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OMGENO

Genetics for people

Genetic Testing
Diabetes

# My Prevention

# DIABETES

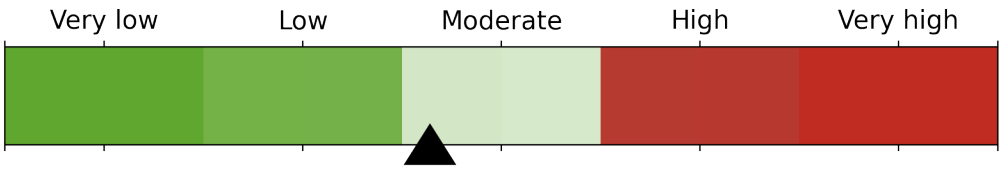
# TYPE 2 DIABETES

## 1- Information on Type 2 Diabetes

**Type 2 diabetes** does not have an immunological origin and is characterised by a slow development of the disease, which is why it is usually diagnosed in adults. The development or onset of this disease is favoured by some risk factors such as family history (**genetic inheritance**), (diets rich in saturated and polyunsaturated fats or hypercaloric diets), high levels of cholesterol in the blood (hyperlipidaemia), high blood pressure or overweight, since the increase in fat makes it difficult for the body to make correct use of insulin; among others.

## 2- Your genetic predisposition to develop Type II Diabetes

Here is your genetic predisposition to develop type 2 diabetes:




**Your conclusion**

You have a moderate genetic predisposition to develop type 2 diabetes, based on the variants analysed and the sub-processes considered (such as the different processes involved in insulin resistance or insulin uptake, among others). On the following page you will find more information about the genetic impact of the sub-processes analysed.

Remember that type 2 diabetes is highly influenced by environmental factors. For example, a sedentary lifestyle and being overweight, among others. Therefore, we recommend you to practice physical activity, watch your diet and avoid excesses in order to prevent complications in the possible development of the disease.

## 3- Metabolic processes related to Type II Diabetes

Type 2 diabetes can be mainly caused by the disruption of three processes:

1. **Reduced insulin sensitivity.** Insulin sensitivity is your body's ability to process the signals transmitted by insulin and carry out its function. If this process is impaired, your body will not be able to pick up the signals transmitted by insulin and, therefore, an excess of glucose will be generated in the blood because it cannot be captured by the corresponding cells.
2. **Reduced insulin production.** Insulin production is the process whereby cells in the pancreas make insulin and release it into the blood so that it can do its job. If this process is disrupted and not enough insulin is produced, the signal produced by insulin is not transmitted and the cells cannot take up the glucose in the bloodstream.
3. **Increased insulin degradation.** Insulin degradation refers to its removal. Currently, only the gene *CELA2A* has been described as involved in this cause. If this process is increased, the result is similar to having low insulin sensitivity.

**Why is there no mention of INCREASED INSULIN RESISTANCE in the report?**

Because there are multiple processes, such as oxidation or inflammation, among others, that influence insulin resistance. However, all these processes are taken into account in the algorithm for calculating the overall predisposition to develop type 2 diabetes, so there is no added value in including them in a separate process.

## 4- Your genetic profile associated with these metabolic processes

Below is the impact that your genetic profile has on different processes involved in the onset and development of type 2 diabetes.

| PROCESS | GENETIC IMPACT |
|---|---|
| **REDUCED INSULIN SENSITIVITY** | ● ○ ○ |
| **REDUCED INSULIN PRODUCTION** | ● ○ ○ |

● ○ ○ Normal ● ● ○ Moderate ● ● ● High

# MODY

## 1- Information on MODY

**MODY** or Maturity Onset of the Diabetes in Young, is a type of diabetes that usually occurs at an early age, before reaching 25 years old. MODY is a **monogenic** disease, which means its genetic origin is due to the presence of mutations in a single gene that affects the development of the beta-pancreatic cells responsible for the production of insulin. The main difference with type 2 diabetes is that the latter is caused by a large number of mutations in different genes.

Broadly speaking, the main characteristics of this disease are: autosomal dominant inheritance (strongly transmitted from parents to children), diagnosis usually made before the age of 25, absence of autoimmunity against beta-pancreatic cells, no insulin resistance and some capacity for insulin secretion in the pancreas.

There are currently 14 known subtypes of MODY, each associated with mutations in a single gene. Of these subtypes, 9 are the most common, although all 14 subtypes have only been diagnosed in 1-2 % of people with a diagnosis of diabetes.

## 2- Your result

Your genetic risk associated with the most common MODY subtypes is shown below:

| ANALYSED GENE | MODY SUBTYPE | GENOTYPE |
|---|---|---|
| **HNF4A** | **Subtype 1** | ● |
| **GCK** | **Subtype 2** | ● |
| **HNF1A** | **Subtype 3** | ● |
| **PDX1** | **Subtype 4** | ● |
| **HNF1B** | **Subtype 5** | ● |
| **KLF11** | **Subtype 7** | ● |
| **BLK** | **Subtype 11** | ● |
| **ABCC8** | **Subtype 12** | ● |
| **KCNJ11** | **Subtype 13** | ● |

CAPTION: Non-risk homozygote ● Risk heterozygote ● Risk homozygote ●

## 3- Your conclusion

According to your results, you **do not present risk to develop any of the analysed subtypes of MODY**. If you present any symptom that alerts you of its presence, it is advisable for you to consult a specialist doctor and inform them of your results. You will find more information in the **Diabetes Information** annex.

# PHARMACOGENETICS OF DIABETES

Diabetes is a serious disease that, if left untreated, can lead to other conditions such as heart problems, liver disease, neuropathies, among others. For all these reasons, it is essential that once the diagnosis has been made, appropriate treatment is applied to avoid the appearance of side effects derived from this disease.

Below you will find the most commonly used drugs in the treatment of type 2 diabetes **with clinical annotations** regarding the influence of genetics on the drug's activity, transport and/or metabolism. Drugs do not act in the same way for everyone, and genetics helps us to understand these differences.

## Pharmacogenetic results and recommendations

The following tables show all medicines, the single nucleotide polymorphisms (SNPs) of each gene that interact with them, the possible genotypes of each SNP (normal and risk), and the patient's genotype for each SNP.

In addition, the column "Level of evidenceïndicates the maximum level of evidence for the drug-gene variant combination (1A, 1B, 2A, 2B, 3) from the Pharmacogenomics Knowledge Base (PharmGKB), the Medicine Agencies (U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), the two main medicines regulatory agencies in the US and Europe, respectively) and International Pharmacogenetics Consortia (mainly CPIC, DPWG). This column also includes the affected parameter: [**E**]Efficacy, [**D**]Dosage, [**T**]Toxicity, [**ME**]Metabolism, [**PK**]Pharmacokinetics and [**O**]Other.

Finally, there are specific recommendations based on the guidelines in the PharmGKB database for those SNPs affected.

Your genetic compatibility for each of the drugs tested is shown below. In the table your drug compatibility is represented by a circle with three possible colours:

- red: The patient has at least one genetic risk variant with level of evidence 1 and 2.
- yellow: The patient has at least one genetic risk variant with level of evidence 3.
- green: The patient does not have any genetic risk variants for this medicine.

### 1- Biguanidas

Drugs that help to slow down the production of glucose (sugar) by the liver, helping its entry into the cells:

#### Metformina

| Gene | SNP | Possible Genotypes | | Result | Observations | Level of evidence |
|---|---|---|---|---|---|---|
| | | Normal | Risk | | | |
| AMHR2 | rs784892 | GG, GA | AA | GG | - | 3: Pk |
| CAPN10 | rs3792269 | AA | AG, GG | AA | - | 3: E |
| FMO5 | rs7541245 | CC | CA, AA | CC | - | 3: E |
| KCNJ11 | rs5219 | CC | CT, TT | TC | Increased likelihood of treatment failure | 3: E |
| SLC22A1 | rs628031 | GG | AG, AA | GG | - | 3:E |
| | rs12208357 | CC, CT | TT | CC | - | 3:Pk |
| | rs2282143 | CC | CT, TT | CC | - | 3:Pk |
| | rs594709 | AA, AG | GG | AA | - | 3:E |
| | rs622342 | AA | AC, CC | AA | - | 3:E |
| SLC22A2 | rs316019 | CC | CA, AA | CC | - | 3: O |
| SLC22A3 | rs8187725 | CC | CT, TT | CC | - | 3:Pk |
| | rs2076828 | CG | CC, GG | CC | Decreased response | 3:E |
| SLC47A1 | rs2289669 | AA | GA, GG | GG | Decreased response | 3:E |
| SLC47A2 | rs12943590 | AG, AA | GG | GA | - | 3: Pk |
| | rs34834489 | AG, AA | GG | GA | - | 3:Pk |
| AMHR2 | rs784888 | GG | GC, CC | GG | - | 3:E, Pk |
| | rs578427 | TT | CT, CC | CT | Consider dose reduction. Moderate risk of toxicity | 3: Pk |

**Most common side effects:** Diarrhoea, indigestion, nausea or vomiting, bloating, weakness, headaches.

### 2- DPP-4 inhibitors

These drugs help your body release more insulin.

#### Sitagliptin

| Gene | SNP | Possible Genotypes | | Result | Observations | Level of evidence |
|---|---|---|---|---|---|---|
| | | Normal | Risk | | | |
| GLP1R | rs6923761 | GG | GA, AA | GG | - | 3: E |

**Most common side effects:** Upper respiratory tract infections and headaches.

### 3- Meglitinides

This group of drugs is used to generate more insulin at mealtimes.

#### Repaglinide

| Gene | SNP | Possible Genotypes | | Result | Observations | Level of evidence |
|---|---|---|---|---|---|---|
| | | Normal | Risk | | | |
| CYP2C8 | rs10509681 | TT | TC, CC | TT | - | 3:O |
| | rs11572080 | CC | CT, TT | CC | - | 3:D |
| IGF2BP2 | rs4402960 | TG,TT | GG | GG | Decreased response | 3:E |
| | rs1470579 | AA | AC, CC | AA | - | 3: E |
| KCNQ1 | rs2237895 | AC, CC | AA | AC | - | 3:E |
| | rs2237892 | CT, TT | CC | CC | Decreased response | 3:E |
| NEUROD1 | rs1801262 | TT, CT | CC | CC | Reduced efficacy | 3: E |
| NOS1AP | rs10494366 | TT | GT, GG | GT | Reduced efficacy | 3: E |
| NR1I2 | rs2276706 | GA | GG, AA | GG | Decreased metabolism | 3:O |
| | rs3814058 | TC | TT, CC | TC | - | 3:O |
| SLCO1B | rs2306283 | AA | GA, GG | AG | - | 3:O |
| | rs4149056 | TC | TT, CC | TT | Decreased response | 3:E |
| SLC30A8 | rs13266634 | CT, TT | CC | CC | Decreased response | 3: E |
| TCF7L2 | rs290487 | TT | CT, CC | CC | Decreased response | 3: E |
| PAX4 | rs114202595 | AA, GA | GG | GG | Reduced efficacy | 3: E |

**Most common side effects:** Hypoglycaemia (low blood sugar levels).

### 4- Sulfonylureas

These drugs help your body produce more insulin.

#### Glimepiride

| Gene | SNP | Possible Genotypes | | Result | Observations | Level of evidence |
|---|---|---|---|---|---|---|
| | | Normal | Risk | | | |
| NOSA1P | rs10494366 | GG | GT, TT | GT | Higher risk of side effects | 3: T |

#### Glipizide

| Gene | SNP | Possible Genotypes | | Result | Observations | Level of evidence |
|---|---|---|---|---|---|---|
| | | Normal | Risk | | | |
| NOSA1P | rs10494366 | GG | GT, TT | GT | Higher risk of side effects | 3: T |

**Most common side effects:** Hypoglycaemia, weight gain, headaches and dizziness.

### 5- Thiazolidinediones

Drugs that help the body's cells use glucose.

#### Pioglitazona

| Gene | SNP | Possible Genotypes | | Result | Observations | Level of evidence |
|---|---|---|---|---|---|---|
| | | Normal | Risk | | | |
| ADIPOQ | rs2241766 | TG, GG | TT | TG | - | 3: E |
| PPARG | rs1801282 | CG, GG | CC | CC | Decreased response | 3: E |
| PTPRD | rs17584499 | CC | CT,TT | CT | Decreased response | 3: E |

#### Rosiglitazone

| Gene | SNP | Possible Genotypes | | Result | Observations | Level of evidence |
|---|---|---|---|---|---|---|
| | | Normal | Risk | | | |
| LPIN | rs10192566 | CG, GG | CC | CG | - | 3: E |
| PAX4 | rs6467136 | AA, GA | GG | AG | - | 3: E |
| PLIN1 | rs894160 | TT | CT, CC | CC | Higher risk of side effects | 3: T |
| SLCO1B1 | rs4149056 | TC, CC | TT | TT | Decreased response | 3: E |

**Most common side effects:** Anaemia, fluid retention, weight gain, upper respiratory tract infections and heart failure.

# ANNEX 1: ANALYSED GENES

| Genes analysed for type 2 diabetes | | | | | | |
|---|---|---|---|---|---|---|
| (1) GCK* | (2) HNF4A* | (4) ALMS1 | (4) CELF1 | (4) GPD2 | (4) RAI1 | (4) USP3 |
| (1) INS* | (2) IL6* | (4) ANKH | (4) CENPW | (4) HERC2 | (4) RASGRP1 | (4) WRN |
| (1) INSR* | (2) INS* | (4) APOE | (4) CERKL | (4) HMGA1 | (4) RETN | (4) WSCD2 |
| (1) PNPLA3* | (2) KCNJ11* | (4) ARAP1 | (4) CLRN1 | (4) HNF1B | (4) RP1 | (4) XRCC4 |
| (1) PPARG* | (2) PAX4* | (4) ARL15 | (4)CMIP | (4) JADE2 | (4) RPSAP52 | (4) ZBED3-AS1 |
| (1) PRKCQ* | (2) PDX1* | (4) ARL3 | (4) COBLL1 | (4) JAZF1 | (4) RREB1 | (4) ZC3H4 |
| (1) PTPN2* | (2) SLC2A2* | (4) ATP1B2 | (4) CRB1 | (4) JADE2MAEA | (4) SAG | (4) LINC00824 |
| (1) RPE65* | (2) SLC30A8* | (4) BCL2 | (4) CRHR2 | (4) KIZ | (4) SCAPER | (4) LOC101927502 |
| (1) ZFP36L1* | (2) TCF7L2* | (4) BEND3 | (4) CYP19A1 | (4) LIPC | (4) SCYL1 | (4) LOC105369705 |
| (2) ABCC8* | (2) WFS1* | (4) BEST1 | (4) DGKB | (4) LMNA | (4) SLC12A3 | (4) LOC105370275 |
| (2) ADCY5* | (4) ABCA4 | (4) BLM | (4) DMXL2 | (4) MAP2K5 | (4) SNRPN | (4) LOC105375508 |
| (2) G6PC2* | (4) ABO | (4) C5orf67 | (4) EYS | (4) MAPK8IP1 | (4) ST6GAL1 | (4) LOC105378980 |
| (2) GCK* | (4) ADCY5 | (4) CCND2 | (4) FAM234A | (4) MERTK | (4) TUB | |
| (2) GIPR* | (4) AHI1 | (4) CDKAL1 | (4) FTO | (4) PTH1R | (4) UBE2E2 | |
| (2) HNF1A* | (4) AKAP6 | (4) CDKN1B | (4) GCKR | (4) PWRN1 | (4) USH2A | |

(1) Reduced insulin sensitivity

(2) Reduced insulin production

(3) Increased insulin degradation

(4) Miscellaneous

*Involved in more than one process

# ANNEX 2: DIABETES TEST DESCRIPTION

**Diabetes mellitus**, more commonly known as diabetes, is a disease or set of diseases that affects the way the body uses blood glucose. All types of diabetes are associated with an excess of glucose in the blood (hyperglycaemia) caused by a disturbance in the function of insulin. Insulin is the hormone that tells the body when we have eaten and therefore can and must take up the glucose in the bloodstream. A disruption in this insulin-mediated signalling process leads to high blood sugar levels and the development of future health problems. Despite having a common outcome, the underlying cause is different and varies according to the type of diabetes.

According to the underlying cause it is possible to classify diabetes into its two most common forms:

**Diabetes type 1:** also known as autoimmune diabetes, is characterised by the production of antibodies by the body, which attack and destroy the beta-pancreatic cells responsible for insulin production. People diagnosed with this type of diabetes are insulin-dependent and it is a chronic form of the disease. Type 1 diabetes has a genetic component that favours its onset and development. However, the full genetic profile of markers involved is unknown.

**Diabetes type 2:** is the most common form of the disease and can be caused mainly by impaired insulin production or uptake, although the origin of insulin deficiency varies widely. Type 2 diabetes has a chronic variant, as well as other reversible forms of the disease, such as pre-diabetes or gestational diabetes, which occurs in pregnant women. The origin of this disease is multifactorial, with both genetics and environment playing an important role in the development of the disease. **Through a genetic test, it is possible to determine the genetic predisposition of a woman to the disease. genetic predisposition of a person to develop it can be determined.**

There are other less common forms of diabetes, such as MODY diabetes (Maturity Onset of the Diabetes in Young) with very similar characteristics to type 2 diabetes, but unlike type 2 diabetes, MODY diabetes is purely genetic in origin. When an individual has diabetes, it is essential to have a thorough understanding of their lifestyle and health status in order to ensure the well-being of the individual and to prevent secondary complications. It is now known that the approach to preventing or treating diabetes must be different and personalised for each individual. This difference lies in the genes, the building blocks that make each person unique, as genes contain information specific to each individual, which is of great value in designing and optimising personalised health plans according to the specific needs of each person.

## WHAT DOES THE TEST CONSIST OF?

Diabetes is a highly prevalent disease worldwide, with approximately 10.5 % of the world's adult population suffering from diabetes, of which between 85 % and 95 % of all cases are diagnosed as type 2 diabetes. On the other hand, MODY type diabetes is estimated to occur in 1 in 1000 diabetics. Despite this, an additional genetic test is needed to confirm the clinical diagnosis and to avoid errors that can lead to ineffective treatment. This test has two main objectives:

1) To identify your genetic predisposition to develop type 2 diabetes and type MODY diabetes.
2) To know your pharmacogenetic compatibility, in terms of efficacy and toxicity, with some of the most commonly used treatments for diabetes.

This knowledge will allow you to modulate and adjust your lifestyle to prevent the onset of diabetes or to carry out a more precise treatment.
To achieve these objectives, we use the power of genetic analysis using Automated Intelligence Genetics (AIG) technology, through the DNA Microarray technique, which allows us to obtain information on the genetic variants of more than 100 genes with a proven impact, according to scientific evidence, in the characterisation of diabetes and its segregation between the types of diabetes analysed.

# ANNEX 3: DIABETES INFORMATION

## 1- General characteristics

| CONDITION | TYPE I | TYPE II | MODY |
|---|---|---|---|
| Cause | Autoimmune | Multigenic | Monogenic |
| Average age at diagnosis | Children and youth | Adults | Children and youth |
| Insulin-dependent | Yes | Not normally, although there are cases that require it | Normally yes, although there are cases that do not require it |

## 2- Common symptoms

The symptoms of diabetes are very diverse and can vary between the different subtypes. The most common symptoms associated with the types of diabetes analysed are shown below:

| SYMPTOMS | | |
|---|---|---|
| Polyuria (excessive urine production) | Polyphagia (incessant sensation of hunger) | Blurry vision |
| Polydipsia (excessive thirst) | Increased urinary and genital infections | Tiredness, weakness and fatigue |

Furthermore, subtypes of diabetes may manifest more specific symptoms depending on the individual. For more information, please visit the links below.

## 3- Would you like more information?

- National Institute of Health: nih.gov
- Spanish Diabetes Federation: fedesp.es
- Center for Disease Control and Prevention: cdc.gov
- Symptomatology of monogenic diabetes (MODY): medwave.cl

# TECHNOLOGY

**DNA Microarray** technology consists of a solid surface with microscopic reactions (microreactions) or DNA chip, on which molecular probes are attached to detect the presence of target DNA molecules. Probe-target hybridization is usually detected and quantified by measuring the intensity of a given fluorescence provided by the molecular probe in samples. This type of technology allows the detection of thousands of specific DNA fragments present in a DNA sample. On the other hand, the specificity in terms of DNA sequence recognition is very high since single nucleotide exchange (single-base resolution) can be detected using short oligonucleotide probes (20-25 nucleotides). As a result, DNA Microarray technology has also evolved to be applied as a DNA sequencing technique to genotype several hundred thousand single nucleotide variants (SNVs) in target genes located throughout the genome (Whole Genome DNA Microarray).

*Bead Chip Infinium Global Screening Array Orion* (GSA Orion) is a line of DNA chips developed by Illumina for its DNA Microarray iScan platform, widely used in population genetic studies and precision medicine, providing optimized content with 100 % reliable and reproducible high-quality genotyping results. The construction of the GSA Chip was carried out in collaboration with a consortium of experts, and for the selection of SNVs, information from prestigious scientific databases such as gnomAD, NHGRI-EBI-GWAS Catalog, ClinVAr, MHC-HLA-KIR and PharmGKB has been used. The GSA allows the analysis of approximately 700,000 SNVs that cover variants of interest (hot spots) throughout the entire genome, impacting a wide range of genetic traits with physiological and pathophysiological implications. In addition, it allows the customization by users to incorporate Ad Hoc 50,000-100,000 variants of interest.

# RISK AND LIMITATIONS

The results presented in this report are limited to the scientific knowledge available at the date of development of the test. The test only detects the specified genetic variants. The recommendations described throughout this report are for guidance only. Overgenes cannot be held responsible for any misinterpretation of the data provided.

Overgenes Diabetes is not a medical report. This results should **NOT** be interpreted as a diagnostic tool, nor do they indicate whether a person has any type of diabetes; but rather inform about the individual's genetic predisposition to develop diabetes.

## Pharmacological considerations

Pharmacogenetics studies the influence of human genetics on drug activity, transport and metabolism. This allows specific drugs to be targeted to groups of patients classified according to their genetics, known as **Personalised Medicine.**

The main objective of this section is to provide a tool with a high clinical value, with an easy handling and interpretation for the medical specialist. To this end, the SNPs and drugs included in this test have been designed with their clinical usefulness and validity in mind. Therefore, the test includes those SNPs with the highest level of scientific evidence available to date for each of the target genes.

**Pharmacogenomics Knowledge Base** (PharmGKB) is the largest publicly accessible database, formed by a consortium of experts in pharmacogenomics and farmacogenetics, that is in charge of the collection, selection, incorporation and dissemination of all knowledge related to the impact of human genetic variation on drug response.

PharmGKB is funded by the National Institute of Health (NIH) and the National Institute of General Medical Sciences (NIGMS) in the United States, and is a member of the NIH Pharmacogenomics Global Research Network (PGRN). PharmGKB was established by Stanford University in 2000.

The results of this test should serve as a tool to be taken into consideration when taking personalised therapeutic decisions. Drug response is affected by other factors such as concomitant treatments with other drugs, diseases, toxic habits, age, gender, etc.

Remember there are other drugs not included and which are used on a daily basis in the treatment of type 2 diabetes. In case you have diabetes and are being treated with some of the medicines described above and have any annotation, **consult your doctor to adjust the treatment in a more personalised way**.

# GLOSSARY

- **DNA:** abbreviation for deoxyribonucleic acid. Molecule present in our cells that contains the genetic information necessary for the development and proper functioning of living organisms.
- **Allele:** each of the alternative forms of a gene, which may differ in sequence.
- **Autoimmune:** type of disease in which the immune system attacks its own healthy cells because it mistakes them for pathogens.
- **Cell:** asic structural and functional unit of life.
- **Beta-pancreatic cell:** type of cell found in the pancreas in charge of insulin production.
- **Phenotype:** set of observable characteristics of an organism.
- **Gene:** segment of DNA that represents the unit of hereditary information.
- **Genotype:** combination of genetic variants in an individual.
- **Glucagon:** hormone produced in the pancreas that increases blood glucose levels by counteracting the effects of insulin.
- **Glucose:** type of sugar of simple composition obtained through the consumption of food.
- **Haplotype:** set of DNA variations, or polymorphisms, that tend to be inherited together.
- **Heterozygote:** two different alleles for a gene.
- **Homozygote:** two identical alleles for a gene.
- **Insulin:** hormone produced in the pancreas that lowers blood glucose levels, counteracting the effects of glucagon.
- **Metabolism:** set of chemical processes occurring within a cell or organism that serve to produce energy or use it as fuel.
- **Mutation:** nucleotide sequence variation in genes affecting less than 1% of the population.
- **Polymorphism:** nucleotide sequence variation in genes affecting ≥1% of the population.
- **Genetic predisposition:** also called genetic susceptibility. It is the increased likelihood of developing a certain condition or pathology due to the presence of one or more genetic variations.
- **SNP:** single nucleotide polymorphisms.

Genetics for people

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