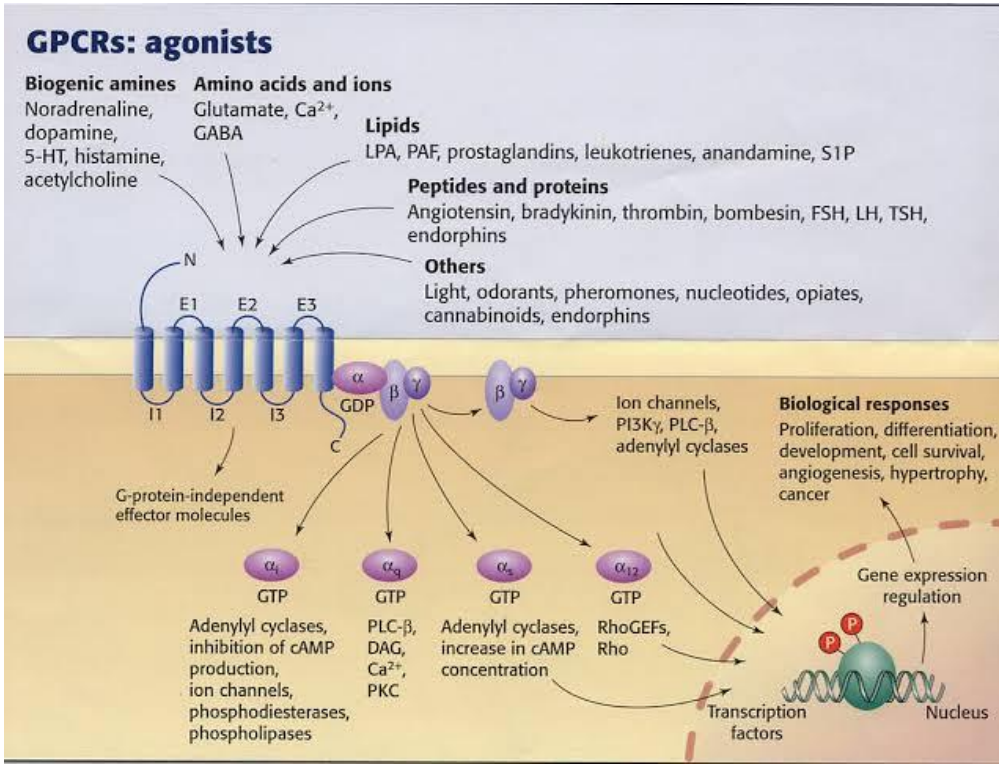
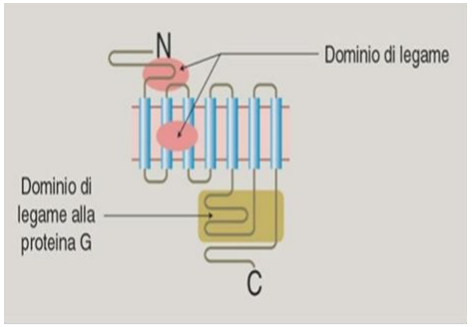
Polymorphisms in genes encoding drug targets

G protein-coupled receptors (GPCRs)





Rang HP, Dale MM, Ritter JM, Flower RJ
Farmacologia Elsevier-Masson S.r.l. (sesta edizione – 2008)

G protein-coupled receptors (GPCRs) are a large family of cell surface proteins which modulate intracellular signaling pathways via G proteins.

Structure:

- extracellular amino-terminal domain
- seven hydrophobic transmembrane α-helical structure
- intracellular carboxy-terminal domain

Approximately 40% of approved drugs target GPCRs and genes encoding them are highly polymorphic.

great variability in the responses of drugs that target these receptors.

Polymorphisms and GPCRs

The functional impact of SNPs depends on their position on the gene sequence. These sequence variations can lead to differences in drug binding, receptor activation, and downstream signaling.

For example, they can affect:

- drug binding site: SNPs may result in a reduced affinity of the drug, or variations in its potency and efficacy.
- G protein binding site: SNPs can promote, after stimulation by the agonist, preferential coupling with a selected G protein
- β-arrestins binding site: SNPs can modify receptors trafficking, increasing or reducing their internalization rate

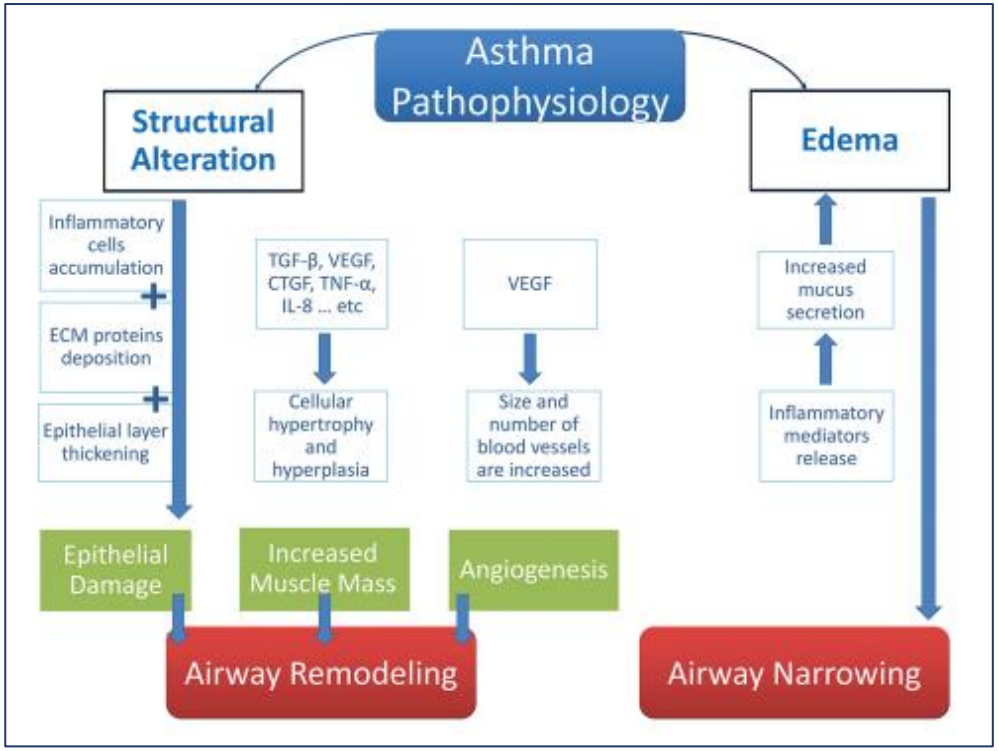
Polymorphisms and GPCRs

Genes encoding GPCRs may also contain CNVs.

Functional consequences are:

- reduced or absent therapeutic response, in the case of deletions
- abnormal therapeutic response, in the case of duplications

Polymorphisms affecting GPCRs function are also present in non-coding regions, such as regulatory regions.



Asthma therapy and polymorphisms

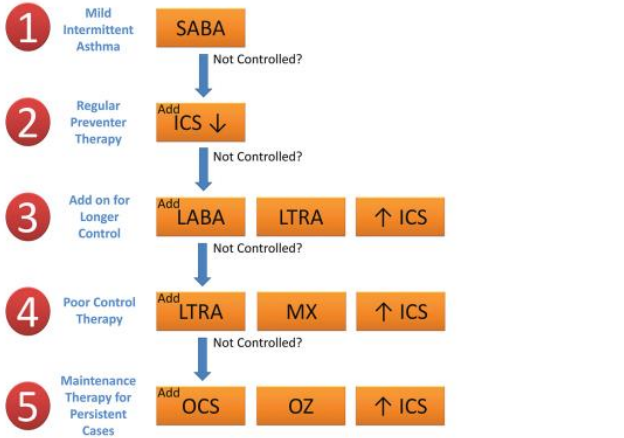
Main classes of asthma medications:

- β_2 adrenergic receptors agonists
- leukotriene receptor antagonists
- corticosteroids
- theophylline

- GPCRs polymorphisms are associated with asthma susceptibility.
- Several polimorphisms affect asthma symptoms and alter therapeutic responses.

Genetics of Allergic Asthma and Current Perspectives on Therapeutic Management
http://dx.doi.org/10.5772/63651

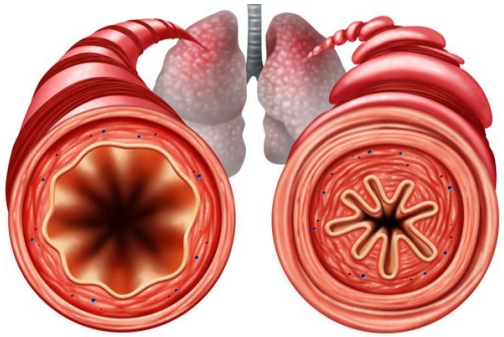
Legend:
SABA: Short acting beta agonists, ICS: Inhaled corticosteroids (arrow down = low dose, arrow up = high dose), LABA: Long acting beta agoints, LTRA: Leukotriene receptor antagonists, MX: Methylxanthines, OCS: Oral corticosteroids, OZ: Omalizumab

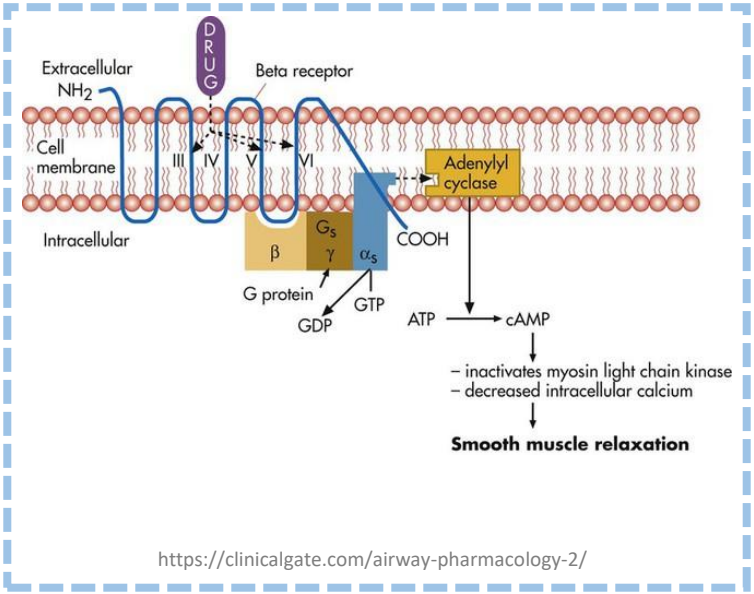


Stepwise approach for controlling asthma symptoms and minimizing future morbidity

Figure 3. Stepwise approach for controlling asthma symptoms and minimizing future morbidity.

β_2 receptors agonists





https://clinicalgate.com/airway-pharmacology-2/

β_2 receptors are highly present in airway smooth muscles: their activation results in increased intracellular cAMP levels and bronchodilation.

There is great individual variability in therapeutic response to bronchodilators (β_2 agonists): 40-70% of patients are poorly responsive.

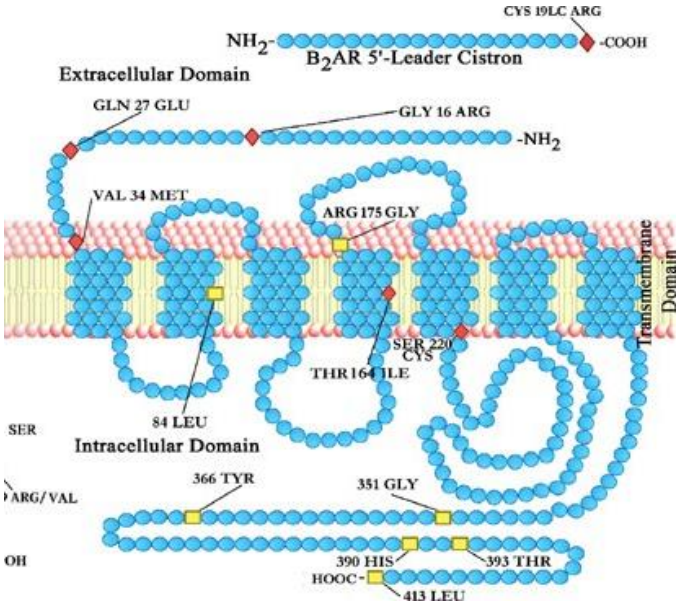
1) Development of tolerance after prolonged exposure to β_2 agonists (down-regulation of β_2 receptors)

2) **Polymorphisms**

β_2 receptors polymorphisms

Several SNPs have been identified:

- **12 SNPs in gene coding region**:
  - 5 are synonymous
  - 5 are non-synonymous and cause change in the amino acid sequence of the protein affecting the functional properties of the receptor (amino acid positions 16, 27, 34, 164, 220)
- **10 SNPs in the 5' upstream regulatory region of the gene**:
  - 1 in the sequence encoding for the Beta Upstream Peptide (BUP, 19 aa) which regulates β_2 receptor expression



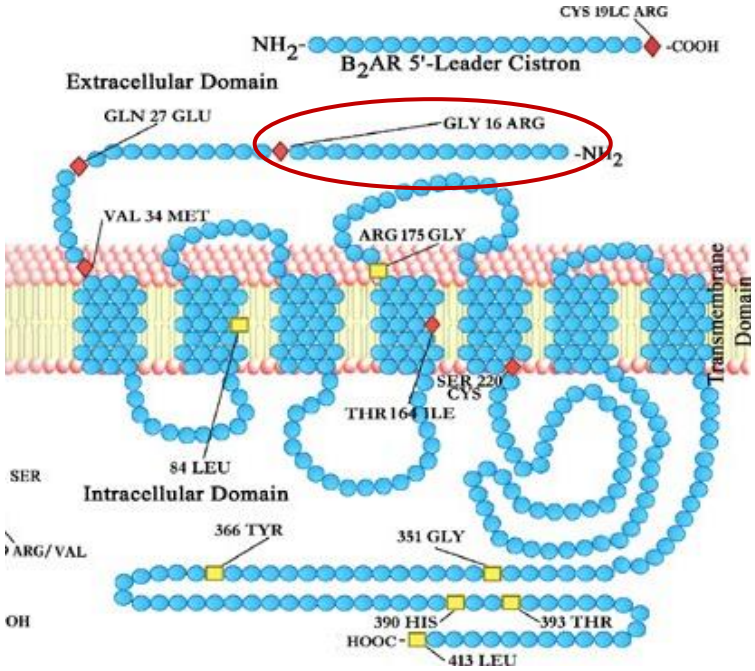
Clinically Relevant ß-receptor Single Nucleotide Polymorphisms (SNP)							
Genetic information				Population frequencies of the rare allele			
Nucleotide position	SNP	Amino acid	Common → rare allele	Caucasians	African-Americans	Asians	Latino-Hispanics
ß-1 receptor SNPs							
145	A/G	49	Ser→Gly	12-16%	13-15%	15%	20-21%
1165	C/G	389	Arg→Gly	24-34%	39-46%	20-30%	31-33%
ß-2 receptor SNPs							
- 47	C/T	- 19	Cys→Arg	35%	21%	8-12%	NR
46	A/G	16	Gly→Arg	38-46%	49-51%	54-59%	NR
79	C/G	27	Gln→Glu	35-46%	20-27%	7-20%	NR
491	C/T	164	Thr→Ile	2-4%	2-4%	0-1%	3%
ß-3 receptor SNPs							
190		64	Trp→Arg	9-13%	NR	10-19%	NR

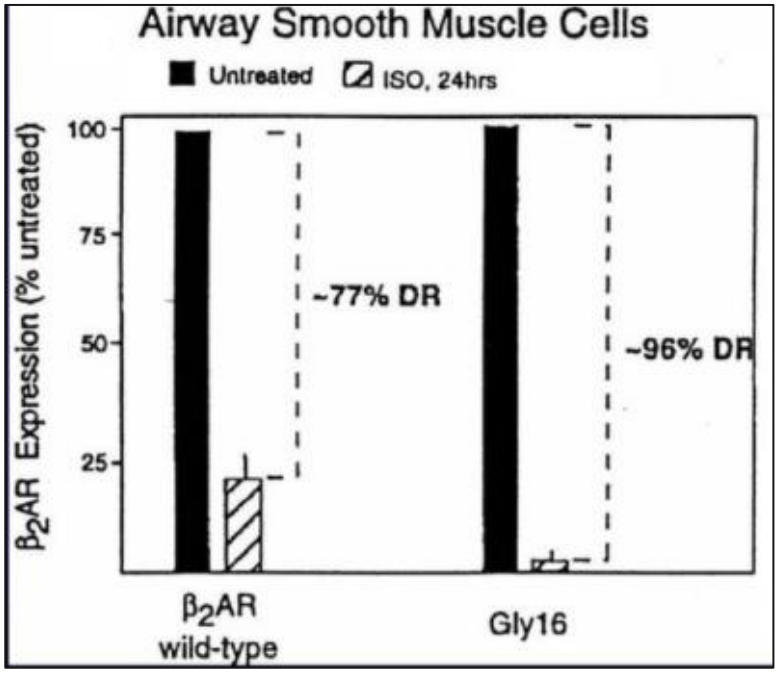
Abbreviations: A, adenine; C, cytosine; G, guanine; T, thymine; NR, not reported

Taylor, M. Pharmacogenetics of the human beta-adrenergic receptors. Pharmacogenomics J 7, 29–37 (2007).

Polymorphism at nucleotide position 46 (Arg16Gly)

It favours β_2 receptors desensitization and down-regulation after prolonged activation by β_2 agonists: lower pharmacological responses.

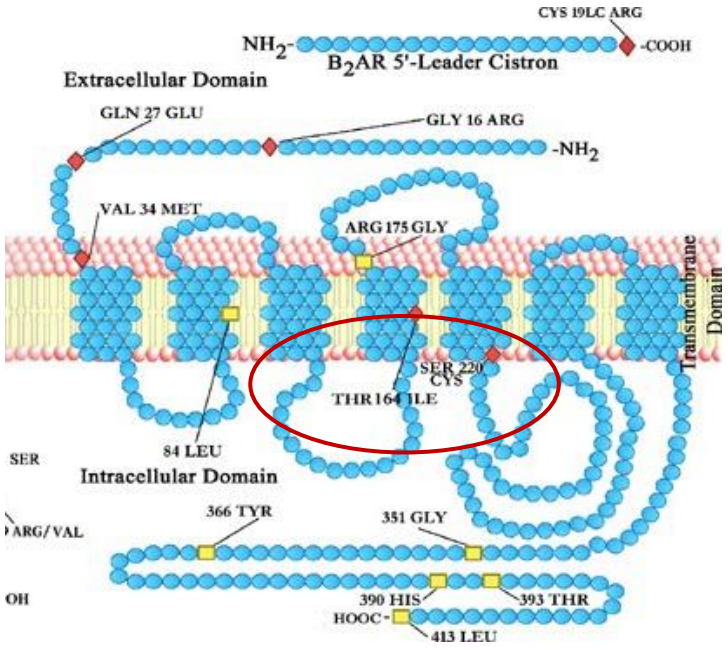


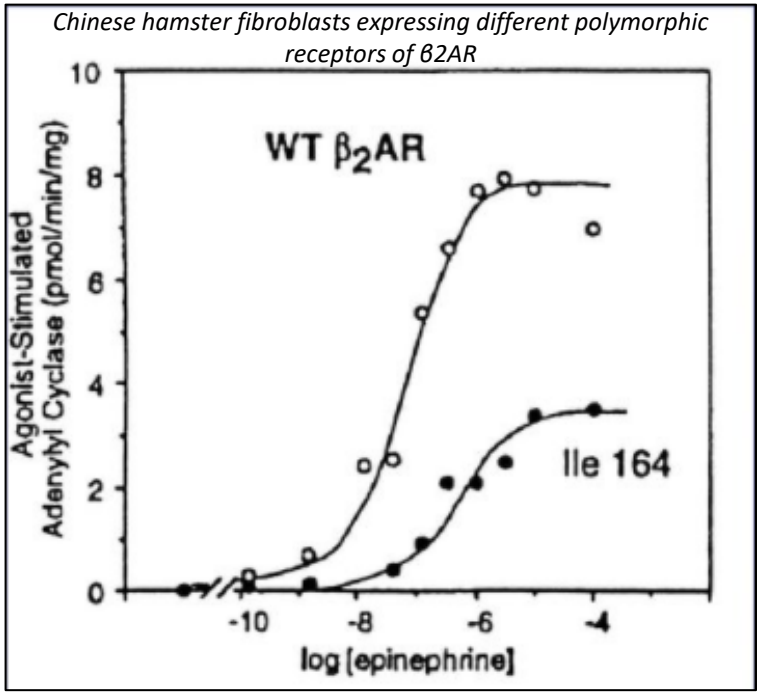


Liggett (2000) ß2-Adrenergic Receptor Pharmacogenetics

Polymorphism at nucleotide position 491 (Thr164Ile)

This polymorphism alters the receptor coupling to G_s protein, with a decrease adenylil cyclase activation.



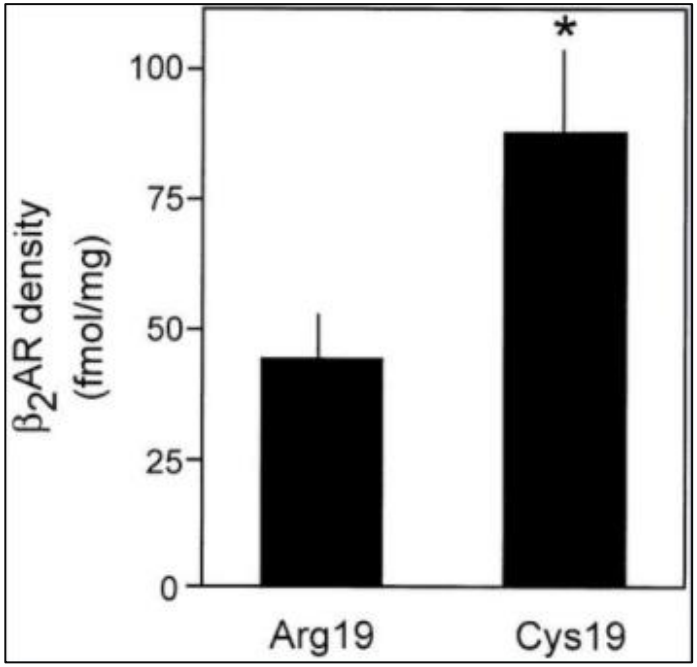


Liggett (2000) β2-Adrenergic Receptor Pharmacogenetics. Am J Respir Crit Care Med. 2000 Mar;161(3 Pt 2):S197-201

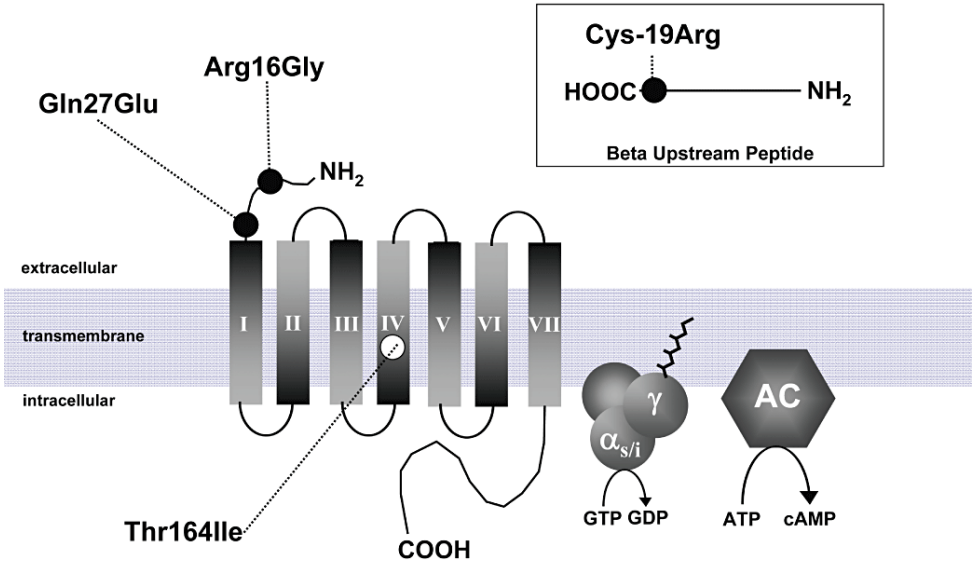
In vitro studies show a decreased noradrenaline-stimulated adenylyl cyclase activity in cells with Ile 164 substitution in β2 receptor amino acid sequence.

Polymorphism in the BUP encoding sequence (Arg19Cys)

Arginine substitution with cystein in position 19 of BUP increases the number of β2 receptors in cell membranes, causing higher pharmacological response to β2 receptor agonists.



McGraw (1998) J Clin Invest 102:1927-1932



Polymorphisms in genes encoding for leukotriene receptors (CysLTR)

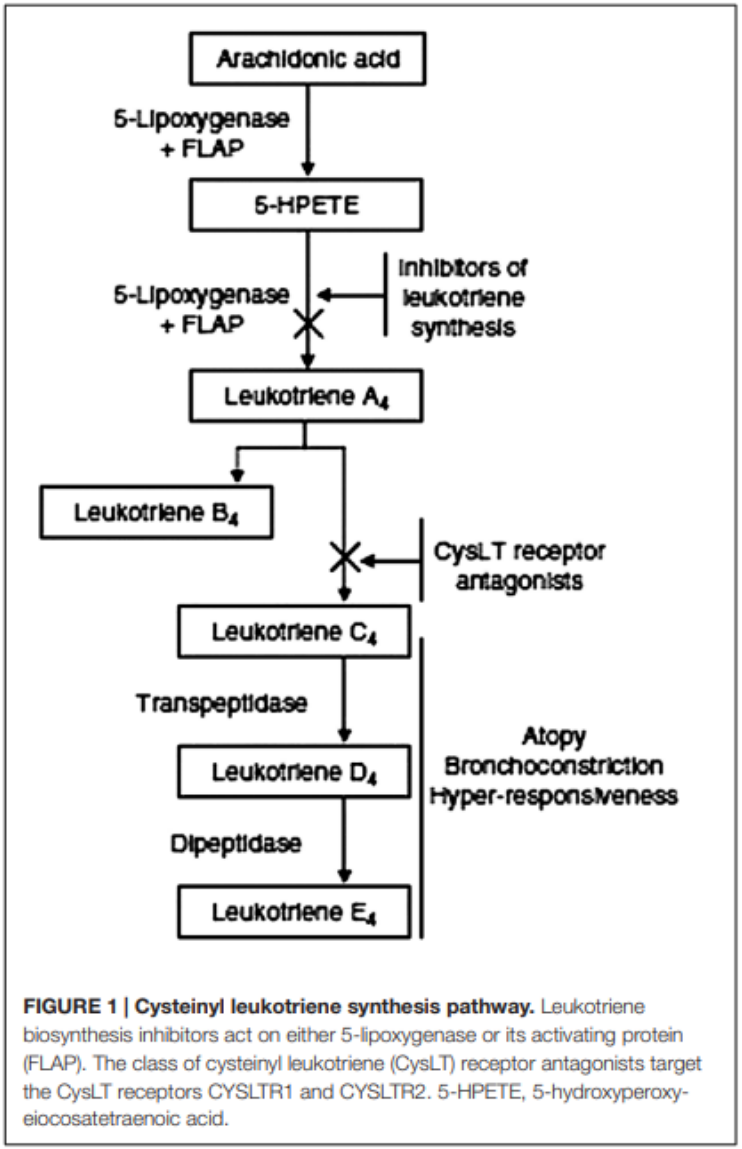


FIGURE 1 | Cysteinyl leukotriene synthesis pathway. Leukotriene biosynthesis inhibitors act on either 5-lipoxygenase or its activating protein (FLAP). The class of cysteinyl leukotriene (CysLT) receptor antagonists target the CysLT receptors CYSLTR1 and CYSLTR2. 5-HPETE, 5-hydroxyperoxy-eiocosatetraenoic acid.

Thompson et al., 2016. Frontiers in pharmacology vol. 7 299

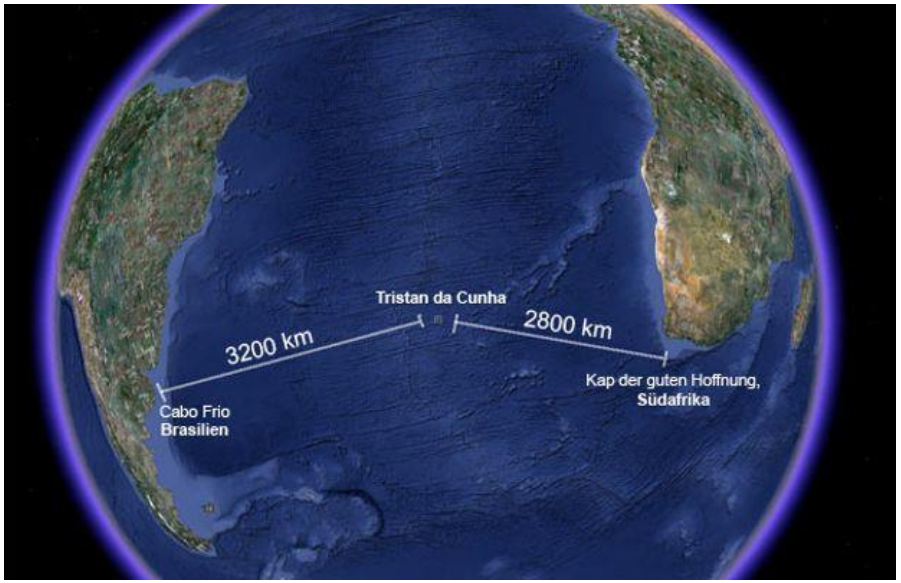
Leukotriens are important mediators of inflammation and bind two GPCRs subtypes (**$CysLTR_1$ e $CysLTR_2$**), which are both encoded by polymorphic genes.

CysLTR1 is involved in smooth muscle contraction, increased vascular permeability, and the recruitment of inflammatory cells like neutrophils and macrophages.

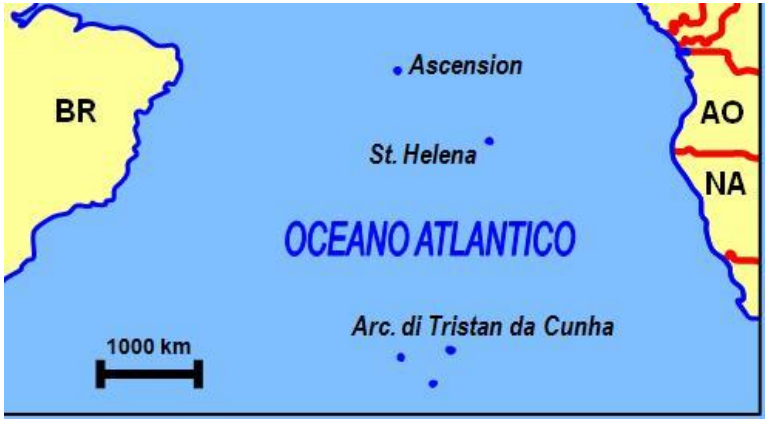
It represents the preferential target of leukotriene receptor antagonists, such as montelukast, parnlukast and zafirlukast.

20% of asthmatic patients do not respond as expected to these drugs.

CysLTR2 is not functional, but can interact with CysLTR1 and negatively regulate its function.



The population of Tristan da Cunha, a small and isolated island in South Atlantic Ocean, has a significantly higher prevalence of asthma (36%) and atopy (45%)



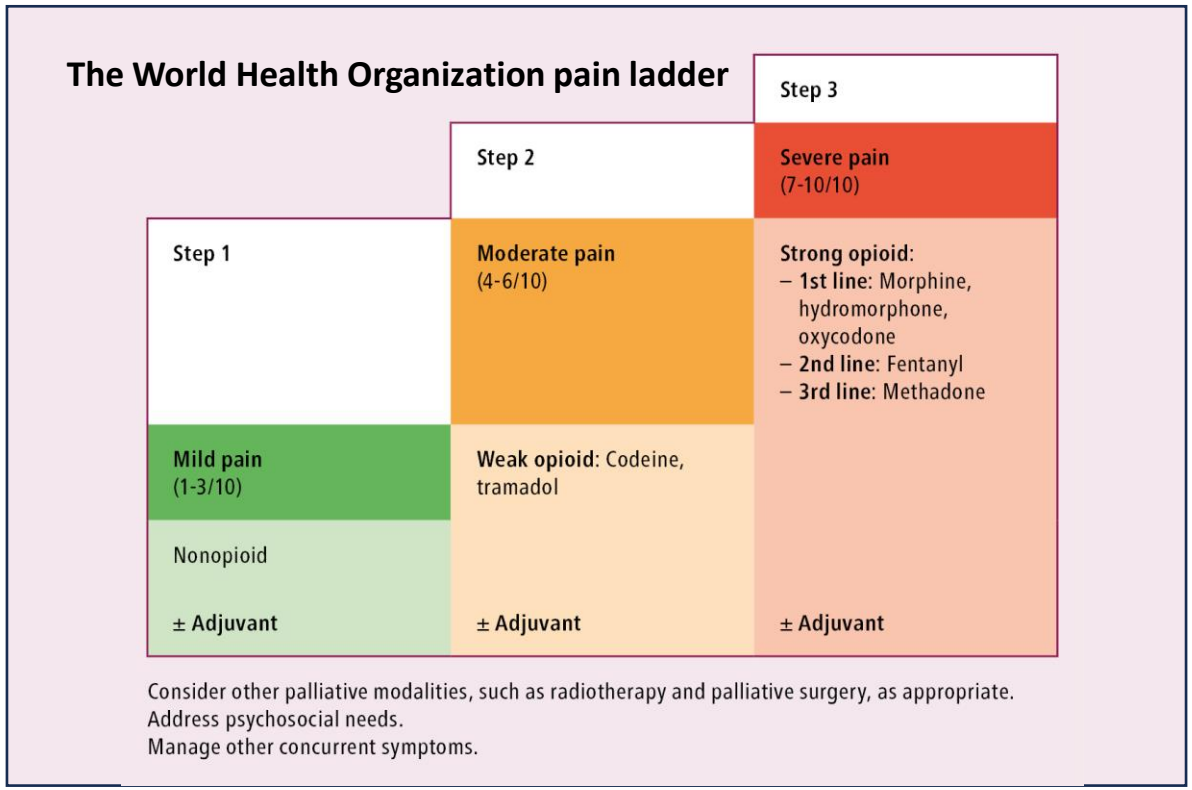
Genome-Wide Association Studies demonstrated the prevalence of the **CYSLTR1 Gly300Ser variant** in the island population, which makes the receptor more sensitive to LTD_4 and LTC_4: this hypersensitivity is associated with atopy. **$CysLTR_2$ Met201Val variant** has been also discovered, which inactivates the receptor and its inibitory control on $CysLTR_1$. These polymorphisms are often associated.

TABLE 1 | Human G-protein-coupled receptor (GPCR) variants associated with asthma endophenotype or altered pharmacology.

Receptor (gene name)	Variant/allele	Disease/phenotype	Pharmacology	Reference
Endothelin-1 receptor type A (*EDNRA*)	*Afi* II	Atopy; IgE levels increased	Altered receptor expression	Mao et al., 1999; Michel et al., 2010
Beta2-adrenergic receptor (*ADRB2*)	R16 > G	Reduced lung function; nocturnal asthma/severity	Downregulation enhanced; albuterol response decreased	Hawkins et al., 2008; Basu et al., 2009
	Q27 > E	Hypertension risk; obesity; IgE levels increased	Downregulation resistant; albuterol response increased; drug hypersensitivity	Reihsaus et al., 1993; Dewar et al., 1997; Drysdale et al., 2000
	G16/E27 haplotype	Asthma, heart disease, immune disorders		Drysdale et al., 2000
	C341 > G	None known	Uncoupling from Gs/adenylyl cyclase system	Lachance et al., 1999
Prostaglandin D2 receptor (*PTGDR*)	Promoter SNPs undermine normal helper T anti-inflammatory response	Asthma	Altered receptor expression anti- immune response to PGD2	Cookson and Moffatt, 2004; Oguma et al., 2004
Chemoattractant receptor on Th2 cells (*CRTH2/GPR44*)	3′ UTR SNPs: 1651G > A, 1544C/1651A	Asthma	Altered receptor expression; inflammatory response to PGD2	Hirai et al., 2001; Wang et al., 2009
Thromboxane A2 receptor (*TBXA2R*)	TP-alpha and TP-beta isoforms SNPs	Asthma, atopy and aspirin-intolerant asthma		Unoki et al., 2000; Kim et al., 2005
Cysteinyl leukotriene receptor 1 (*CYSLTR1*)	G300S	Atopy	Receptor activation	Thompson et al., 2007; Yaddaden et al., 2016
Cysteinyl leukotriene receptor 2 (*CYSLTR2*)	M201V	Various populations	Receptor inactivation	Thompson et al., 2003, 2005b; Pillai et al., 2004; Brochu-Bourque et al., 2011
Prostaglandin D2 receptor (PTGDR)	-441T/C	No disease association	Montelukast response	Kang et al., 2011
Chemokine [C-C motif] receptor 5 (*CCR5*)	32 bp deletion; 59029 A > G	Risk of asthma decreased	Diminished CCR5 expression on Th1 cells results in a preponderance of Th2 cells; decreased binding to activity; decreased binding to CC	Hall et al., 1999; Srivastava et al., 2003; Agrawal and Bharadwaj, 2005
G-protein-coupled receptor associated with asthma (*GPRA* or *GPSR154*)	GPRA-B isoform over-expressed in bronchial epithelia of asthmatics	Asthma	Altered RANTES, MIP-1-alpha ligand suggests that GPRA is a potential drug target	Laitinen et al., 2004; Kormann et al., 2005; Melén et al., 2005; Pietras et al., 2011

IgE, immunoglobulin E; MIP-1alpha, macrophage inhibitory protein; PGD2, prostaglandin D2; RANTES, regulated on activation, normal T cell expressed and secreted; SNP, single nucleotide polymorphism; UTR, untranslated region.

Pain therapy and polymorphisms

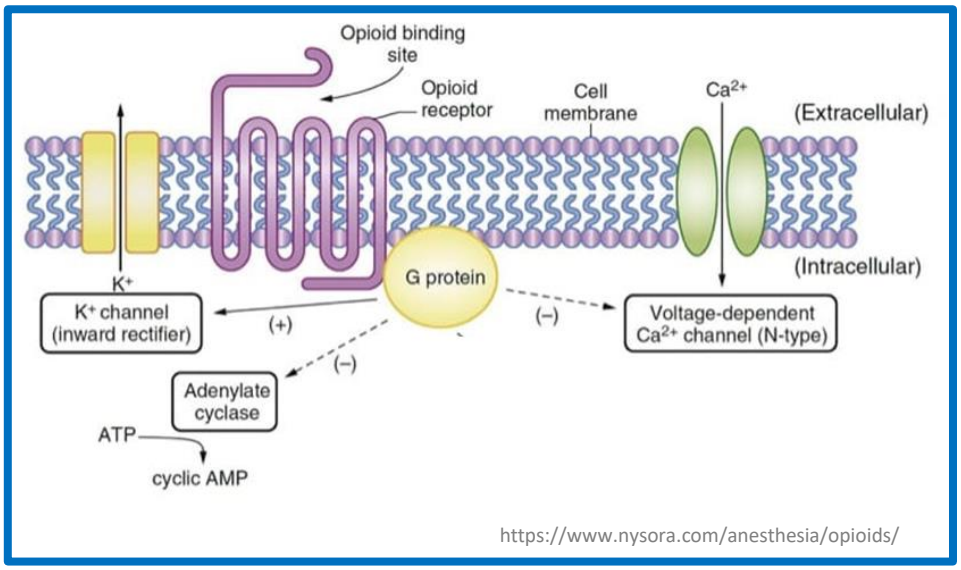


Genetic polymorphisms contribute to the variability in response to nociceptive stimuli and to treatment with analgesics, particularly opioids.

The genetic individual variability in the response to different opioids depends on:

1) Polymorphisms in metabolic enzymes genes (e.g. CYP2D6 and codein)
2) Polymorphisms in transporters genes (e.g. P-glicoprotein and morphin)
3) **Polymorphisms in opioid receptors genes**

Polymorphisms and μ-opioid receptors (MOR)



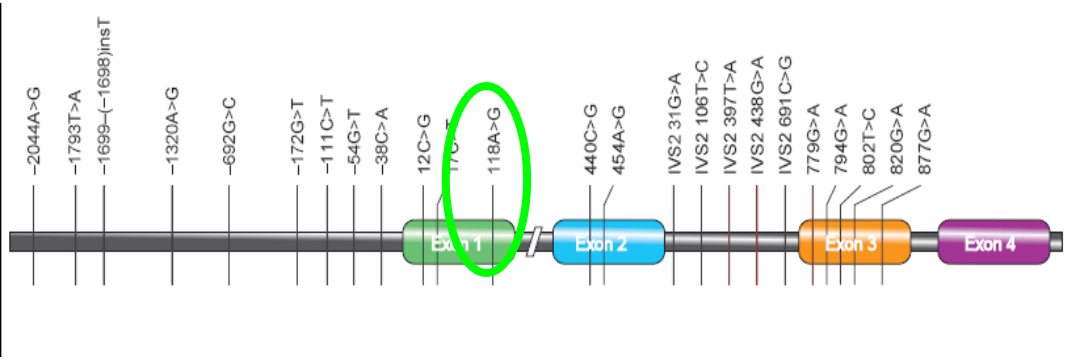
MORs are the preferential target of opioid analgesics.

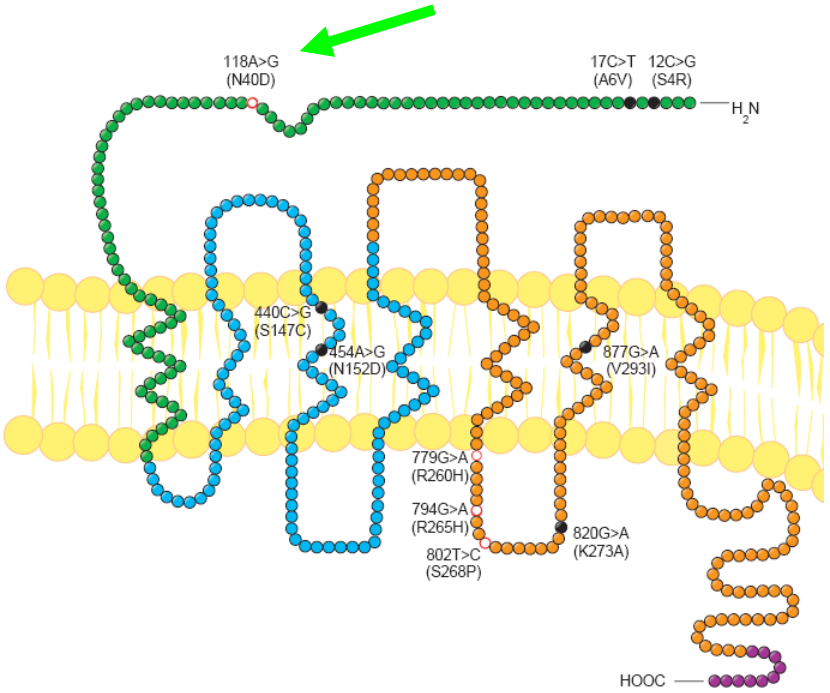
They are encoded by **OPRM1 gene** located on chromosome 6 (q24-q25) which can lead to the syntesis of 4 different subtypes (MOR-1, MOR-1A, MOR-1X e MOR-1O).
This gene is highly polymorphic (more than 800 polymorphisms).

At least 20 polymorphisms:

- cause changes in the amino acid sequence
- have a functional impact
- have a high frequency in population

118A>G polymorphism



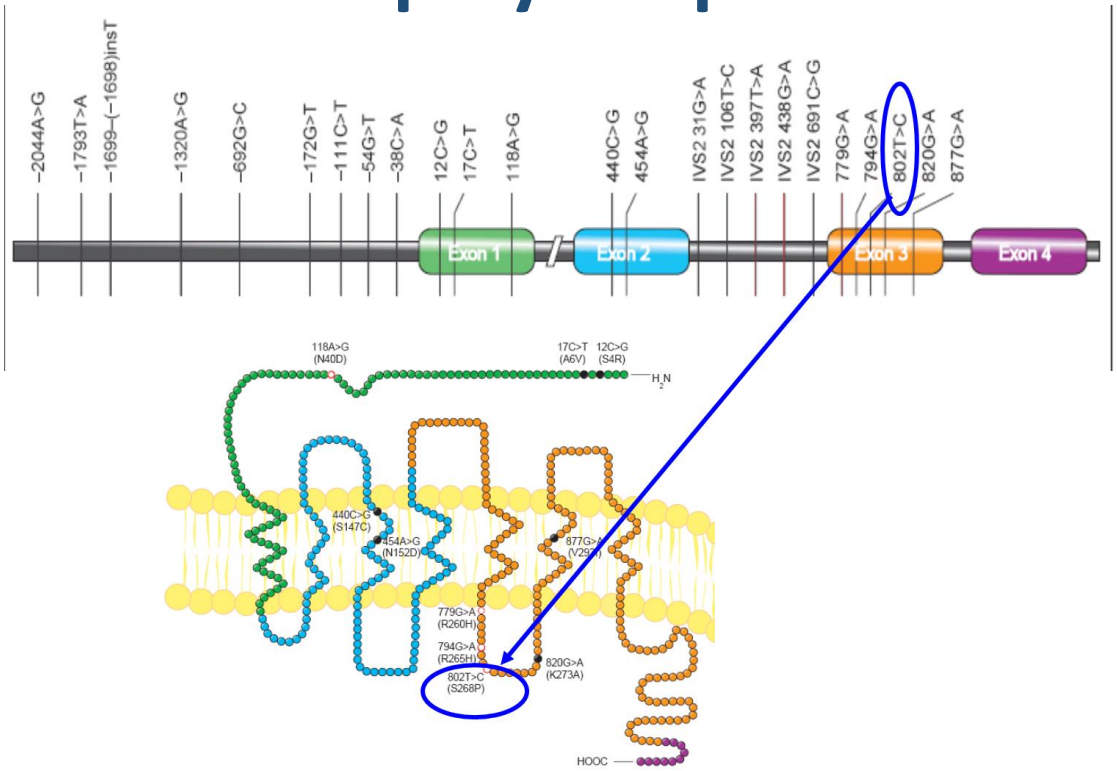


It causes a substitution of the amino acid asparagine (N) with aspartic acid (D) at position 40 of the extracellular receptor domain of μ receptor (Asn40Asp, N40D). This variation cause the deletion of a N-glycosilation site, modifying the ligands binding to the receptor.

Opioids analgesic effect is reduced of about 2-3 times. Individuals carrying the 118G allele may require higher doses of opioids to achieve analgesic effects.

This polymorphism is present in 10-15% of the Caucasian population.

802T>C polymorphism



This polymorphism causes a change from serine to proline in 268 position (Ser268Pro) in the third intracellular loop of the receptor.

This single amino acid substitution disrupts G protein coupling, causing a drastic reduction of the analgesic effect of opioids.

Other polymorphisms with a similar functional impact are: SNP 779G>A encoding for Arg260His (R260H) e SNP 794G>A encoding for Arg260His (R265H).

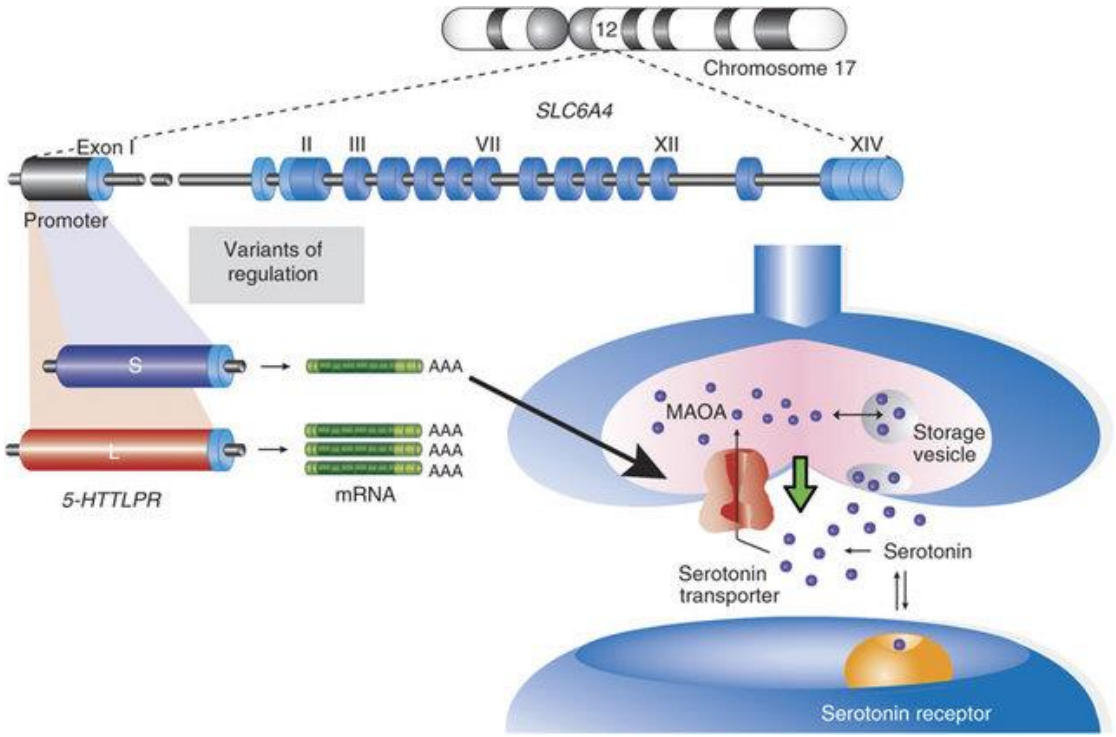
Box 3. Selected *OPRM1* polymorphisms with reported allelic frequency of at least 5%

- **–172G>T**: (allelic frequency 3.4–11.4% [4,49]) located in the 5′ untranslated region. The molecular consequences are unknown, but it does not appear to be associated with substance abuse [4,29,52,53]. It is associated with idiopathic absence epilepsy, especially when in a haplotype together with the 118A>G mutation [54].
- **17C>T**: (allelic frequency 1–10% [5,49]) located in exon 1 and causes an amino acid exchange from alanine to valine at receptor protein position six of the extracellular receptor terminal. It has been reported to occur in a higher overall proportion of opioid-dependent persons [5], but the majority of studies have reported no correlation with substance abuse [34,52,53,55]. It is not associated with decreased alfentanil analgesia [17].
- **118A>G**: (allelic frequency 10.5–18.8% [5]) located in exon 1 and causes an amino acid exchange from asparagine to aspartate at receptor protein position 40 of the extracellular receptor terminal. It has been both positively [32,53,56–59] and negatively [4,5,34,52,55,60–63] associated with substance abuse and is associated with other psychiatric and neurological disorders [54,64,65] and decreased opioid effects [17,21,22,50,51].
- **31G>A**: (allelic frequency 4.2–14.3 [4,31]) located in intron 2, involving an A/TGGG motif [14]. It is often found in a haplotype with the IVS2 691C>G polymorphism, and both the presence and absence of an association with substance abuse have been reported [31,62].
- **691C>G**: (allelic frequency 43% [4,60]) located in intron 2. Has not been associated with substance abuse [56,58,60,62].

μ-opioid receptors play a key role in the mechanisms of addiction.

118A>G polymorpism has been associated with substance abuse (e.g. alcohol dependence) or other psychiatric disorders such as obsessive-compulsive disorder.

Depression and serotonin transporter gene polymorphisms

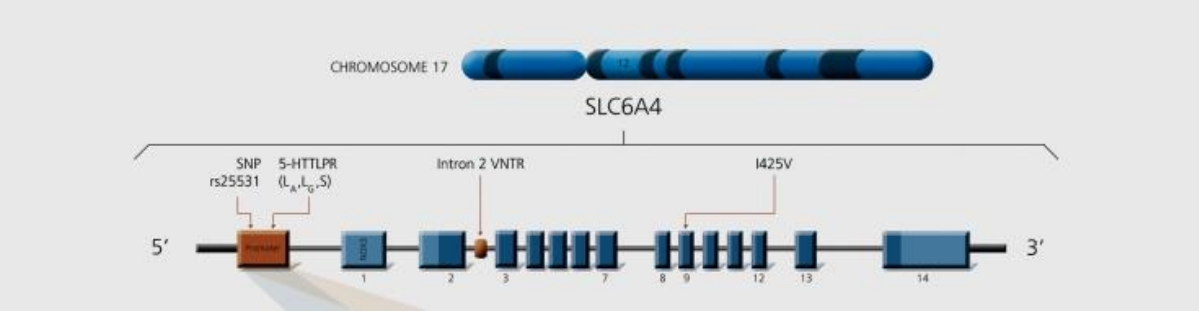


Canli T, Lesch KP. Long story short: the serotonin transporter in emotion regulation and social cognition. Nat Neurosci. 2007 Sep;10(9):1103-9.

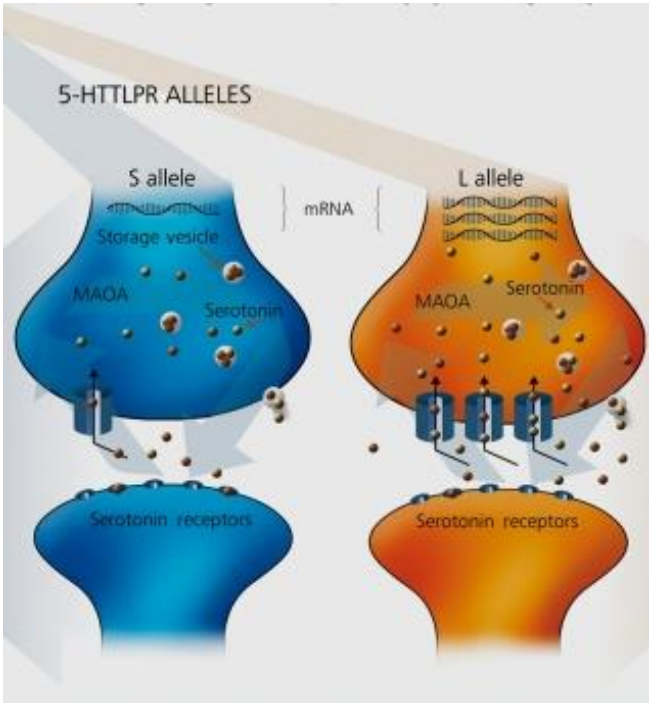
The serotonin transporter (SERT) is encoded by the SLC6A4 gene located on chromosome 17. The transcriptional activity of this gene is regulated by a promoter (5-HTTLPR). Several polymorphisms in the SLC6A4 gene have been identified, which may affect the function and expression of the protein and the activity of antidepressant drugs. The have been also associated with an increased risk of developing depression or other psychiatric diseases.

5-HTTLPR polymorphisms

The most studied polymorphism is the variation in the number of repeated elements in the 5-HTTLPR promoter region. There is a distinction between a short version (short, S), with 14 repeats, and a long version (long, L), with 16 repeats. The S version is linked to lower SERT mRNA levels and thus reduced serotonin reuptake. Individuals carrying the S variant may have a reduced response to SSRIs.



Gerretsen et al. The intersection of pharmacology, imaging, and genetics in the development of personalized medicine. Dialogues Clin Neurosci. 2009;11(4):363-376.



Science. 2003 Jul 18;301(5631):386-9. doi: 10.1126/science.1083968.

Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene

Avshalom Caspi [1], Karen Sugden, Terrie E Moffitt, Alan Taylor, Ian W Craig, HonaLee Harrington, Joseph McClay, Jonathan Mill, Judy Martin, Antony Braithwaite, Richie Poulton

Affiliations + expand

PMID: 12869766 DOI: 10.1126/science.1083968

GENE-ENVIRONMENT INTERACTION (GXE)

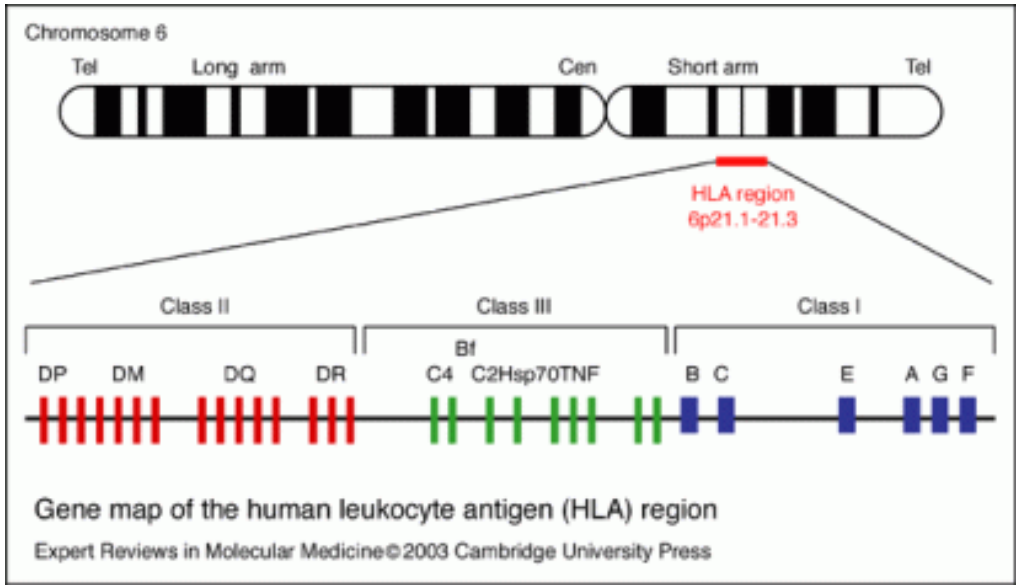
Studies have found an interaction between 5-HTTLPR and environmental adverse events for various neuropsychiatric disorders.

Subjects with one or two S alleles were found to have a higher risk of depression after exposure to adverse events, compared to those with L alleles. Those with the L/L genotype were protected from depression, despite severe trauma.

The presence of the S allele has been hypothesized to alter serotonergic transmission, modifying the response to stress and causing dysregulation in emotion processing, increasing susceptibility to psychiatric illness.

Polymorphisms in Human Leucocyte Antigen (HLA) genes

HLA (Human Leukocyte Antigen)



HLA genes (approximately 200) are located on chromosome 6 and encode for glycoproteins on the surface of cells that can bind foreign peptides (antigens), triggering the immune system response.

They play an important role in self/non-self discrimination and contribute to both humoral and cell-mediated immunity.

- **class I HLA genes:** they encode proteins that are expressed on the surface of all nucleated cells (no in red blood cells). These proteins present antigens (intracellular peptides, such as viral fragments or tumor proteins) to cytotoxic T lymphocytes (CD8+), causing cell death.
- **class II HLA genes:** they encode proteins expressed on macrophages, dendritic cells, B lymphocytes. They present exogenous antigens to T helper lymphocytes (CD4+).
- **class III HLA genes**: they encode secreted proteins with immune functions (complement proteins, cytokines...)

The HLA system is polymorphic and codominant, i.e. products of both alleles are expressed in each individual.

HLA and autoimmune diseases

HLA class I associated disease	HLA	Relative Risk
Ankylosing spondylitis	B27	90
Reiter disease	B27	35
Psoriatic spondylitis	B27	12
Idiopatic hemochromatosis	A3	8
Psoriasis vulgaris	Cw6	13
Behçet disease	B51	16
HLA class II associated diseases	**HLA**	**Relative risk**
Rheumatoid arthritis	DR4	6
SLE	DRB1*1501 DRB1*0301	3 3
Sjögren disease	DQB1*0201	12
IDDM **Type 1 diabetes**.	DR3 DR4 DR3/4 DR2	5 6 15 0.2
Addison disease	DR3	6
Graves disease	DR3	3
Hashimoto disease	DQ7	5
Celiac disease	DR3	11
Pemphigus vulgaris	DR4	25
Hodgkin disease	DPw2	0.1
Multiple sclerosis	DRB1*1501 DQB1*0602	6 6
Narcolepsy	DRB1*1501	29
Myasthenia gravis	DR3	7

HLA genes polymorphisms and adverse drug reactions

Pharmacogenetic studies aimed at identifying genetic markers of susceptibility to severe adverse drug reactions have shown the role of polymorphisms in genes that encode the HLA system.

The presence of these gene variants has been linked to an increased risk of cutaneous drug reactions, including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in specific populations.

Haplotype	Drug	Adverse event	Ethnic group
HLA-B*1502	Carbamazepine	Drug hypersensitvity	Han Chinese
HLA-A*3101	Carbamazepine	Drug hypersensitvity	European
HLA-B*5701	Abacavir	Drug hypersensitvity	Mixed ancestry
HLA-B*5801	Allopurinol	Severe skin rash	Various populatons
HLA-B*3505	Nevirapine	Skin rash	Thai
HLA-B*5701	Flucloxacillin	Liver injury	Mixed ancestry
HLA-B*1502	Phenytoin	Drug hypersensitvity	Han Chinese, Thai

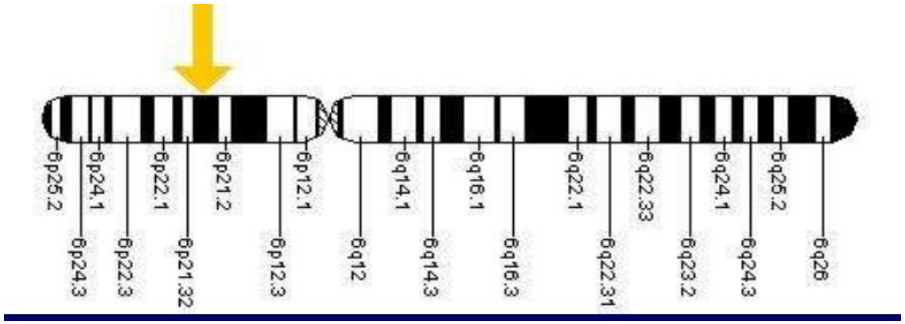
Derived from Phillips et al. (2011).

Abacavir and HLA-B polymorphisms

Abacavir is an antiretroviral drug used to treat HIV. It is a guanosine nucleotide analogue that inhibits retrotranscriptase. It's an effective drug, but 5% of patients develop hypersensitivity reactions (including fever, skin rash, headache and gastrointestinal disorders) within the first six weeks of treatment, which can sometimes have serious or even fatal outcomes.

There is a strong correlation between hypersensitivity reactions and the presence of the **HLA-B*5701** allele of the class I HLA genes, which is mainly found in Caucasian or Hispanic people.

The FDA and EMA therefore require pharmacogenetic screening before starting Abacavir in therapy.



Nota Informativa Importante su Ziagen compresse e soluzione orale, Kievex compresse e Trizivir compresse (abacavir solfato) (07/03/2008)

La presenza dell'allele HLA-B*5701 è associata ad un incremento significativo del rischio di reazione di ipersensibilità ad abacavir. L'utilità clinica dello screening dell'allele HLA-B*5701 in ogni paziente affetto da HIV, a prescindere dalla razza è stata dimostrata in uno studio controllato prospettico, randomizzato (CNA106030 [PREDICT - 1]. I risultati di questo studio hanno portato alla modifica del Riassunto delle Caratteristiche del Prodotto (RCP) e del Foglio Illustrativo dei medicinali contenenti abacavir solfato.

Tali modifiche sono state esaminate dal CHMP con una variazione di Tipo II che modifica le Autorizzazioni all'Immissione in Commercio dei medicinali ottenute mediante procedura Centralizzata.

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Pubblicato il: 07 marzo 2008

AIFA note about the use of Abacavir in therapy and medication package insert.

4.4 Avvertenze speciali e precauzioni d'impiego

Reazioni di ipersensibilità (vedere anche paragrafo 4.8)
Abacavir è associato ad un rischio di reazioni di ipersensibilità (HSR) (vedere paragrafo 4.8) caratterizzate da febbre e/o eruzione cutanea con altri sintomi che indicano un coinvolgimento multi-organico. Le HSR sono state osservate con abacavir, alcune delle quali erano pericolose per la vita e in rari casi ad esito fatale, quando non gestite in maniera appropriata. Il rischio che si verifichi una HSR ad abacavir è elevato nei pazienti con test positivo per la presenza dell'allele HLA-B*5701. Tuttavia, le HSR ad abacavir sono state riportate con una frequenza minore nei pazienti che non possiedono questo allele.

Pertanto, deve sempre essere rispettato quanto segue:

- la presenza o meno dell'allele HLA-B*5701 deve essere sempre confermata prima di iniziare la terapia.
- Abacavir non deve mai essere iniziato nei pazienti con positività per la presenza dell'allele HLA- B*5701, nemmeno nei pazienti con negatività per l'allele HLA-B*5701 che hanno avuto una sospetta HSR ad abacavir in un precedente regime terapeutico contenente abacavir (ad esempio abacavir/lamivudina, abacavir/lamivudina/zidovudina, abacavir/ dolutegravir/ lamivudina).
- se si sospetta una HSR, **abacavir deve essere interrotto immediatamente** anche in assenza di allele HLA-B*5701. Un ritardo nella sospensione del trattamento con abacavir dopo l'insorgenza di ipersensibilità può provocare una reazione pericolosa per la vita.
- dopo l'interruzione del trattamento con abacavir per motivi di sospetta HSR, **Abacavir Mylan o qualsiasi altro medicinale contenente abacavir** (ad esempio abacavir/lamivudina, abacavir/lamivudina/zidovudina, abacavir/dolutegravir/lamivudina) **non devono mai più essere ripresi.**
- la riassunzione di medicinali contenenti abacavir dopo una sospetta HSR ad abacavir può provocare un'immediata ricomparsa dei sintomi entro poche ore. La ricomparsa dei sintomi è generalmente più grave della presentazione iniziale e può includere ipotensione pericolosa per la vita e morte.

Agenzia Italiana del Farmaco

Carbamazepine and HLA-B polymorphisms

Carbamazepine is a drug used for epilepsy, trigeminal neuralgia and obsessive-maniacal disorders.

It can cause severe skin reactions such as Steven Johnson syndrome and toxic epidermal necrolysis.

Reactions are associated with the **HLA-B*1502** allele, typical of Asian individuals.

Associazione con l'allele HLA-B*1502 –nella popolazione cinese di etnia Han, tailandese e nelle altre popolazioni asiatiche

Negli individui di origine cinese di etnia Han e di origine tailandese, la positività all'allele HLA-B*1502 (allelle dell'antigene leucocitario umano, Human Leukocyte Antigen, HLA) ha dimostrato di essere fortemente associata con il rischio di sviluppare gravi reazioni cutanee come la Sindrome di Stevens-Johnson (SJS) e la necrolisi epidermica tossica (TEN) durante il trattamento con carbamazepina. La prevalenza dell'allele HLA-B*1502 è di circa il 10% nelle popolazioni cinesi di etnia Han e tailandesi.
Quando possibile, questi pazienti dovrebbero essere sottoposti a screening per questo allele prima di iniziare il trattamento con carbamazepina (vedere paragrafo 4.2 e "Informazioni per gli operatori sanitari"). Se questi pazienti risultano positivi al test, il trattamento con la carbamazepina non deve essere iniziato, a meno che non vi sia nessuna altra alternativa terapeutica. I pazienti testati che sono risultati negativi per HLA-B*1502 sono a basso rischio di insorgenza di Stevens-Johnson (SJS), sebbene tale reazione possa ancora verificarsi anche se molto raramente.

Alcuni dati suggeriscono un aumentato rischio di reazioni gravi quali SJS/TEN associate a carbamazepina in altre popolazioni asiatiche. A causa della prevalenza di questo allele in altre popolazioni asiatiche (ad esempio superiore al 15% nelle Filippine e Malesia), il test nelle popolazioni geneticamente a rischio per la presenza dell'allele HLA-B*1502 può essere considerato.

La prevalenza dell'allele HLA-B*1502 è trascurabile, ad esempio nelle popolazioni di origine europea, africana, in un campione di popolazione ispanica, nei giapponesi e nei coreani (<1%).
Le frequenze alleliche qui descritte rappresentano la percentuale di cromosomi di quella specifica popolazione che portano l'allele interessato, il che significa che la percentuale di pazienti portatori di una copia dell'allele su almeno uno dei loro due cromosomi (cioè la "frequenza del portatore") è circa due volte la frequenza allelica. Pertanto la percentuale di pazienti a rischio è circa due volte la frequenza allelica.
La presenza dell'allele HLA-B*1502 può essere un fattore di rischio per lo sviluppo di SJS/TEN nei pazienti cinesi che assumono altri farmaci antiepilettici che possono determinare SJS/TEN. Pertanto, in pazienti positivi per l'allele HLA-B*1502, si deve prestare attenzione ad evitare l'uso di altri farmaci che possono determinare SJS/TEN qualora siano disponibili terapie alternative parimenti accettabili.
Lo screening non è generalmente raccomandato in pazienti che derivano da popolazioni in cui la prevalenza

Screening for this allele is recommended before starting carbamazepine treatment. If patients are positive, carbamazepine should not be used unless no valid therapeutic alternatives are available.

Informazione di sicurezza dell'MHRA su carbamazepina, oxcarbazepina e eslicarbazepina

La MHRA (Medicines and Healthcare products Regulatory Agency) ha pubblicato un'informazione di sicurezza destinata agli operatori sanitari sui potenziali rischi di gravi reazioni cutanee derivanti dall'uso di carbamazepina, oxcarbazepina e eslicarbazepina in presenza dell'allele HLA-A * 3101.

Il rischio di gravi reazioni avverse correlate alla pelle, tra cui la sindrome di Stevens-Johnson, che si verificano con la carbamazepina può aumentare in presenza dell'allele HLA-A * 3101 in pazienti di discendenza europea o di origine giapponese. Tuttavia, vi sono dati sufficienti a supportare screening per questo allele prima di iniziare il trattamento con carbamazepina. I pazienti di discendenza europea o di origine giapponese, che sono noti per essere positivi per questo allele, dovrebbero ricevere carbamazepina, oxcarbazepina o eslicarbazepina solo dopo un'attenta valutazione dei benefici e dei rischi.

La carbamazepina è un farmaco antiepilettico che è indicato per il trattamento delle crisi tonico-cloniche generalizzate. Carbamazepina è anche concesso in licenza per trattare il dolore parossistico di nevralgia del trigemino e per la profilassi della malattia maniaco-depressiva in pazienti che non rispondono alla terapia con litio.

L'oxcarbazepina è indicata per il trattamento delle crisi parziali con o senza generalizzazione secondaria ed è strutturalmente correlata alla carbamazepina.

L'eslicarbazepina è il metabolita attivo di oxcarbazepina e indicato come terapia aggiuntiva negli adulti con crisi parziali con o senza generalizzazione secondaria.

E 'ben noto che le reazioni avverse gravi correlate alla pelle, potenzialmente pericolose per la vita, tra cui la sindrome di Stevens-Johnson (SJS) e la necrolisi epidermica tossica (TEN), possono verificarsi raramente in associazione con carbamazepina. La frequenza delle reazioni della pelle è stata stimata in circa 1-6 casi ogni 10.000 nuovi pazienti che assumono carbamazepina negli Stati Uniti e in Europa.

L'Agenzia invita quindi i professionisti della salute a somministrare carbamazepina, oxcarbazepina, o eslicarbazepina in pazienti di discendenza europea o di origine giapponese, noti per essere positivi per l'allele HLA-A * 3101, solo dopo un'attenta valutazione dei benefici e dei rischi. Se appaiono segni o sintomi indicativi di reazioni cutanee gravi, il trattamento dovrebbe essere immediatamente interrotto e dovrebbe essere considerato un trattamento alternativo.

Leggi sul sito dell'MHRA

Associazione con l'allele HLA*3101 – nella popolazione a discendenza europea e nella popolazione giapponese

Alcuni dati suggeriscono che l'HLA-A*3101 è associata ad un aumentato rischio di gravi reazioni avverse cutanee indotte da carbamazepina tra cui SJS e TEN, rash con eosinofilia (DRESS), o una pustolosi esantematica acuta generalizzata (AGEP) meno grave e rash maculopapulare (vedere paragrafo 4.8) nelle persone di discendenza europea e giapponese.
La frequenza dell'allele HLA-A*3101 varia ampiamente tra le popolazioni etniche. L'allele HLA-A*3101 ha una prevalenza da 2 a 5% nelle popolazioni europee e circa il 10% nella popolazione giapponese.

La presenza dell'allele HLA-A*3101 può aumentare il rischio di reazioni cutanee (per lo più gravi) indotte da assunzione di carbamazepina dal 5,0% nella popolazione generale al 26,0% tra i soggetti di origine europea, mentre la sua assenza può ridurre il rischio dal 5,0% al 3,8%.

Le frequenze alleliche qui descritte rappresentano la percentuale di cromosomi di quella specifica popolazione che portano l'allele interessato, il che significa che la percentuale di pazienti portatori di una copia dell'allele su almeno uno dei loro due cromosomi (cioè la "frequenza del portatore") è circa due volte la frequenza allelica. Pertanto la percentuale di pazienti a rischio è circa due volte la frequenza allelica.
Non vi sono dati sufficienti a sostegno di una raccomandazione per uno screening dell'HLA-A*3101 prima di iniziare il trattamento con carbamazepina.

Se i pazienti di discendenza europea o di origine giapponese risultano essere positivi all'allele HLA-A*3101, l'uso di carbamazepina può essere preso in considerazione solo se i benefici attesi sono superiori ai rischi.

The **HLA-A*3101** allele, typical of patients of European or Japanese descent, can also lead to severe skin reactions after taking carbamazepine.