COMT Val158Met polymorphism in Eastern Uttar Pradesh population

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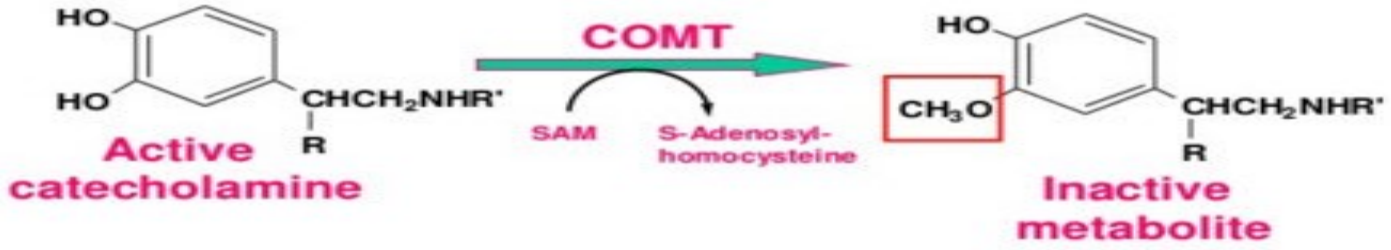
Catechol-o-methyl transferase(COMT)

- COMT is one of the major intracellular methylation enzymes involved in the metabolic degradation of catecholamines and thus inactivates them.
- It play crucial role in modulating nerve function and physiology.
- Important for **regulating dopamine levels** in PFC.



- First discovered by biochemist **Julius Axelrod** in 1957.

Zhu et al., 2002 ; Coyle et al., 2005; Synder et al., 2005

Distribution of COMT in body

- Throughout the body (brain and various peripheral tissues)

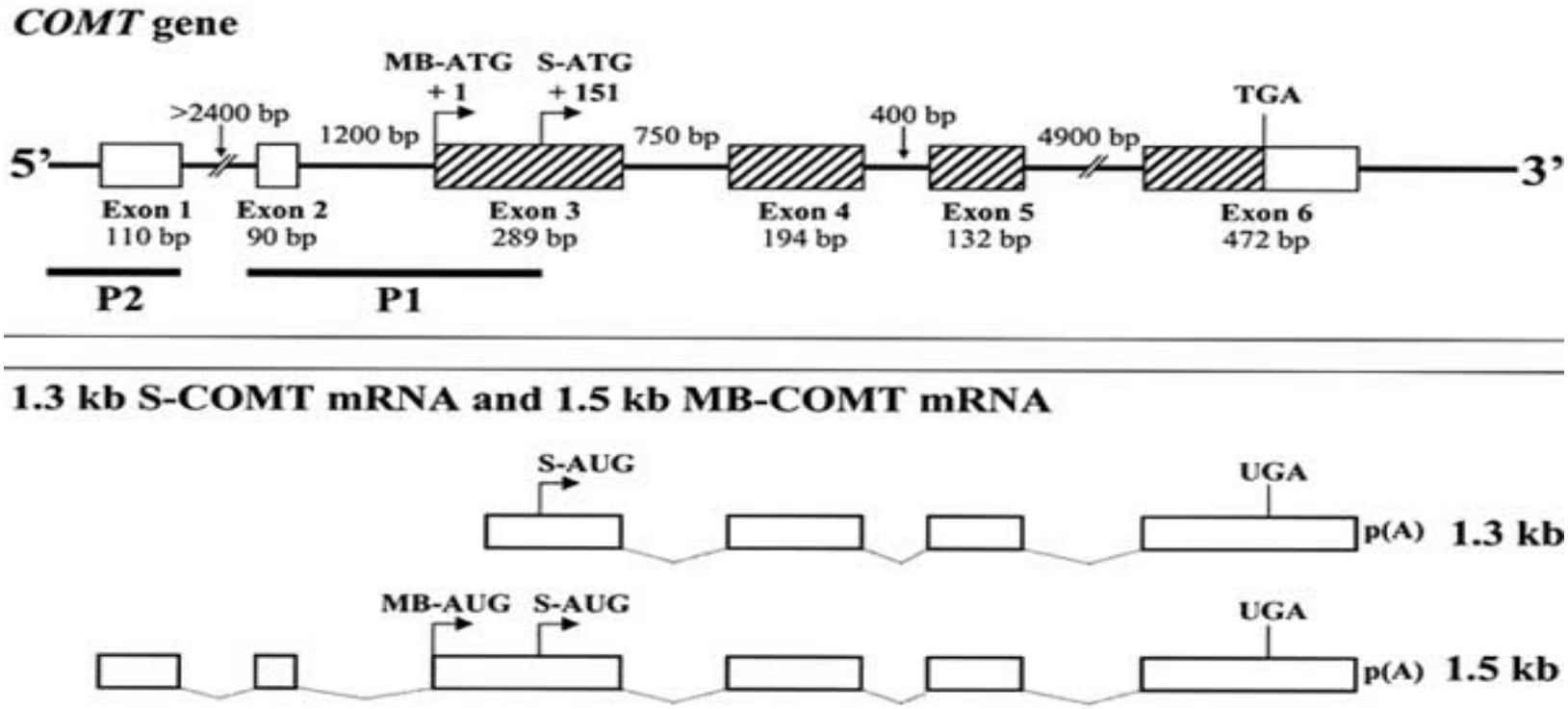
- Highest protein and activity level in liver, kidney, adrenal gland, gut, esophagal mucosa, spinal cord and peripheral nerves.

Tissue distribution of enzyme isoform :

- S-COMT- predominant in periphery
- M-COMT- in human brain (PFC)

(Mamisto et al., 2016, Lundstorm et al., 1995)

Structure of Human COMT gene and the structures of S-COMT and MB-COMT mRNAs



(Zhu et al., 2002)

Functions of COMT

- In placenta, during first trimester it protect embryo from activated hydroxylated compound.
- As detoxifying barrier between blood and peripheral tissue.
- Modulate excretory function in kidney and intestinal tract.
- In brain (PFC) associated with modulation of several behavioural and cognitive function.

(Mamisto et al., 1992, Tunbridge et al., 2006, Mir et al., 2018)

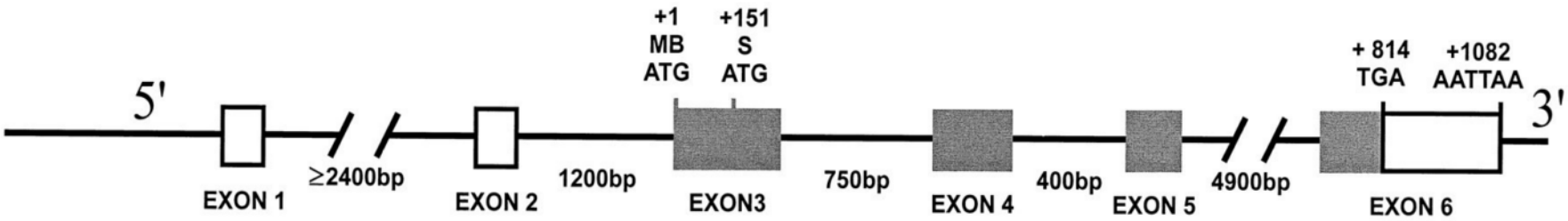
COMT gene location

- **COMT gene** is located on chromosome 22q11.1
- Contains 6 exons and is of 27000 bp size.

COMT gene encodes for two differentisoforms of COMT

- soluble COMT and
- membrane bound COMT

- Hence, there are two primary transcripts of COMT of 1.3 and 1.5 kb transcribed from 2 distinct promotors, P1 and P2 respectively.



- Goldberg and weinberger, 2004- Mamisto et al., 2016

Polymorphism and Genotypes

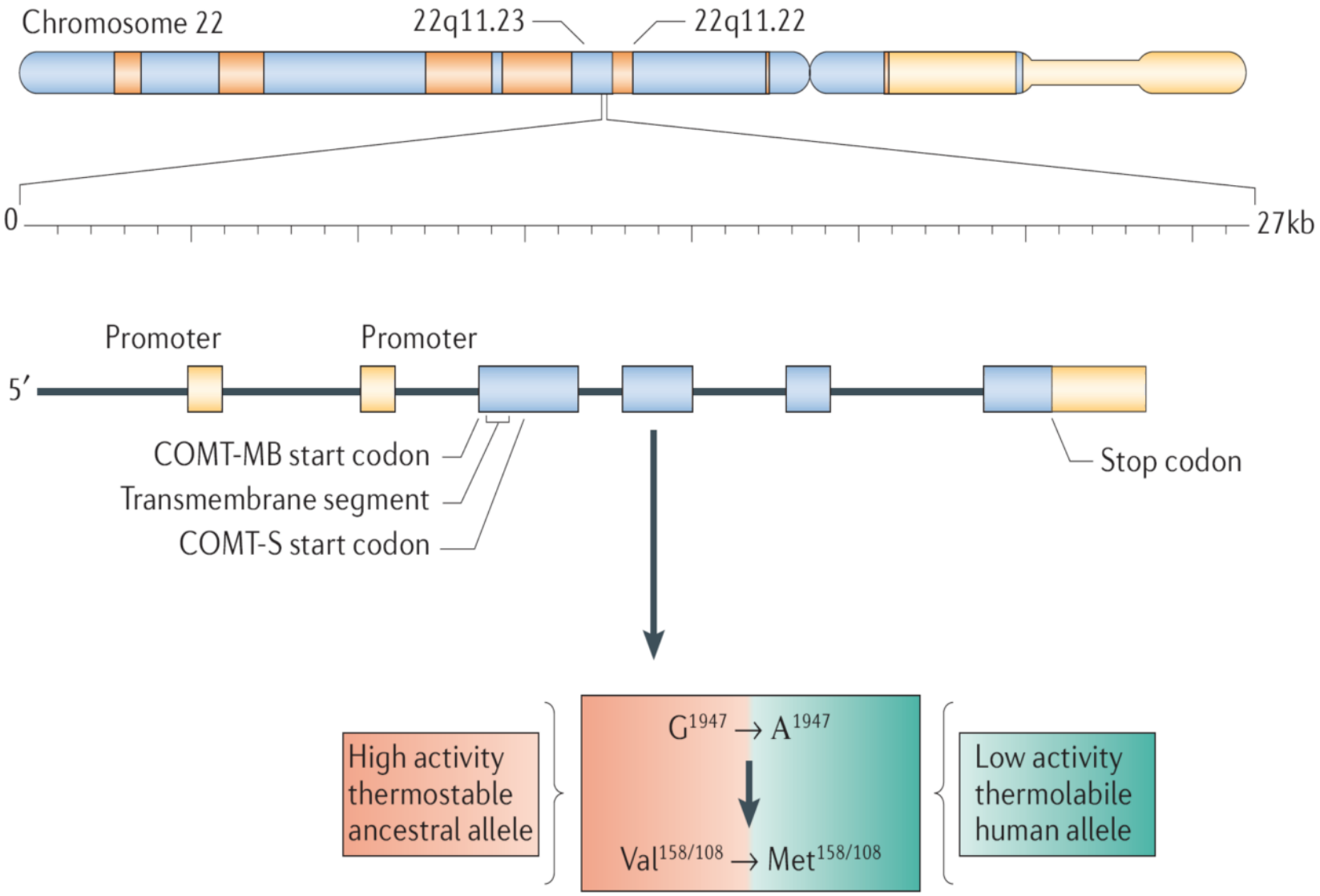
The COMT gene has a functional polymorphism Val158Met.

Met /met genotype is associated with 3 to 4 fold lower enzyme activity than val/val genotype.

Thus, lower activity COMT of met allele carrying subject may lead to higher dopamine levels in CNS.

Single base pair G→A substitution at position 472 in exon 4 results in (**Valine** (G) for **Methionine** (A) substitution at codon 158.

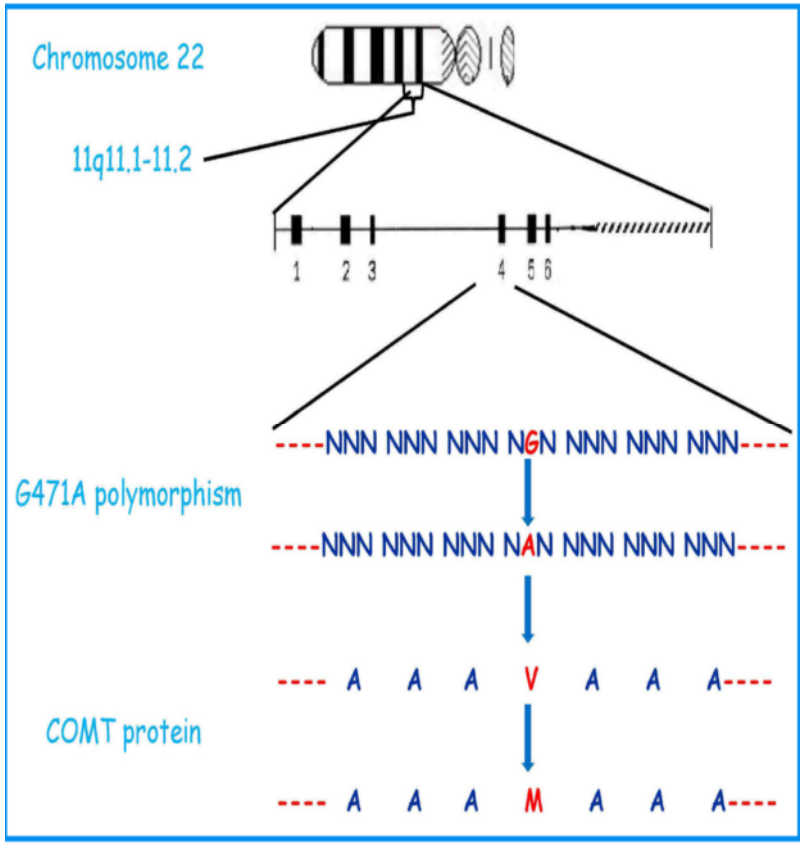
(Lachman et al., 1996 ,Mir et al., 2018)



Meyer-Lindenberg A, Weinberger DR. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. Nat Rev Neurosci. 2006;7:818–27

Genotypes:

- **A/A** (mutant type) has lowest COMT activity;
- **A/G** (co-dominant alleles) intermediate COMT activity;
- **G/G** (wild type) highest COMT activity;



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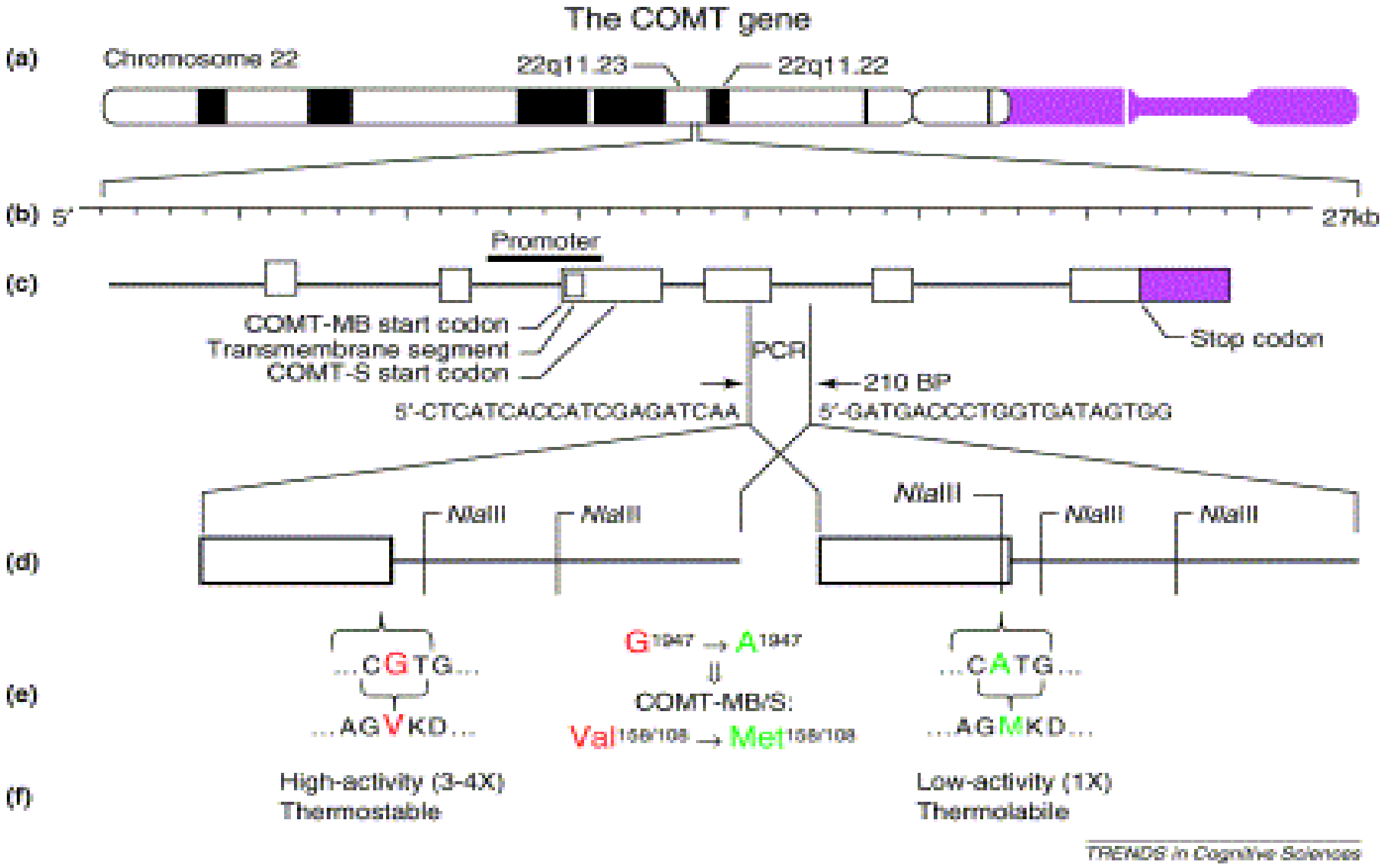


- Goldman and Weinberger, 2004

Potential impact of reduced enzyme function of this SNP

- Catecholamines (Dopamine, epinephrine, nor-epinephrine and estrogens) may build up.
- Increase risk of psychiatric disorder due to impaired PFC function.
- May have greater aggression in behaviour.
- Cognitive performance may be affected.
- Patient may feel excessive stimulation-alertness, sleeplessness, restlessness (as epinephrine, nor epinephrine are stimulants).

Catechol-O-methyltransferase
COMT

COMT is found in a wide range of tissue types kidneys, liver, intestinal tract and brain tissue.

Catechol-*O*-methyltransferase (COMT, EC 2.1.1.6) is a ubiquitous enzyme that is crucial to the metabolism of carcinogenic catechols and catecholamines

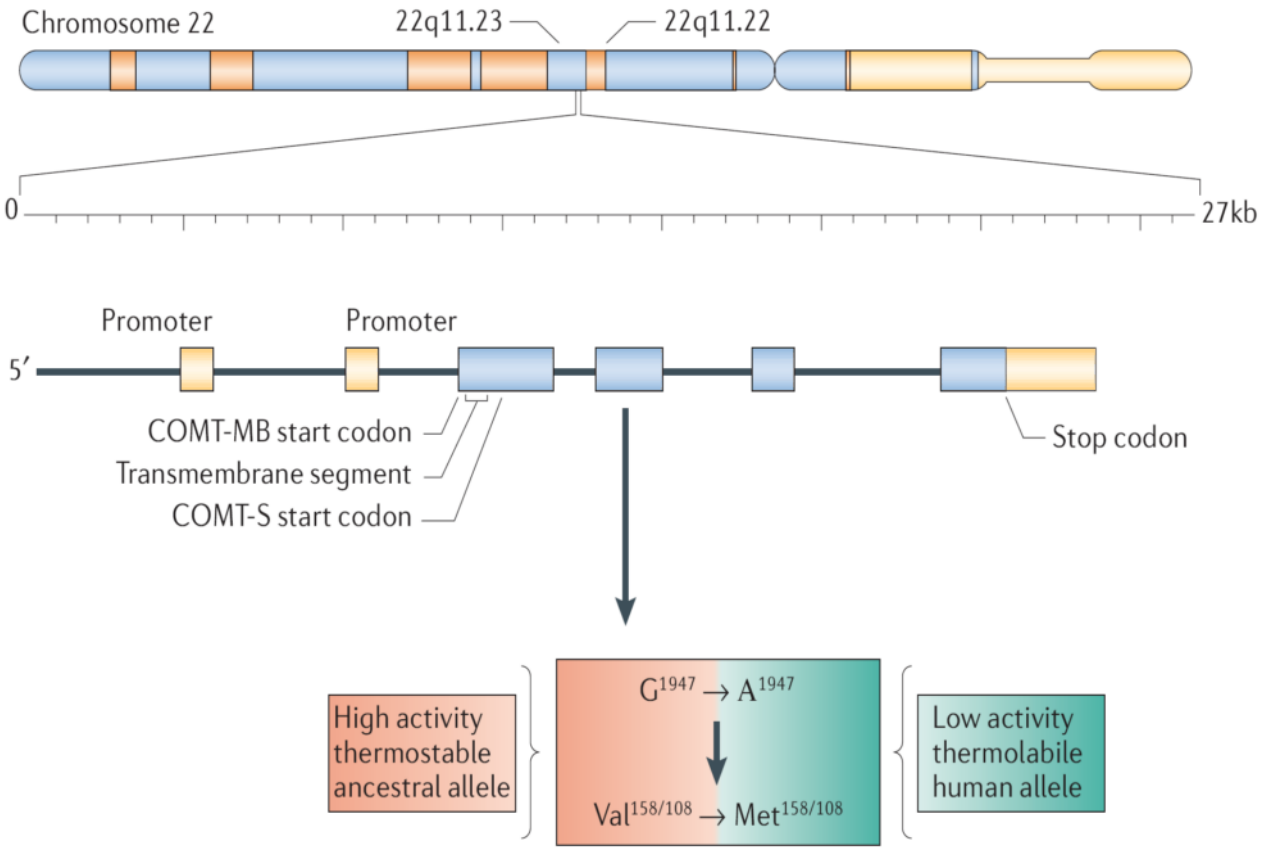
- **Catechol estrogens have been shown to have the ability**
  - **to damage DNA and**
  - **carcinogenetic potential.**
- **Therefore, the loss of or changes in COMT is supposed to contribute to genomic instability and tumor genesis.**

The catechol-O-methyltransferase (COMT) Gene

The COMT gene is located on chromosome 22q11.2 and consists of six exons.

Common Val158Met substitutions in exon 4 that affect the thermal stability of the COMT protein.

This leads to a conformational change and significant decrease in enzyme activity for Met alleles.



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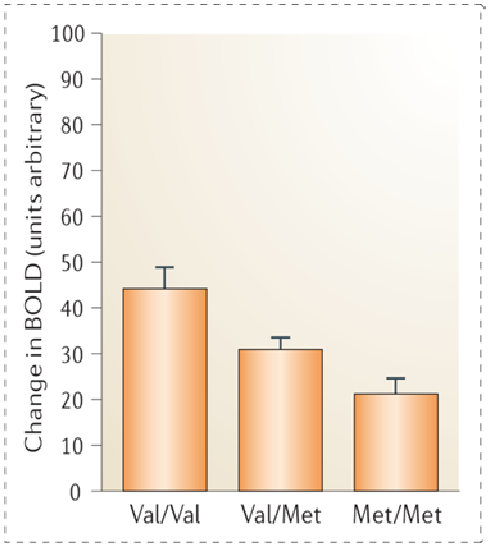
COMT Gene and Polymorphism

- **Single nucleotide polymorphism** (SNP), involving a **G to A transition at 472** nucleotide (G472A), codon **158**, results in an amino acid change

- This makes the enzyme prone to **active-site distortion** and **protein aggregation at physiological temperature**, leading to **a four times reduction** in enzymatic activity when in homozygosity for the Met allele.

- The Val/Val, Val/Met and Met/Met genotypes are associated with high, intermediate and low activity phenotypes of the enzyme, respectively.



COMT Val158Met polymorphism has been investigated in several countries

Frequency of Met allele

0.56	**In Americans**
0.5	**In Europeans**
0.27	**In Chinese**
0.31	**In Han Chinese**
0.35	**In Japanese**
0.64	**In Europeans**
0.43	**In Spanish population**

- Population frequency of this clinically important polymorphism is not well reported from Indian population

- Only few reports are available based on case control studies.

Rai , et al.2017

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Prevalence of COMT Val158Met polymorphism in Eastern UP population

P. Kumar, U. Yadav, V. Rai*

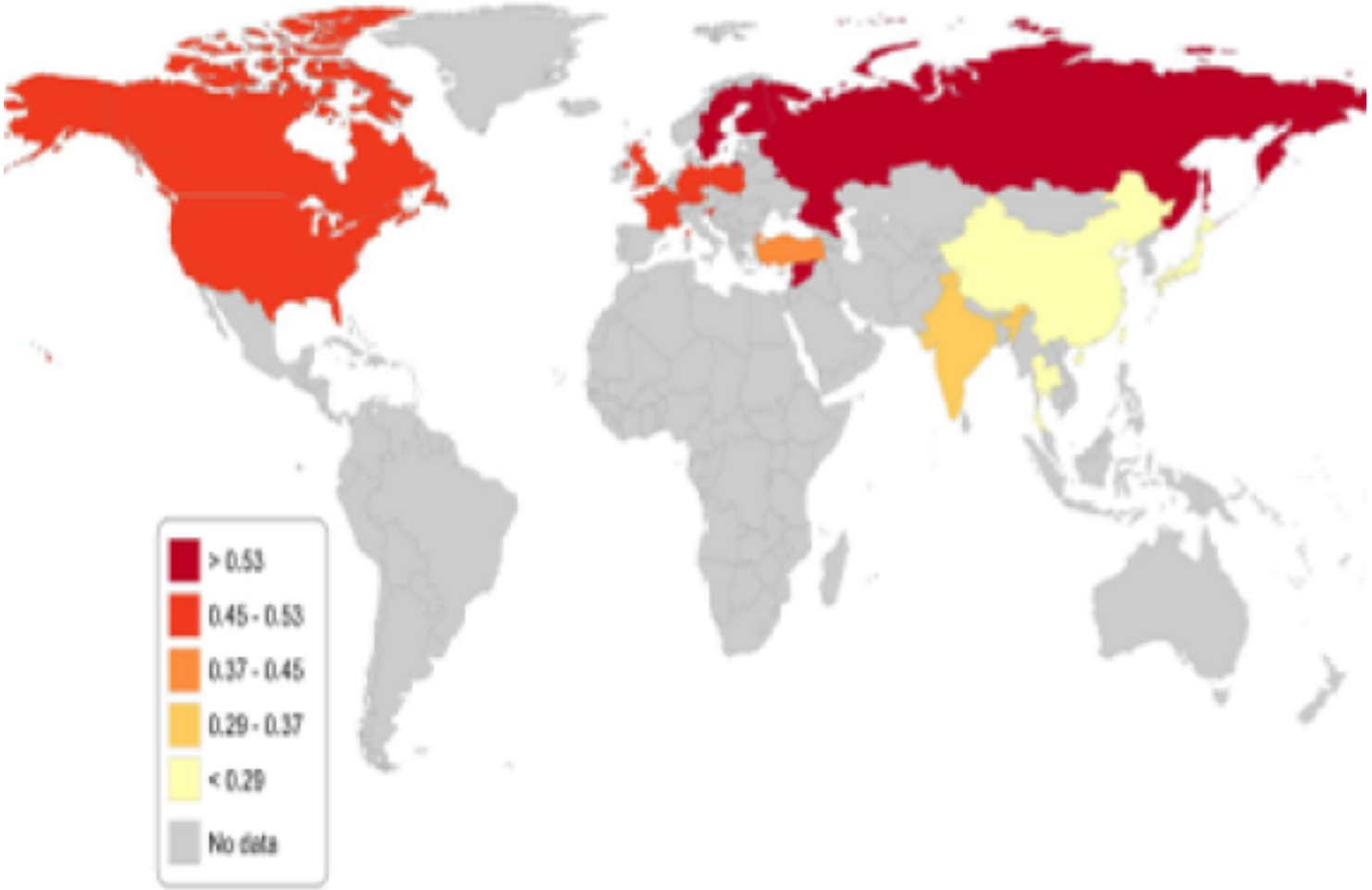
Genotype frequencies of Val/Val, Val/Met and Met/Met were 0.48, 0.40 and 0.12 respectively.

The allele frequency of Val allele was found to be 0.68 and Met allele frequency was 0.32.

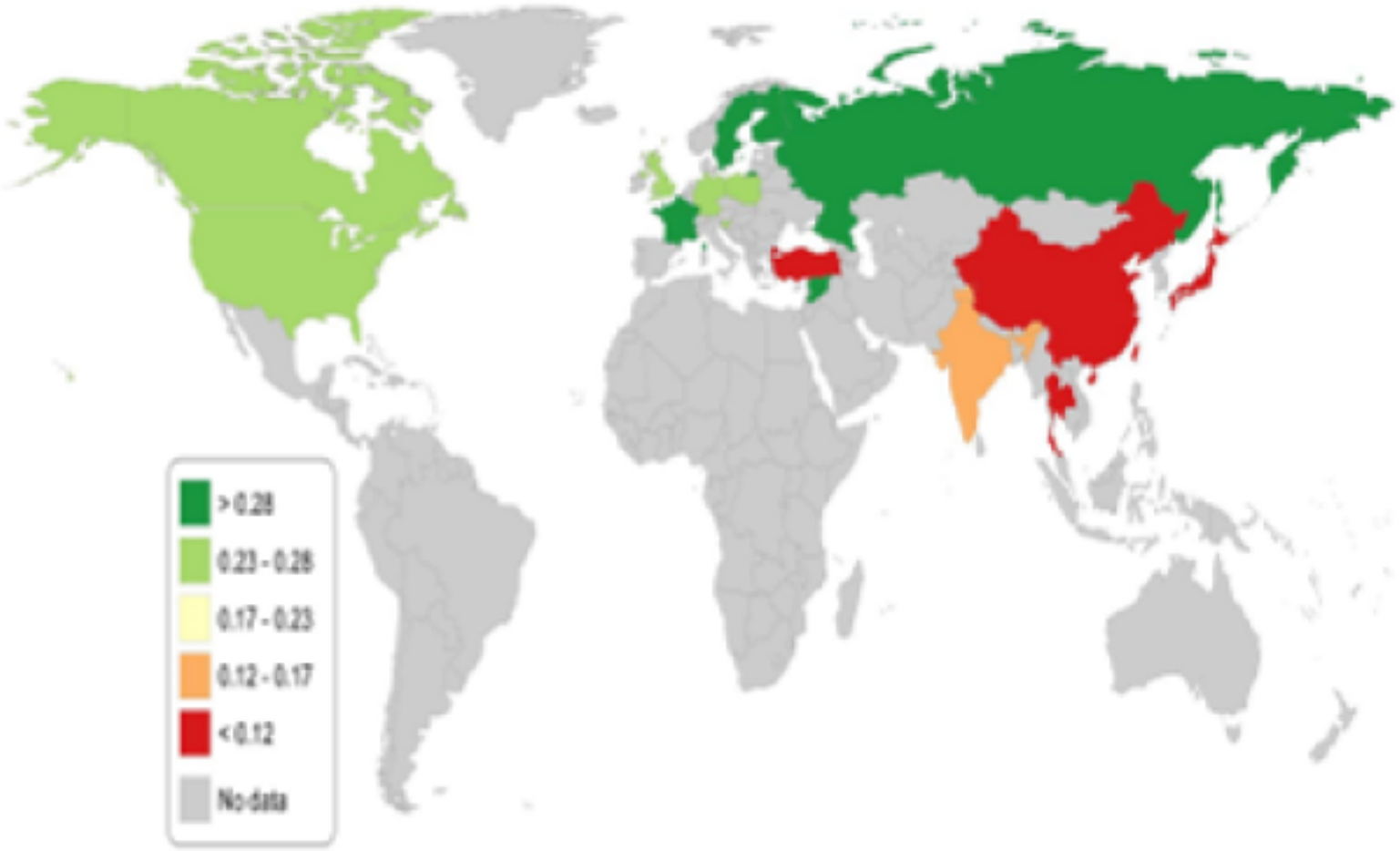
Val158Met Polymorphism Frequency

S. No.	Study	Country	Control No	No of alleles	Control Alleles		Frequency of Met alleles
					Val	Met	
1.	Wieres,2002	Austria	92	184	93	91	0.494
2.	McGrath,2004	America	641	1282	630	652	0.508
3.	Zimarina,2004	Russia	140	280	119	161	0.575
4.	Doherty,2005	America	420	840	387	453	0.539
5.	Juo,2006	Taiwan	306	612	481	131	0.214
6.	Tao,2006	America	1026	2052	1493	559	0.272
7.	Liu,2007	China	84	168	116	52	0.309
8.	Szyllo,2007	Poland	165	330	206	188	0.569
9.	Zhao,2007	China	110	220	154	66	0.3
10.	Hirata,2008	America	165	330	186	144	0.43
11.	Ashton,2010	Australia	290	580	277	303	0.522
12.	Li,2010	China	114	228	177	51	0.22
13.	Zhang,2011	China	65	130	92	38	0.29
14.	Trabert,2011	America	567	1134	578	556	0.49
15.	Christofolini,2011	Brazil	168	336	196	140	0.41
16.	Li,2013	China	38	76	58	18	0.23
17.	Peng,2013	China	100	200	121	79	0.39
18.	Shi,2013	China	40	80	56	24	0.3

World wide distribution of A allele



World wide distribution of AA genotype



Association of Val158Met with different types of psychiatric diseases /disorders

Psychiatric diseases/disorders	Association	Reference
Schizophrenia	Yes	Shifman et al., 2002
Bipolar disorder	Yes	Zhang et al., 2009
Depression	Yes	Opmeer et al., 2013
Autism	Yes	Guo et al., 2013
Obsessive Compulsive Disorder	Yes	Javeria et al., 2017
Attention Deficient Hyperactive Disorder	Yes	Gothelf et al., 2007
Posttraumatic Stress Disorder	Yes	Amstadter et al., 2009

Association of Val158Met with different types of cancer

Cancer type	Association	Reference
Lung Cancer	Yes	Zhang et al.,2013; Wu et al., 2014
Esophageal Cancer	No	Zhu et al., 2008; Huang et al., 2011
Colon Cancer	No	Huber et al., 2005; Zhou ,2009
Renal cancer	No	Heck et al., 2012
Bladder Cancer	No	Wolpert et al., 2012
Breast cancer	Yes	Rai et al., 2017
Prostate Cancer	Yes	Xiao et al., 2013
Ovary Cancer	No	Du et al., 2014
Endometrial Cancer	No	Lin et al., 2013

- **The study of the distribution of SNPs, particularly in different populations, is valuable for investigating molecular events that underlie evolution.**
- **The Generation of a comprehensive SNP catalog offers the possibility to identify many disease loci and, eventually, pinpoint functionally important variants in which the nucleotide change alters the function or expression of a gene that directly influences a disease outcome.**
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