of UDP-glucuronyl transferase are a risk factor for the development of Gilbert's syndrome. The function of the UGT1A1 gene is to convert estrogens into their conjugates with glucuronic acid. The conjugation process allows the body to safely metabolize and eliminate estrogens from the body.

Glutathione-S-transferases (GSTs): Catalyze the conjugation of glutathione to reactive intermediates, neutralizing them and making them more water-soluble.

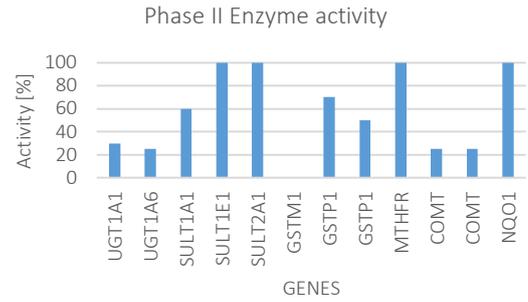
Glutathione S-transferase Pi (GSTP1) is an isozyme encoded by the GST Pi gene that plays an important regulatory role in detoxification, anti-oxidative damage, and the occurrence of various diseases. Polymorphism in this gene reduces the activity of the enzyme, which inhibits phase II xenobiotics, including detoxification of medicinal derivatives.

Sulfotransferases (SULTs): Transfer sulfate groups to hydroxyl groups on toxins, increasing their water solubility. Sulfotransferase enzymes family (SULT1A1, SULT1E1, SULT2A1) catalyze the sulfate conjugation of many hormones, neurotransmitters, drugs, and xenobiotic compounds.

The end products of Phase II detoxification are generally non-toxic, highly water-soluble, and can be readily excreted from the body through urine or bile.

**Genotypes and activity of Phase II enzymes**

GENES	Genomic Coordinates	Genotype	Zygoty	Enzyme activity
<b>Glucoronidation</b>				
UGT1A1	Chr2: 233764076	GG	Homozygous	30
UGT1A6	Chr2:233693631	TT	Homozygous	25
<b>Sulphation</b>				
SULT1A1	Chr16:28606193	TC	Heterozygous	60
SULT1E1	Chr4: 69860103	CC	Homozygous	100
SULT2A1	Chr19:47868938	TT	Homozygous	100
<b>Glutathion Conjugation</b>				
GSTM1	Null Allele	AA	Homozygous	0
GSTP1	Chr11: 67585218	GA	Heterozygous	70
GSTP1	Chr11:67586108	TT	Heterozygous	50
<b>Methylation</b>				
MTHFR	Chr1: 11796321	GG	Homozygous	100
COMT	Chr22: 19963748	AA	Homozygous	25
COMT	Chr22: 19962712	TT	Homozygous	25
NQO1	Chr16: 69711242	GG	Homozygous	100



Global activity: 57%

**GENETIC ANALYSIS RESULTS of Phase III enzymes**

**Role:** Phase III detoxification involves elimination of water-soluble molecules out of the body through bile/intestine (stool), kidneys (urine) and skin (sweat).

**Key Enzymes:** ABCB1 enzyme regulates Phase III of the detoxification process and allows toxins to move across cellular barriers in the liver, gastrointestinal system, kidneys, and the blood-brain barrier.

The ABCB1 gene regulates the production of important ATP-dependent Phase 3 antiporter protein responsible for transporting various xenobiotics, drugs, lipids, and other exogenous and endogenous toxins out of cells for excretion. It can also be found under the name of MultiDrug Resistance 1 (MDR1) or the P-Glycoprotein (P-GP).

**Genotypes and activity of Phase III enzymes**

GENES	Genomic Coordinates	Genotype	Zygoty	Enzyme activity
ABCB1	Chr7:87509329	GG	Homozygous	20

Phase III Enzyme activity



Global activity: 20%

**GENETIC ANALYSIS RESULTS of Methylation / Neurotransmitters**

**Role:** Neurotransmitter imbalance causes fatigue, mood swings, sleep disorders, depression and aggression. Neurotransmitter levels relate to adrenaline, noradrenaline, dopamine, serotonin whose levels depend on the methylation processes and hypothalamic-pituitary-adrenal system activity.

**Key Enzymes:** Variants on COMT, MAOA & MAOB, MTHFR relate to neurotransmitter levels and lead to imbalances causing mood swings and chronic fatigue.

Mutations in the DRD2 gene can reduce dopamine production and activity, which may result in psychiatric and psychotic symptoms, along with a higher risk of addiction and neuropsychiatric disorders. Each dopamine D2 receptor is involved in functions such as attention, sleep, memory, and learning.

Gene expression of PNMT (phenyl-ethanolamine N -methyl

The ADRB1 gene encodes the  $\beta$ 1-adrenergic receptor, located on various cells throughout the body. These adrenergic receptors respond to hormones that help regulate the sleep-wake cycle.

transferase), the enzyme catalyzing the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to norepinephrine in the final step of the biosynthesis of epinephrine.

It is related to adrenaline and noradrenaline.

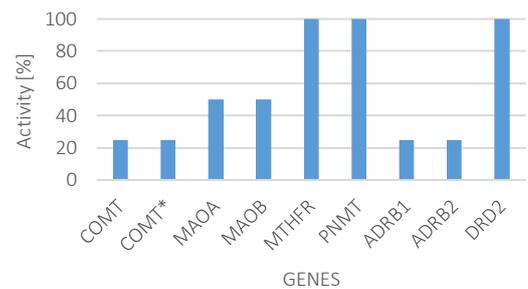
DRD2 functions to regulate synthesis, storage and release of dopamine.

ADRB2 controls the physiological response to adrenaline, as it stimulates heart rate, blood flow, and availability of glucose for immediate energy.

**Genotypes and activity of Methylation / Neurotransmitters**

GENES	Genomic Coordinates	Genotype	Zygoty	Enzyme activity
COMT	Chr22: 19962712	TT	Homozygous	25
COMT*	Chr22: 19963748	AA	Homozygous	25
MAOA	ChrX: 43731789	TT	Homozygous	50
MAOB	ChrX: 43768752	CC	Homozygous	50
MTHFR	Chr1: 11796321	GG	Homozygous	100
PNMT	Chr17:39668292	GG	Homozygous	100
ADRB1	Chr10:114045297	CC	Homozygous	25
ADRB2	Chr5: 148826877	GG	Homozygous	25
DRD2	Chr11:113412966	CC	Homozygous	100

Methylation / Neurotransmitters Enzyme activity



Global activity: 56%

## GENETIC ANALYSIS RESULTS of Prostate Health

**Role:** Activity of enzymes influences the level of cortisol, androgens and estrogens.

**Key Enzymes:** CYP17A1 enzymatic activity shows conversion from progesterone to cortisol, androgens and estrogens. This activity can be upregulated by stress, blood sugar dysregulation, excess insulin, and alcohol. Adequate physical activity and stress management needs to be ensured.

CYP19A1 enzymatic activity shows conversion of androgens to estrogens. Inflammation, high levels of insulin and chronic stress will increase CYP19A1 activity.

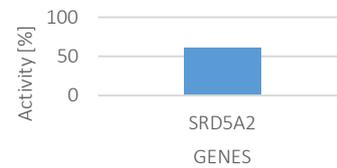
SRD5A2 enzymatic activity shows conversion from testosterone to 5a-DHT. Controlling SRD5A2 activity gives benefit in cancer prevention.

Genotypes and activity of Conversion of testosterone to dihydrotestosterone

GENES	Genomic Coordinates	Genotype	Zygoty	Enzyme activity
SRD5A2	Chr2: 31580636	CG	Heterozygous	60

Global activity: 60%

Conversion of testosterone to dihydrotestosterone  
Enzyme activity

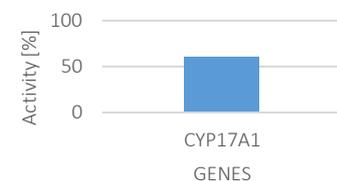


Genotypes and activity of DHEA / Testosterone Production

GENES	Genomic Coordinates	Genotype	Zygoty	Enzyme activity
CYP17A1	Chr10: 102837395	GT	Heterozygous	60

Global activity: 60%

DHEA/Testosterone  
Production Enzyme activity



## GENETIC ANALYSIS RESULTS of Estrogen receptors / Osteoporosis

**Role:** Steroid hormones are a group of hormones that are synthesized from cholesterol.

Sensitivity of steroid receptors, such as estrogen, is associated with polymorphisms in the ESR1, ESR2 genes.

These genes encode receptors that interact with hormones and can affect various physiological processes.

**Key Enzymes:** ESR1: This polymorphism can affect the expression of estrogen receptor and is associated with the risk of development of various diseases, such as prostate cancer and osteoporosis.

ESR1: This polymorphism can also affect the function of the estrogen receptor and is associated with the risk of cardiovascular disease, prostate cancer, dyslipidemia, hypertension, obesity, and cognitive brain function.

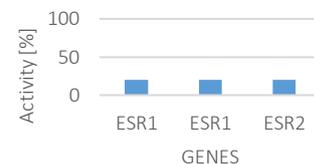
ESR2: Polymorphism in the ESR2 gene can affect sensitivity to estrogen and is associated with the risk of cancer. ESR2 is activated by estrogen, with generally anti-cancer effects. This genotype has more risk of cardiovascular, metabolic condition.

Genotypes and activity of Sensitivity of estrogen receptors

GENES	Genomic Coordinates	Genotype	Zygoty	Enzyme activity
ESR1	Chr6: 151842246	GG	Homozygous	20
ESR1	Chr6: 151842200	CC	Homozygous	20
ESR2	Chr14: 64233098	TT	Homozygous	20

Global activity: 20%

Sensitivity of Estrogen receptors  
Enzyme activity



## Method

DNA was extracted from a cheek swab sample in accordance with the kit manufacturer's instructions. Genotyping was performed using Agena's MassARRAY © System. In a first step, raw results were analyzed using the MassARRAY Report software. In a second step, this report was generated using proprietary scripts.

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