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Genetic Factors Affecting Tobacco Cessation

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INTRODUCTION

Tobacco dependence is a multifactorial disorder which is influenced mainly by genetic, epigenetic and neurobiological mechanisms. The genes involved in receptor signaling of nicotine, dopamine levels regulation, and nicotine metabolism play important roles in determining individual susceptibility to nicotine addiction and cessation outcomes.

AIM

Analyzed important genes involved in nicotine dependence for polymorphisms, structural features, and functional relevance to tobacco cessation.

METHOD

➢ **Gene selection**
After a literature survey of 120 papers (published in mean time of 2020-2025), 16 genes were selected. (which had direct or indirect roles in nicotine dependence)

➢ **Sequence and structure retrieval**
FASTA sequences were obtained from NCBI, 3D structures were sourced from PDB, Uniprot & AlphaFold (used when experimentally resolved PDB structures were unavailable).

➢ **Variant Analyses and mapping**
Polymorphisms were identified and compiled from GenBank, dbSNP, PDB and Ensembl. Sites were mapped using ChimeraX.

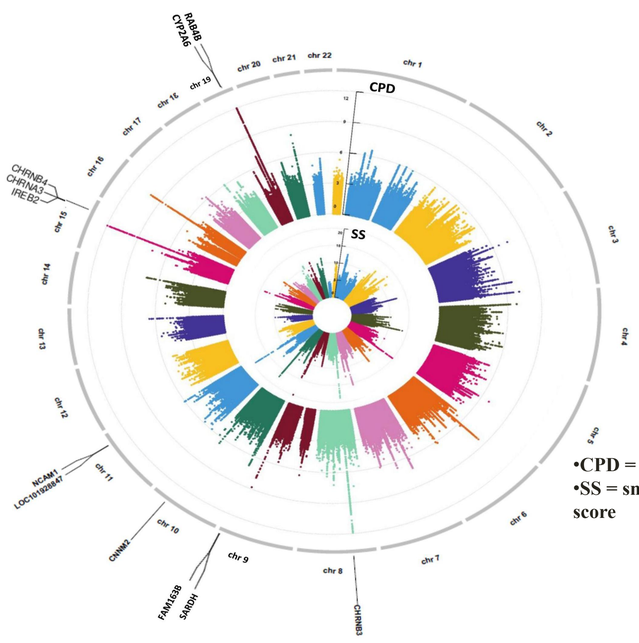
➢ **Binding Site Analysis**
Nicotine/neurotransmitter interaction sites were identified through literature and NCBI.

➢ **Comparative analysis and pattern visualization**
BLAST was used for sequence alignment and comparison which further supported pattern visualization using UMAP (created using python and its libraries).

RESULTS & DISCUSSION

CORE FINDINGS

CHRNA5/A3/B4 cluster showed the highest number of polymorphisms among the analyzed genes with CYP2A6 showing a lot of variations as well.
MAOA showed no coding-region polymorphisms, but methylation in regulatory/untranslated regions was implicated in nicotine dependence.
Nicotine dependence is therefore shaped by both **sequence variation** and **epigenetic regulation**.



•CPD = cigarettes per day
•SS = smoking severity score

Fig. Heatmap showing the severity score of smoking after the number of cigarettes per day

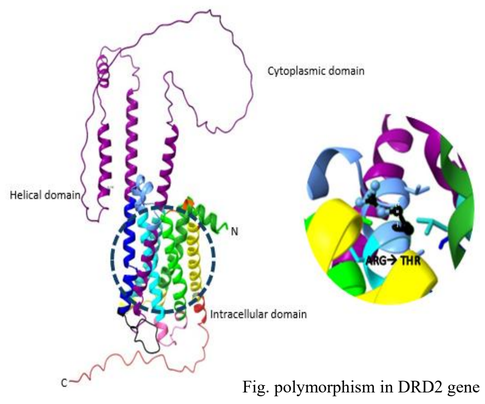


Fig. polymorphism in DRD2 gene

MAJOR GENETIC SYSTEMS

•**Nicotinic system:** CHRNA4, CHRNA5, CHRNA3, CHRNA7, CHRNB4.
•**Dopaminergic system:** DRD2, DRD3, DRD4.
•**Cellular transport:** SLC1A2, SLC6A4.
•**Serotonergic system:** HTR3A.
•**Opioidergic signaling:** OPRM1.
•**Nicotine metabolism:** CYP2A6.

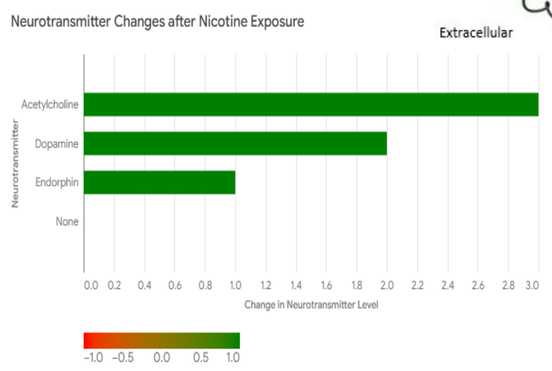


Fig: The chart above illustrates the changes in neurotransmitter levels after nicotine exposure.

EFFECTS OF GENETIC VARIANTS

•**CHRNA5 rs16969968:** associated with increased nicotine dependence and cigarette consumption.
•**DRD2 rs1800497 (TaqIA):** A1 allele is linked to greater vulnerability and smoking-related behaviors.
•**DAT1:** promoter methylation suggests altered dopamine transporter expression in nicotine-dependent individuals.
•**COMT Val158Met:** modulates dopamine neurotransmission and nicotine susceptibility, with sex-specific effects.
•**CYP2A6 variants:** alter nicotine metabolism rate and affect consumption as well as cessation success.

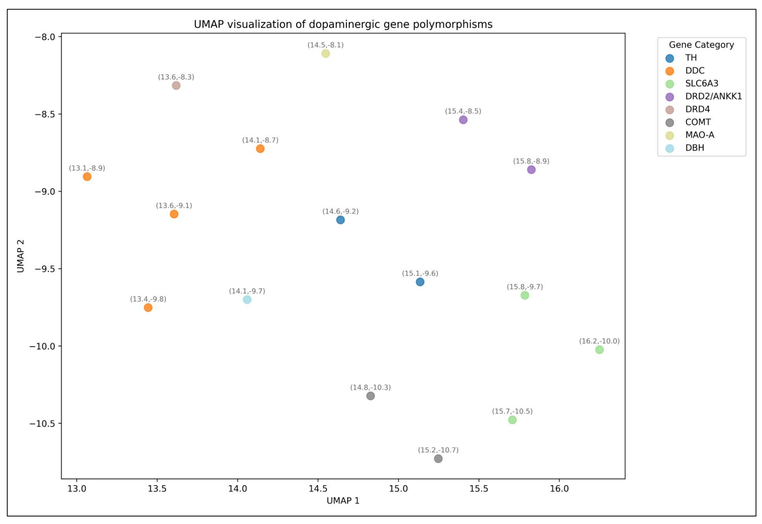


Fig. UMAP showing expression levels of genes before and after nicotine intake

FUNCTIONAL INTERPRETATION

•Genetic influence extends beyond classical polymorphisms and includes sequence changes in **MAOA, MAOB, DAT1, DRD1, and GABA-related genes**.

GABA receptor subunits, including GABRA2 and GABBR1, contain conserved domains involved in inhibitory neurotransmission relevant to nicotine dependence.

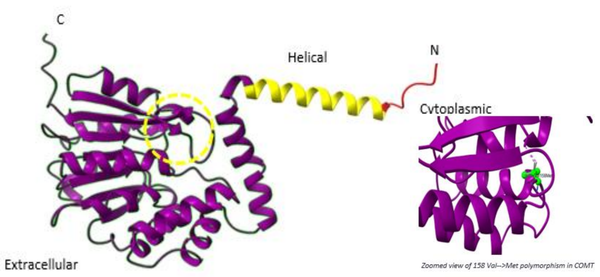


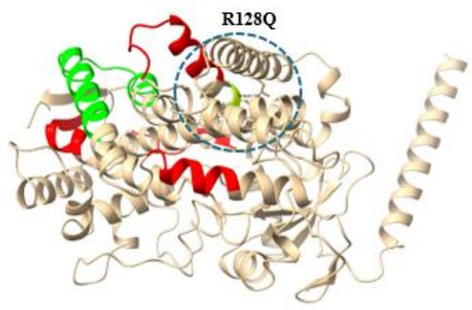
Fig. polymorphism in COMT gene

INDIRECT REGULATORY EFFECTS

•**CYP2A6, DAT1, MAOA, MAOB, COMT, and tyrosine hydroxylase** do not show direct nicotine-binding sites.
•Their effects are mediated indirectly through **methylation, dopamine transport modulation, or altered enzyme activity**.

DIRECT RECEPTOR ASSOCIATED AFFECTS

Several nicotine-related molecules show binding at **subunit pockets or α/β interfaces**.



CYP2A6 structural molecule [105]

CONCLUSIONS

The study reflects upon the major facts which state that nicotine dependence is governed not just by a single gene but its pleiotropic.
People suffering from nicotine dependence show polymorphisms in specific genes which show direct or indirect effects towards nicotinic gene polymorphisms and its binding sites.
ChimeraX modelling enables locating exact mutation sites as well as binding sites which help in precision medicine and personalized drug delivery systems.

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