

Effect of Genetic Polymorphism in TNF on the Severity of Rheumatoid Arthritis

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Polymorphisms

- ▶ Polymorphisms are defined as variations in the genome that occur at a frequency of **at least 1%** in the human population.
- ▶ Polymorphism has major contribution to the disease risk, genetic predisposition and susceptibility.
- ▶ In contrast, mutations occur **in less than 1%** of the population and cause **inherited diseases** such as cystic fibrosis, hemophilia, and Huntington's disease.

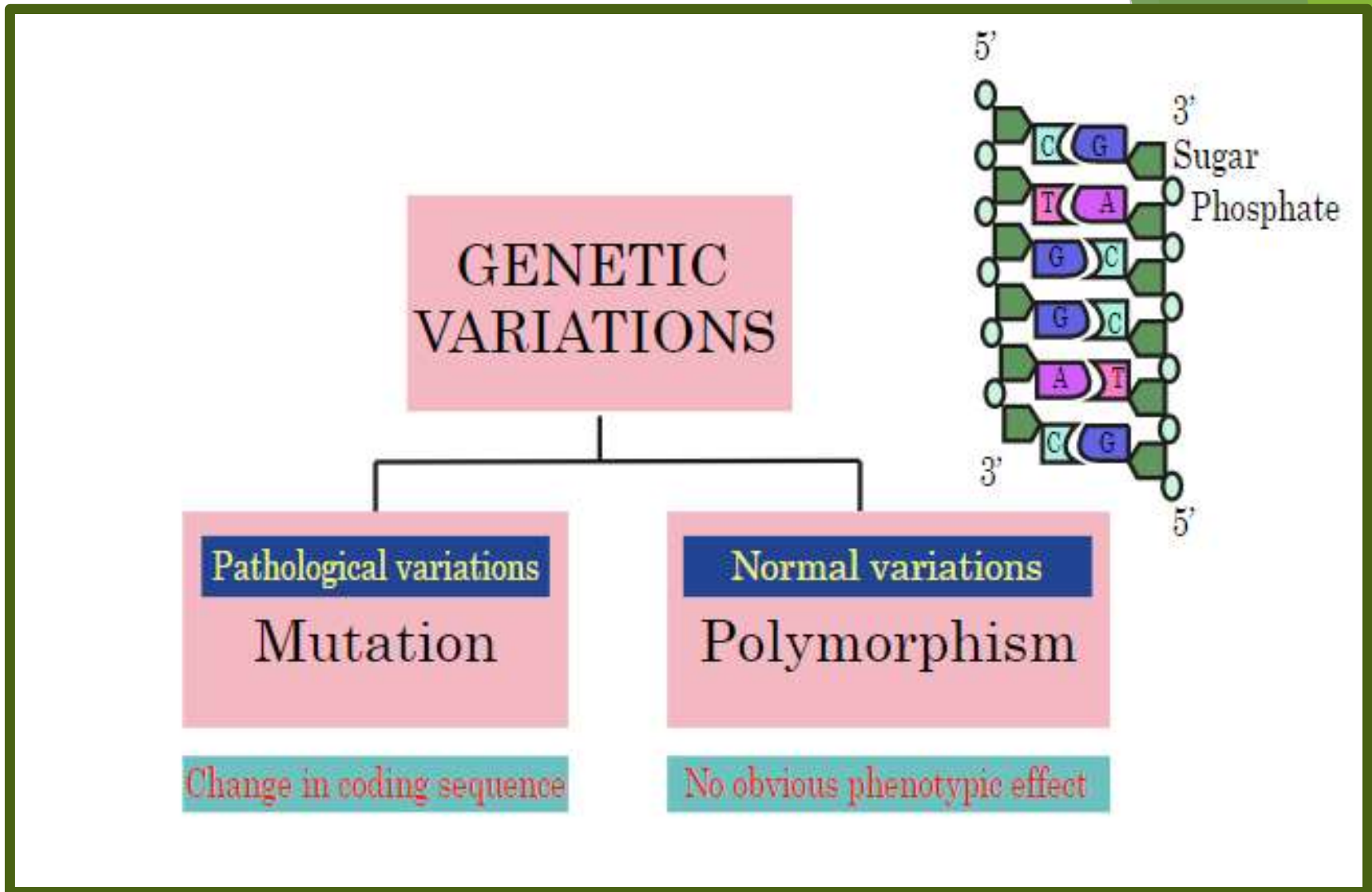


Figure 1: genetic variation

- ▶ Single-nucleotide polymorphisms (SNPs) are the most common genetic variations in human DNA, occurring **once approximately every 300 base pairs**.
- ▶ More than **20 million** SNPs have been mapped in the human genome.
- ▶ SNPs occur when one nucleotide base pair replaces another.
- ▶ **Guanine (G)** may change to **Adenine (A)**
- ▶ **Cytosine (C)** may to change **Thiamine (T)**

SNPs nomenclature

- ▶ SNPs can be presented by different ways, however the most common ways are
- ▶ SNPs either presented as **rs###**, uses the prefix "rs", for "reference SNP", followed by a number.
- ▶ Or by the gene name followed by codon number then nucleotide undergo substitution. example **TNF –308 G>A**

Codon	13	14	15	16	17	18	19
Nucleotide	...GCA	CCC	AAT	<u>A</u> GA	AGC	CAT	GCG...
Amino acid	Ala	Pro	Asn	Arg	Ser	His	Ala
				↓ A to G SNP			
Codon	13	14	15	16	17	18	19
Nucleotide	...GCA	CCC	AAT	<u>G</u> GA	AGC	CAT	GCG...
Amino acid	Ala	Pro	Asn	Gly	Ser	His	Ala

Figure 2: single nucleotide polymorphisms

► Nucleotide substitution results in two possible alleles.

1. **Normal or wild type allele:** the most commonly occurring allele or the allele originally sequenced.

2. **The variant allele:** is the alternative allele.

■ Two identical alleles make up a **homozygous genotype**, and two different alleles make up a heterozygous genotype.

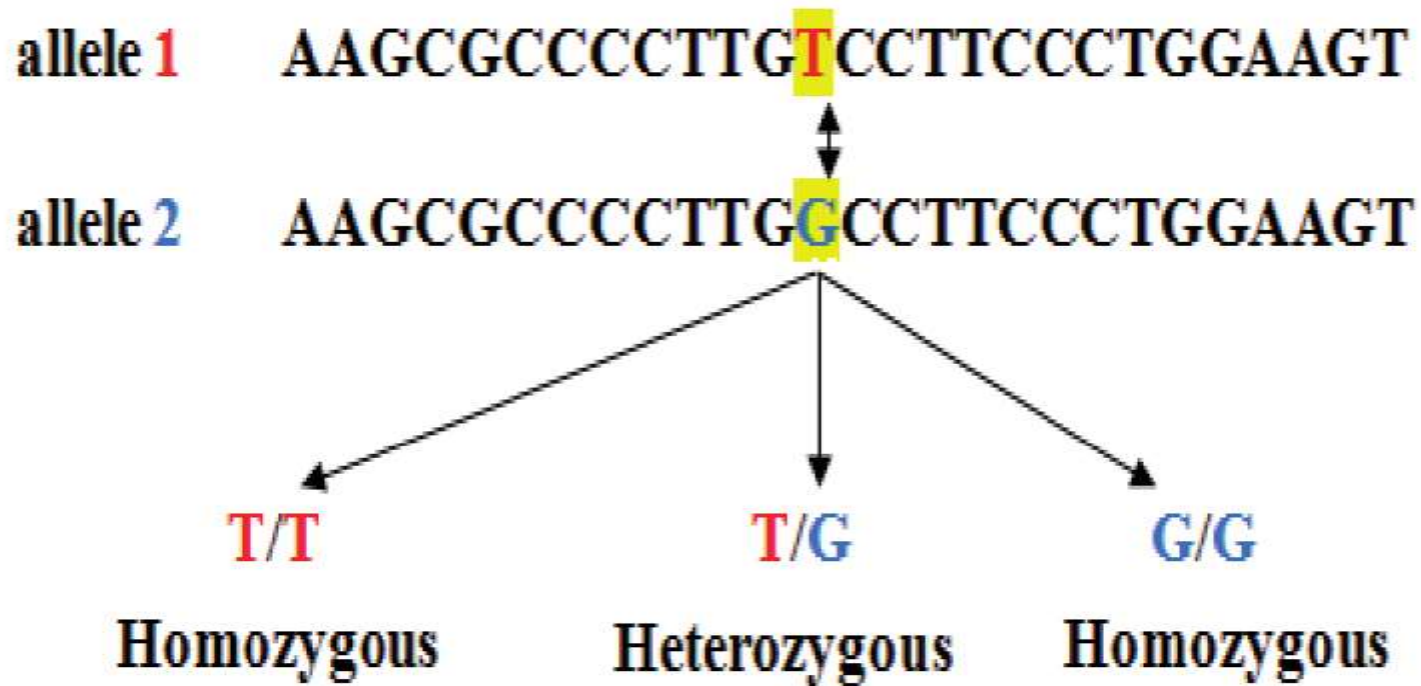


Figure 3: single nucleotide polymorphisms

- **Missense SNP:** results in the change of one amino acid for another, affecting the protein sequence coded by a gene and therefore may lead to its **dysfunction**.
- **Nonsense SNP:** Altered DNA sequence that cause a stop codon and **premature terminating** polypeptide sequence (**shorter protein**) or a stop codon is abrogated, producing an **elongated protein**.
- In both cases the function of the resultant protein was affected.

❖ **SNPs in the promoter regions:**

- ▶ Affects their activity and regulation, producing changes in gene expression levels.

❖ **SNPs in Untranslated region (UTRs) or intron regions**

Affects protein translation or the production of splice variants of transcripts, leading to longer or shorter protein sequences, respectively.

Types of SNPs and Consequences

Non-Coding Region
of DNA (in between genes)

Coding Region
of DNA (in the gene)

Non-Synonymous SNP

Synonymous SNP

Silent change. Change of codon, but **no change** of amino acid in the protein

Missense SNP

Change of codon results in a **change of 1 amino acid in the protein**

Nonsense SNP

Creates a stop codon in the gene and **results in premature truncation of the protein (incomplete protein made)**

Figure 4: Types of SNPs

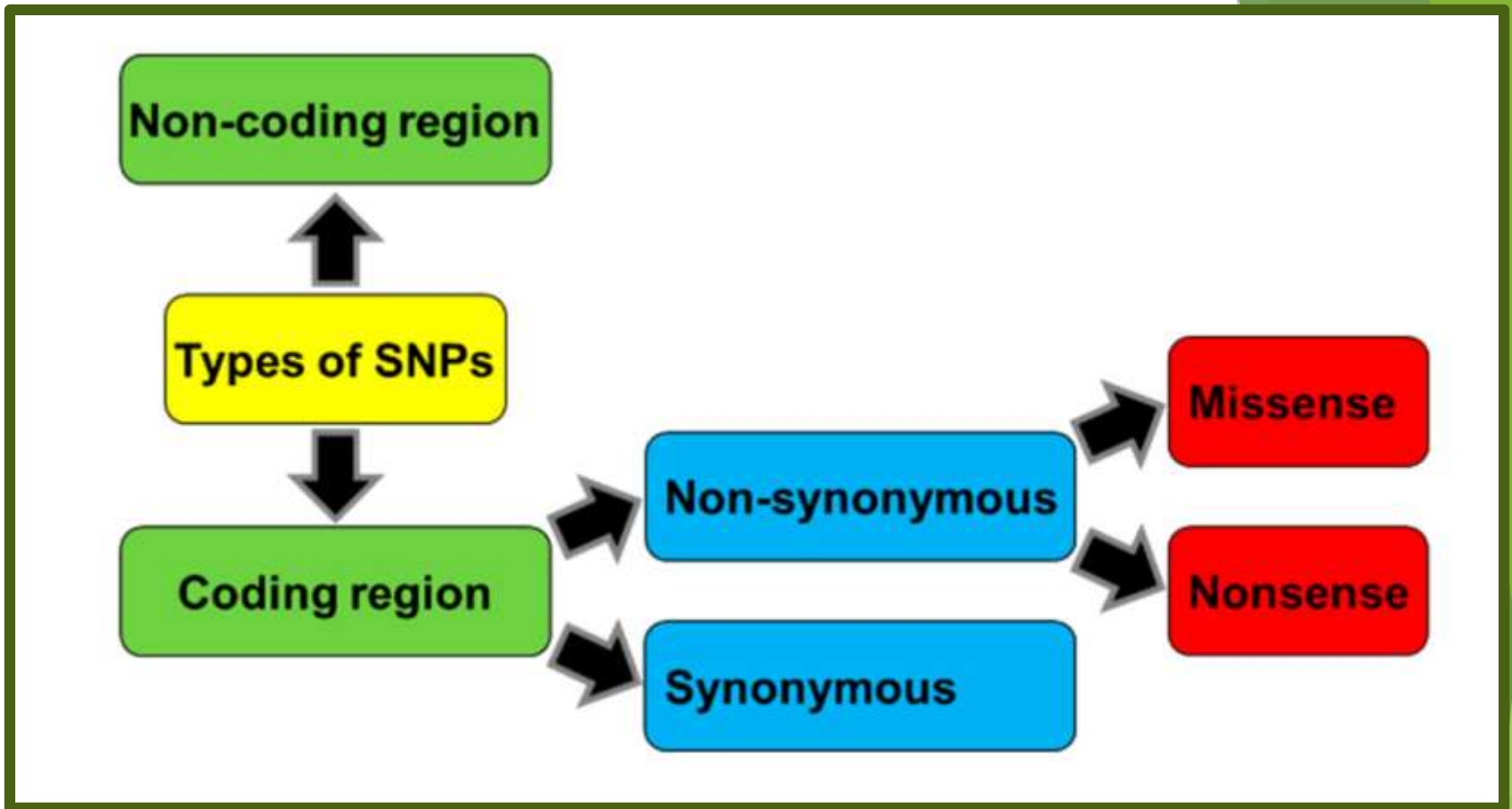


Figure 5: Types of SNPs

Rheumatoid arthritis

Rheumatoid arthritis (RA): is a chronic inflammatory autoimmune disease, which affects millions of people all around the world.

The disease first affects the synovium, resulting in synovial proliferation and inflammatory changes followed by involvement of the articular cartilage and bones.

Permanent disability occurs in **10%-20%** of the affected population.

- ▶ The clinical course of the disease is **extremely variable** ranging from **mild self limiting** arthritis to rapidly progressive **multi-system inflammation** with profound **morbidity and mortality**.
- ▶ Essentially all patients with RA exhibit some systemic features such as **fatigue**, **low-grade fevers**, anemia, and elevations of acute phase reactants like erythrocyte sedimentation rate (**ESR**) or C-reactive protein (**CRP**).

- ▶ Selection of the appropriate treatment and monitoring the disease progress is usually achieved by assessment of **disease activity**.
- ▶ The disease activity was measured either clinically by calculating the disease activity score in 28 joints (**DAS28**) and the simplified disease activity index (**SDAI**).
- ▶ or by measuring the **markers of inflammation** which includes erythrocyte sedimentation rate (**ESR**), rheumatoid factor (**RF**), high sensitive C-reactive protein (**hs-CRP**), $\text{TNF-}\alpha$, among others.

- ▶ Rheumatoid arthritis have **complex polygenicity and heterogeneity**.
- ▶ Genetics plays a significant role in determining both the **risk** of developing RA and the **severity** of the disease.
- ▶ The possibility that RA might have a genetic component was considered as long ago as 1806 by William Heberden in his book *Commentaries on the History and Cure of Diseases*

- ▶ The human leukocyte antigen (**HLA**) locus, particularly major histocompatibility complex, class II, DR beta 1(HLA-DRB1), carries the **strongest genetic risk** determinant across ethnicities. Several other genes, including Protein tyrosine phosphatase, non-receptor type 22 (**PTPN22**) and Peptidyl arginine deiminase type IV (**PADI4**), show modest association with RA, other regions associate with the **TNF- α pathway**.

- ▶ The genome-wide association (GWAS) technique allows scientists to discover hundreds of genetic risk factors for RA. There are about 100 loci in the HLA associated with RA risk.

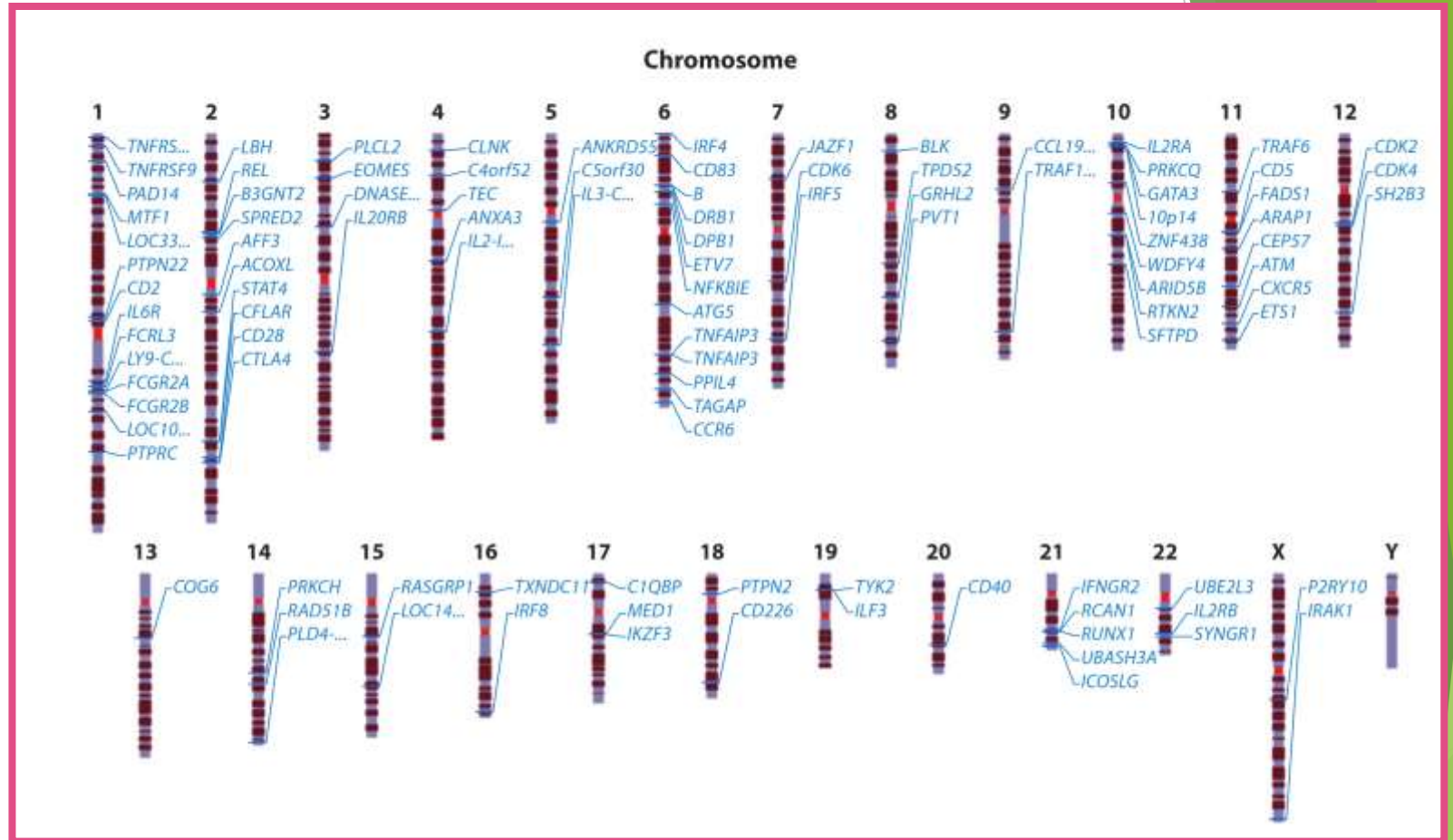


Figure 6: loci outside major histocompatibility complex associated with RA

Table 1: polymorphisms in non-human leukocyte antigen associated with rheumatoid arthritis

Gene	Polymorphism
Protein tyrosine phosphatase , non-receptor type 22	rs2476601 rs11203367 rs2488457
Peptidyl arginine deiminase 4	rs884871 rs2240340
Tumor necrosis factor, alpha-induced protein 3	rs2230926 rs5029937
Cytotoxic T-lymphocyte associated protein 4	rs231775
Signal transducer and activator of transcription 4	rs7574865
C-C motif chemokine ligand 2 (monocytes chemo-attractant)	rs1024611
Methylene tetrahydrofolate reductase	rs1801133 rs1801131 rs1800896
Interleukin-10	rs3021097 rs1800872 rs11209026
Interleukin-17	rs2275913
Transforming growth factor beta and its receptors	rs1800470 rs1800469

Tumor Necrosis Factor Alpha Gene Polymorphisms

- ▶ The gene for TNF- α (figure 7) is positioned on the **sixth chromosome** between HLA-DR and HLA-B genes in the class III zone of the MHC.
- ▶ The majority of the SNPs in TNF- α located in the *promotor region*

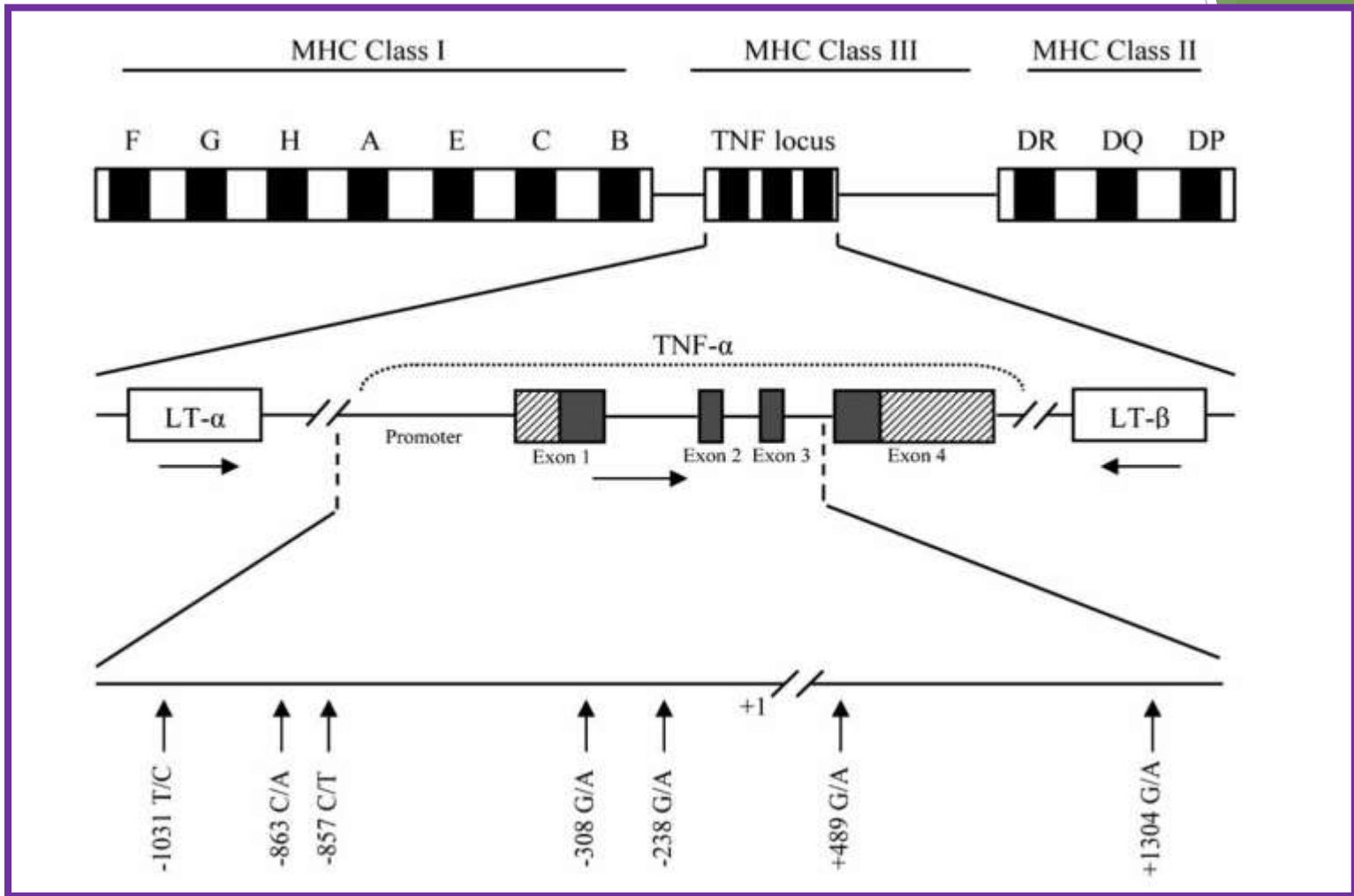


Figure 7: Tumor necrosis factor alpha gene.

Table 2: Tumor necrosis factor alpha polymorphisms in rheumatoid arthritis

Gene Symbol	Polymorphism Position	Alleles	Possible Effect of Polymorphism
TNF	+1304	G A	May contribute to the susceptibility to RA
	+489	G A	More severe erosive disease
	-238	G A	More severe articular erosions Less severe articular erosions
	-308	G A	Normal production of TNF Up-regulation of TNF production
	-857	C T	May contribute to the susceptibility to RA / High TNF production
	-863	C A	May contribute to the susceptibility to RA / High TNF production
	-1031	T C	May contribute to the susceptibility to RA / High TNF production

- ▶ The first polymorphism identified is a guanine (G) to adenine (A) transition at position -308 in TNF called rs1800629 (TNF -308 G>A).
- ▶ The presence of the A allele associated with **increase the disease activity.**
- ▶ A meta analysis include a total of (2,053) RA patients from 10 published studies, confirm that patients carrying the common GG genotype have worse radiologic outcomes.
- ▶ Also another different study showed that TNF α (-308 G>A) are associated with severity of RA.
- ▶ O’Rielly et al meta-analysis also found an association between TNF α (-308 G>A) and the severity of RA.

- ▶ For (-238 and +489) SNPs, the genotype GG is correlated with more vigorous disease.
- ▶ Multiple studies have been linked the risk for RA severity with SNPs in (-238 and +489) loci, however conflicting result founded in other studies.
- ▶ other studies showed an association between TNF- α -857 polymorphism and the susceptibility to RA and High TNF production.



**THANK YOU
FOR
LISTENING**

