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This issue contains:



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# Deep brain stimulation: selection of target in treatment resistant schizophrenia

- The nucleus accumbens may represent the strongest candidate for DBS electrode placement in schizophrenia
- Second comes the substantia nigra pars reticulata showing promise in a single case report.
- Ventral tegmental area is also of potential interest, though remains untried.

Schizophrenia is a chronic psychiatric disorder with a heterogeneous genetic and neurobiological background. The mean lifetime prevalence of the disorder is just below 1%, but large regional differences in prevalence rates are evident owing to disparities in urbanicity and patterns of immigration. [1] The main approach of Schizophrenia treatment involves treatment with anti-psychotics which act by blocking the post-synaptic dopaminergic (D2) receptor family. However, about 30% patients taking these drugs are resistant to it and less than half of these respond to the second generation antipsycotics also called as atypical antipsycotics. Other approaches including Cognitive behavioural therapy (CBT) and psychotherapeutic approach has proved with minimal effects.

Deep brain stimulation (DBS) is a well-established treatment technique [2] It is believed to work primarily by producing functional inhibition in the region around the electrode, but excitatory effects on local axons and more distant excitatory effects may also play a part. It has additionally been argued that the intervention may act in the longer term to correct pathological brain activity in brain networks with connections to the implantation site. Importantly, unlike other forms of psychosurgery, DBS is reversible, i.e., the stimulation can be turned off (and if necessary the electrodes explanted) without any permanent loss of function. The potential use of DBS in treatment resistant schizophrenia is currently a topic of considerable discussion. with much of the debate focusing on where to site the electrodes. This article examines rationales for electrode placement for DBS in schizophrenia.

| | Samples | Effect size (d) | % volume change |
|---|---|---|---|
| Main cortical divisions | | | |
| Frontal lobe grey matter | 17 | −0.49 (−0.64/−0.34) | −4.8 |
| Temporal lobe grey matter | 19 | −0.43 (−0.60/−0.26) | −4.1 |
| Parietal lobe grey matter | 9 | −0.31 (−0.54/−0.08) | −2.5 |
| Occipital lobe grey matter | 9 | −0.22 (−0.37/−0.07) | −2.7 |
| Other cortical regions | | | |
| Prefrontal grey matter | 16 | −0.44 (−0.48/−0.31) | −6.1 |
| Orbitofrontal cortex | 19 | −0.21 (−0.37/−0.05) | −3.0 |
| Superior temporal gyrus grey matter | 16 | −0.58 (−0.75/−0.41) | −8.2 |
| Fusiform gyrus | 10 | −0.52 (−0.76/−0.29) | −7.6 |
| Insula | 14 | −0.44 (−0.67/−0.20) | −5.2 |
| Parahippocampal gyrus | 20 | −0.24 (−0.39/−0.09) | −4.5 |
| Anterior cingulate gyrus | 29 | −0.34 (−0.46/−0.22) | −5.8 |
| Posterior cingulate gyrus | 10 | −0.32 (−0.56/−0.09) | −6.1 |
| Subcortical structures | | | |
| Hippocampus | 87 | −0.52 (−0.60/−0.44) | −6.3 |
| Amygdala | 40 | −0.31 (−0.43/−0.19) | −4.8 |
| Thalamus | 35 | −0.31 (−0.40/−0.22) | −3.4 |
| Caudate nucleus | 35 | −0.03 (−0.14/+0.07) | n/a |
| Putamen | 28 | +0.10 (−0.07/+0.26) | n/a |
| Globus pallidus | 15 | +0.26 (+0.02/+0.50) | +5.2 |
| Cerebellum | 20 | −0.15 (−0.30/−0.01) | −1.5 |

Meta-analysis of volume reductions in selected brain regions in schizophrenia [5]

Changes in the brain structure are well established in Schizophrenia involving lateral ventricular enlargement (25%), reduction of grey matter (4%), white matter reductions (2%). However, the changes in brain structure in all regions is prominent irrespective of volume of changes yet not uniform. [4]

Functional imaging has a better precipitating factor to schizophrenia when compared to structural imaging. Functional imaging carried out during task performance, in particular, has also revealed a more complicated pattern of frontal activation in schizophrenia. The hippocampus of the brain has been of keen interest among researchers for its involvement in schizophrenia. A recent study showed that volume and neuron number were significantly reduced in multiple hippocampal subfields in left, but not right hippocampus, whereas neuron density was not significantly different in any hippocampal subfield.

But the FIDMAG trial [2] in 2020, mainly focused on positive symptoms but its possible effects on negative symptoms were also of keen interest. This trial recruited 8 treatment resistant schizophrenic patients and electrodes were placed in two regions namely, nucleus accumbens (N=4) and subgenual medial frontal cortex (N=4) as these sites had been previously employed in treatment of Obsessive Compulsive Disorder (OCD) and Major Depressive disorder (MDD). 7 patients completed the trial (One patient with nucleus accumbens placement had post-operative complications and electrodes had to be removed). Improvement appeared to be more marked for the nucleus accumbens than for the subgenual anterior cingulate cortex placement, with two out three of the former patients undergoing nearly complete remission of positive symptoms. Both the patients, however, later developed significant psychiatric side-effects, of apathy/negative symptoms and mood instability respectively.

The best established site of brain dysfuntion in schizophrenia is the dorsolateral prefrontal cortex, but this region does not promise a good target site for the placement of electrodes. The hippocampus has been a questionable target for DBS but there has been no functional evidence rooting for its activity in schizophrenia. Substantia nigra pars reticulata placement has also shown promise in a single case report. The ventral tegmental area, is also a possible location but has to be further evaluated.

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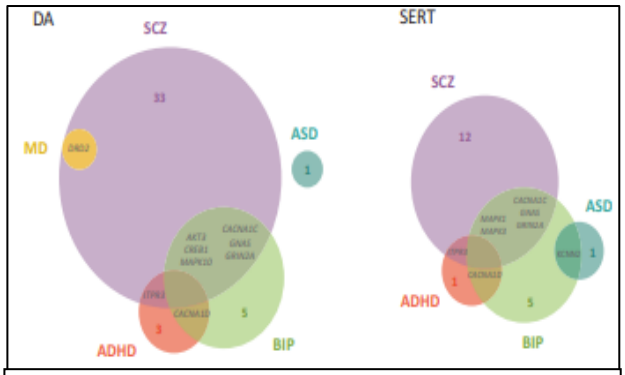
# Dopaminergic and Serotonergic pathways: Genetic Contribution in psychiatric disorders

Presence of complex traits in an individual in interaction with various genetic and environmental risk factors precipitate the heritability of the factors immensely. [1] Psychiatric disorders have considerably overlapped these factors along with increased severity and resistance to treatment. [2] A recent study conducted in 2019, called the Genome-wide association study (GWAS) meta-analysis, conducted a study on genetic correlations on eight psychiatric disorders namely, attention-deficit hyperactivity disorder (ADHD), Anorexia nervosa (ANO), autism spectrum disorder (ASD), Bipolar disorder (BIP), Major depression (MD), obsessive compulsive disorder (OCD), Schizophrenia (SCZ) and Tourette's syndrome (TS) and concluded that these conditions can be explained by shared genetic risk factors, supporting the existence of a set of genes that confer relatively broad liability to psychiatric disorders. [4]

- Systematic genetic study of the dopaminergic and serotonergic neurotransmitter systems in eight psychiatric disorders (ADHD, ANO, ASD, BIP, MD, OCD, SCZ, and TS)
- Identified association of 67 DA and/or SERT genes with at least one of the studied disorders, twelve of them associated with two conditions




Dopaminergic and serotonergic genes associated with the studied disorders

The most studied genes are SLC6A3 and SLC6A4 encoding dopaminergic transporter (DAT) and serotonin transporter (SERT) respectively. Interestingly, the outcome of GWAS [4] evidenced that the classical serotonergic and dopaminergic candidate genes, like transporters (SLC6A3 and SLC6A4) and receptors are not significantly associated with any psychiatric disorder, with one exception, DRD2, that was found associated with both MD and SCZ.

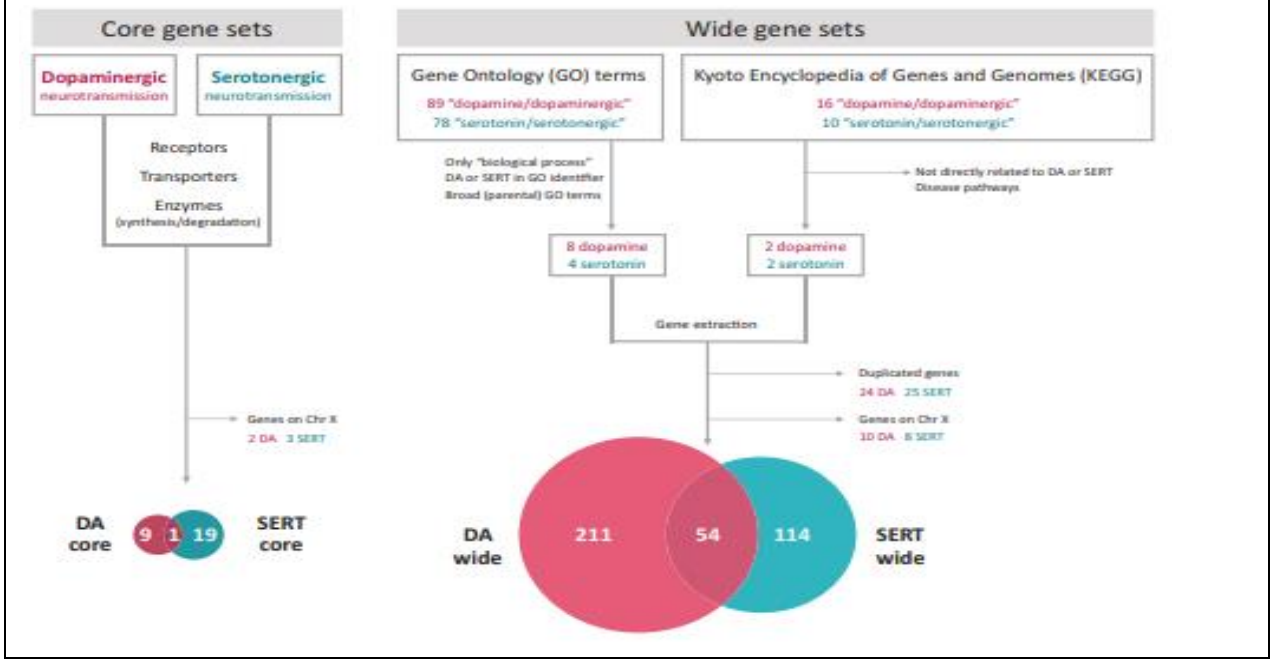

**Results of the MAGMA gene-set association analysis on every phenotype under study**. A small circle represents nominally significant p value, a big circle represents significant p value after the empirical multiple testing correction implemented in MAGMA. DA dopaminergic gene set, SERT serotonergic gene set, ADHD Attention-deficit/hyperactivity disorder, ANO Anorexia nervosa, ASD Autism spectrum disorder, BIP Bipolar disorder, MD Major depression, OCD Obsessive-compulsive disorder, TS Tourette's syndrome SCZ Schizophrenia, CD-MA Cross- disorder.

Initially, this study obtained 2 core gene sets through manual curation (DA core with 12 genes, and SERT core with 23 genes), containing the well-known dopaminergic or serotonergic genes (neurotransmitter receptors*: DRD1-5, HTR1A-B, HTR1D-F, HTR2A-C, HTR3A-E, HTR4, HTR5A, HTR6, HTR7*; transporters: *DAT1/SLC6A3, 5HTT/SLC6A4*; and enzymes involved in their anabolism or catabolism: *DDC, TH, TPH1, TPH2, DBH, COMT, MAOA, MAOB*). Two main databases were used for a wide selection of genes encoding proteins involved in dopamine and serotonin neurotransmission and signalling pathways. Four gene lists were obtained: (i) DA core (10 genes); (ii) DA wide (265 genes); (iii) SERT core (20 genes); and (iv) SERT wide (168 genes). The gene-based and gene-set associations analysis of each phenotype was performed.

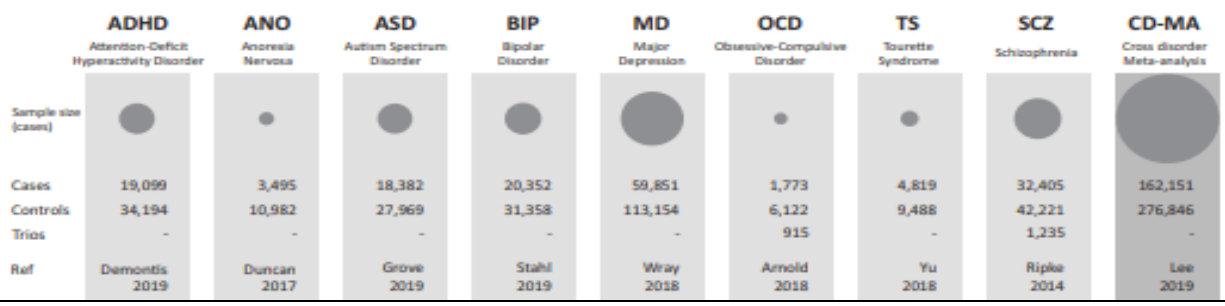
This study was mainly aimed to assess the genetic contribution of the two monoaminergic systems to eight different psychiatric disorders (ADHD, ANO, ASD, BIP, MD, OCD, SCZ and TS) as well as the meta-analyses of all of them. Hence 4 different gene sets were evaluated, and was found that 67 genes from DA and/or SERT gene sets significantly associated with at least one of the studied disorders, and 309 genes were not associated with any of them. Twelve of these genes were associated with two different disorders, eight of them with SCZ and BIP. Eleven out of these twelve genes also showed a significant association with the CD-MA phenotype, *DRD2* from the DA core gene set among them. Interestingly, five out of these twelve genes *(CACNA1C, CACNA1D, GNAS, GRIN2A* and *ITR3*) belong to both the DA and SERT gene sets, highlighting the importance of those genes that are involved in both monoamine pathways. The results obtained were plotted in a Manhattan plot and the DA core and SERT core genes were highlighted to visualise the performance of the gene.

**Workflow of the selection and analysis of dopamine and serotonin gene sets**

Strategy for the selection of the serotonin (SERT) and dopamine (DA) gene sets using Gene Ontology and KEGG's pathways for the wide sets and manual curation for the core sets. All genes of the core gene sets are also included in their corresponding wide gene set.



Description of samples used in this study. The area of the circles is proportional to the sample size of the disorder




The dopaminergic gene sets, in this analysis, were associated with most of the investigated traits, such a trans-diagnostic efficacy of dopamine-modulating drugs might be explained on the genetic level. At gene level, the study identified association of 67 DA and/or SERT genes with at least one of the studied disorders, twelve of them associated with two conditions. Gene-set analysis revealed significant associations with the DA gene sets for ADHD, ASD, and the cross-disorder GWAS meta-analysis, and with SERT gene sets for MD and BIP. The results obtained support a cross-disorder contribution of these two neurotransmitters systems in several psychiatric conditions.

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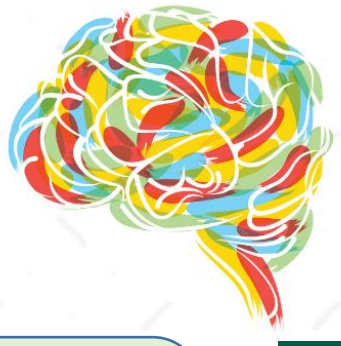

## Disease progression predictors of Parkinson's disease

- Study demonstrated the motor progression over 1 year in an under-investigated population that showed high annual worsening.
- Showed significant associations between motor progression over 1 year and baseline scores.

Parkinson's disease (PD) is known as a chronic neurodegenerative disorder with a relentlessly progressive course of illness. The most important predictors for worse motor progression are age and motor disability at baseline. [1] Recent studies suggest that cardiovascular risk factors contribute to more severe PD phenotype. [2] The problem with early diagnosis if the condition is that there is no real biomarker that predicts the onset of the illness [3] and thus investigating the available laboratory tests and MRI brain findings are more feasible. This study aims to assess the predictors of motor progression of PD over 1 year either clinical (baseline characteristics), neuroimaging or biochemical (serum uric acid, lipid profile, glycated hemoglobin (HbA1c)).

This study was a prospective cohort study with a sample size of 75 patients with prior informed consent were recruited out of which 45 patients had completed the assessments at baseline, 6 months and after 1 year. Comprehensive medical history, neurological examination, laboratory testing, as well as brain imaging were done initially, followed by assessment scales at baseline, 6 months, and at 1 year. They included motor assessment using MDS-UPDRS ( Movement Disorder Society- Unified Parkinson's Disease Rating Scale) during OFF state, Hoehn and Yahr, Schwab and England Activities of Daily Living Scale , baseline gait assessment during OFF state by New Freezing of Gait Questionnaire (NFOG-Q) , Berg Balance Scale (BBS) , 10-Meter Walking Test (10-MWT) , and Time Up and Go Test (TUG) , physical activity through International Physical Activity Questionnaire short form (IPAQ) , baseline assessment of nonmotor symptoms using the Non-Motor Symptoms Scale (NMSS), depression assessment by the Arabic version of Beck Depression Inventory (BDI), as well as quality of life testing using the Arabic version of PD questionnaire 39 (PDQ-39), and cognitive assessment at baseline was done by Mini-Mental State Examination (MMSE). Levodopa equivalent daily dosage (LEDD) was calculated at baseline as the sum of the daily dose of all dopaminergic agents [4]. Mean difference was obtained and percentage value was calculated. Alongside these evaluations, serum uric acid levels. Lipid profile and HbA1c were measured at baseline and MRI of brain was done to assess white matter hyperintensities lesions (WMHL).

The study showed a high rate of motor progression. The mean difference of MDS-UPDRS III was − 11.83, while the rate of progression was 26.93% within 1 year and showed that the mean annual progression rates of motor impairment and disability ranged from 2.4 to 7.4%. This could be explained by the lower age of onset and severity of the current cohort, as motor progression decrease with advancing disease. [5] Moreover, the presence of medical comorbidities in about half of recruited patients (46.7%) also could explain this higher rate of progression.

In addition to individual variability, motor progression of PD is variable between patients and disease subgroups. But there was no significant difference in progression in either males or females. Minimal differences in motor progression were detected between TD (tardive dyskinesia) and non-TD (non- tardive dyskinesia) subtypes including disease severity (Hoehn

and Yahr) and physical activity. Comparing early-onset and late-onset PD at baseline showed no significant difference in motor progression.

This is inconsistent with a previous study that found slower progression in EOPD (Early Onset of Parkinson's Disease) and suggests that the pre-clinical interval in this group is longer. [6]

The current study showed variability of White Matter Hyperintensities (WMH) in size in agreement with previous studies, yet these changes could not predict progression over 1 year. Inconsistency with other studies may be attributed to different methodology, a small number of

| Mean difference between baseline and 1-year follow-up | | Age | AOO[a] | DOI[a] | Baseline MDS-UPDRS-OFF-Total score | Baseline MDS-UPDRS-III | Baseline PIGD OFF[a] | Baseline Hoehn and Yahr OFF[a] | Baseline TUG OFF[a] | Baseline NFOG-Q OFF[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| Δ MDS-UPDRS total score OFF | Pearson | − 0.024 | − 0.060 | 0.073 | − 0.170 | − 0.045 | − 0.029 | 0.152 | 0.078 | − 0.025 |
| | Sig | 0.876 | 0.698 | 0.640 | 0.269 | 0.773 | 0.851 | 0.324 | 0.614 | 0.874 |
| Δ Axial OFF[a] | Spearman | 0.059 | 0.024 | − 0.015 | − 0.168 | − 0.143 | − 0.172 | 0.011 | 0.070 | − 0.016 |
| | Sig | 0.702 | 0.879 | 0.923 | 0.275 | 0.355 | 0.263 | 0.945 | 0.652 | 0.918 |
| Δ PIGD OFF[a] | Spearman | − 0.033 | − 0.053 | 0.010 | − 0.110 | − 0.044 | − 0.226 | 0.078 | 0.117 | − 0.047 |
| | Sig | 0.830 | 0.734 | 0.951 | 0.476 | 0.775 | 0.140 | 0.616 | 0.450 | 0.764 |
| Δ Motor complication total score[a] | Spearman | − 0.186 | − 0.281 | 0.084 | − 0.194 | − 0.095 | − 0.183 | − 0.193 | − 0.273 | − 0.137 |
| | Sig | 0.227 | 0.065 | 0.586 | 0.208 | 0.539 | 0.234 | 0.210 | 0.073 | 0.375 |
| Δ Hoehn and Yahr OFF[a] | Spearman | 0.006 | − 0.102 | **0.367** | 0.204 | 0.157 | 0.284 | 0.181 | **0.319** | 0.252 |
| | Sig | 0.970 | 0.509 | **0.014** | 0.184 | 0.309 | 0.062 | 0.239 | **0.035** | 0.099 |
| Δ Schwab and England ADL OFF[a] | Spearman | 0.098 | − 0.042 | **0.337** | **0.478** | **0.350** | **0.591** | **0.401** | **0.565** | **0.498** |
| | Sig | 0.526 | 0.785 | **0.025** | **0.001** | **0.020** | **<0.001** | **0.007** | **<0.001** | **0.001** |
| Δ IPAQ | Pearson | 0.055 | 0.199 | − 0.222 | − 0.073 | − 0.045 | − 0.110 | 0.110 | − 0.042 | − 0.231 |
| | Sig | 0.725 | 0.195 | 0.148 | 0.639 | 0.773 | 0.477 | 0.478 | 0.788 | 0.131 |

Correlations between progression of motor and physical activity with baseline demographic and clinical characteristics

patients, using low-resolution MRI, short follow-up and low WMH load of most of the recruited patients. Therefore, further MRI studies are warranted to evaluate short prognostic values of WMH.

Baseline lipid profile was not correlated to motor progression of PD in the current study in agreement with previous studies, which failed to find a significant linkage between lipid profile abnormalities and PD progression. Triglyceride level was correlated to progression of motor complications in this study, which is inconsistent with previous studies demonstrating no significant association between triglycerides and motor or cognitive progression. [7] Serum uric acid was not correlated to PD progression in this cohort, in contrast to previous studies which reported that low levels of serum uric acid associated with a high risk of PD progression and worsening of UPDRS scores. [8] Moreover, HbA1c was not correlated to PD progression in this study in agreement with the uncertainty about the role of HbA1c to predict PD progression in previous studies. [9]

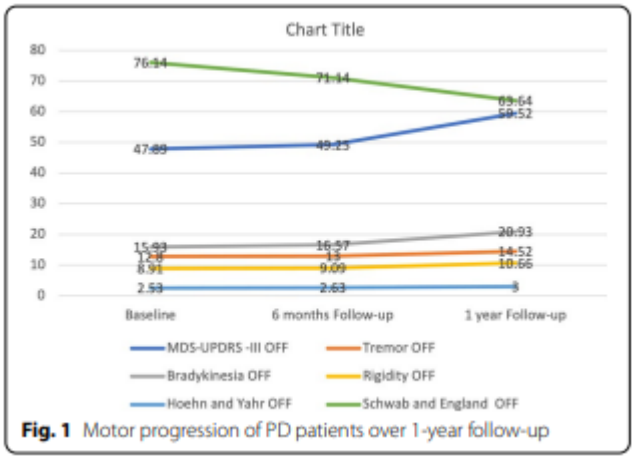


**Fig. 1** Motor progression of PD patients over 1-year follow-up

The current study demonstrated the motor progression over 1 year in an under-investigated population that showed high annual worsening. It showed significant associations between motor progression over 1 year and baseline scores.

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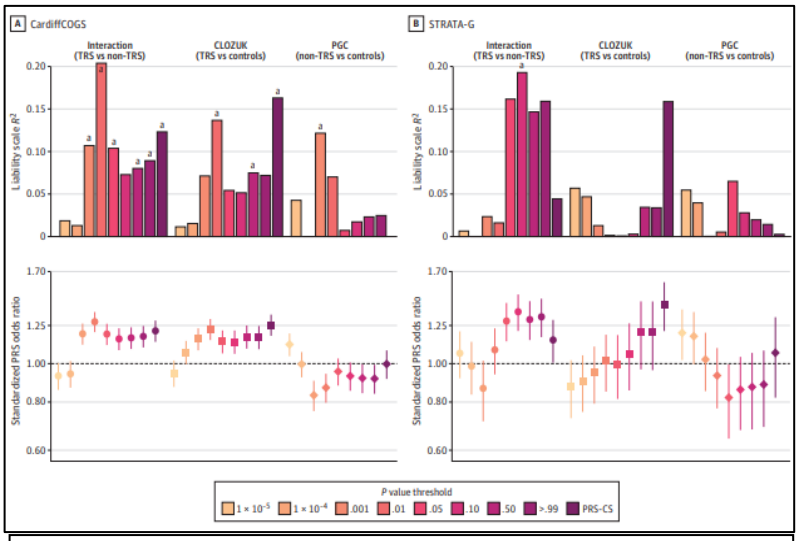
# Estimation of Polygenic Risk Scoring for testing Association of Common Genetic Variants in Treatment Resistance in Schizophrenia

- TRS had a small but detectable heritability associated with common risk alleles.
- The polygenic validation through the PRS method, showed that the contribution of these alleles were similar across incidence and prevalence samples.

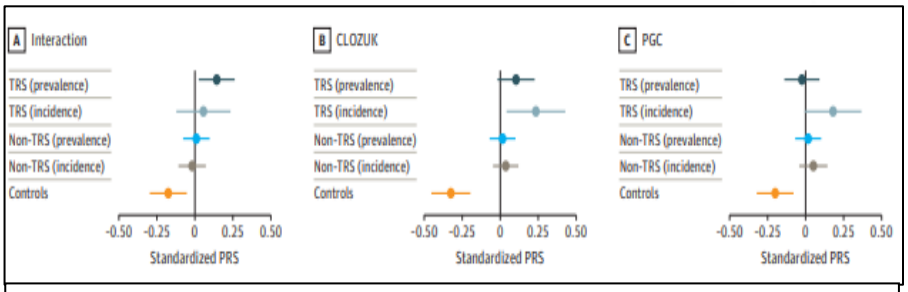
About 20% to 30% of people with schizophrenia have psychotic symptoms that do not respond adequately to first-line antipsychotic treatment. This clinical presentation, chronic and highly disabling, is known as treatment-resistant schizophrenia (TRS). [1] The only treatment that has proved effective in treatment of TRS is clozapine, which is effective in approximately about 60% of the cases. [2] Even though the exact mechanism of clozapine in schizophrenia is not known, several studies have also shown that delay in clozapine prescription is associated with resistance to even clozapine. [3] This study aimed to characterize the contribution of common genetic variants to treatment resistance in schizophrenia by exploiting data generated by large consortium based GWASs (Genome Wide Association Studies) of schizophrenia, [4 ,5] in which individuals with TRS can be formally defined.




Polygenic Score Analysis of the Cardiff Cognition in Schizophrenia (CardiffCOGS) Cohort and Genetics Workstream of the Schizophrenia Treatment Resistance and Therapeutic Advances (STRATA-G) Cohort Using 3 Different Schizophrenia-Related Polygenic Risk Scores (PRS)

For the main analyses, samples from large genomic studies of schizophrenia were used based on clozapine prescription and meta-analytic procedure to assess the difference between GWAS in which individuals with TRS and non-TRS are compared with matched sets of healthy controls, before comparing the allelic association effect sizes of these 2 GWASs on a genome wide basis to create a GWAS specific to treatment resistance. [6] CLOZUK1 and CLOZUK2 cohorts (samples from studies [5,7] ) were taken as primary source of individuals with TRS with total sample of 10501 subjects with TRS and 24542 subjects as controls. These cohorts had been described in previous studies. [5,7] These subjects with TRS in the samples were prescribed

with clozapine after failure of atleast 2 trials of antipsychotics and control individuals were from public databases or through collaboration with population.




Polygenic Profile Derived From Combined Genotype Data From the Cardiff Cognition in Schizophrenia (CardiffCOGS) and Genetics Workstream of the Schizophrenia Treatment Resistance and Therapeutic Advances (STRATA-G) Cohorts Using Scores Calculated With Linkage Disequilibrium–Independent (P < 1) Single-Nucleotide Variants

The association of PRS (Polygenic Risk Score) and treatment resistance status based on (1) the CLOZUK TRS vs healthy control GWAS and (2) the Psychiatric Genomics Consortium (PGC) non-TRS GWAS was investigated. The polygenic validation was conducted by finding the association between TRS, GWAS, PRS and treatment resistance status. The study included a total of 85,490 participants (48 635 [56.9%] male) in its GWAS stage and 1380 participants (859 [62.2%] male) in its PRS validation stage.

The result of the interaction analysis detected a true polygenic signal for treatment resistance, with a greater burden of risk alleles from both this and the CLOZUK TRS GWAS associating with the history of clozapine prescription. Also, the PRS derived from non-TRS samples was not as clearly associated with treatment resistance, and some results of these analyses are even compatible with its enrichment in individuals with non-TRS. These results were used to examine the genetic associations between the treatment-resistant phenotype and other disorders and traits and resulted that 8 of 28 publicly available GWAS summary statistics displayed nominally significant genetic correlations with TRS, of which 5 survived multiple testing correction suggesting that these variants were also associated with general risk of schizophrenia, and that the difference in their associations with the 2 phenotypes may have influenced the polygenic score analyses. These results were consistent with the risk conferred by common single-nucleotide variation (SNVs) being similar regardless of whether individuals respond to first-line treatments. Also by assessing differences at the level of individual allelic associations, our results also support the existence of a polygenic contribution associated with treatment resistance that seems largely distinct from liability to schizophrenia.

A study conducted in 2017, [8] that TRS is categorically different illness subtype to treatment-responsive schizophrenia, and the results from the current study also throws light in that direction. Despite a large genetic correlation between both conditions, the study showed that PRS derived from them perform differently when attempting out-of-sample prediction of TRS, which suggests that the heterogeneous results previously obtained in PRS analyses might have been influenced by the presence of individuals with TRS in the generic schizophrenia training sample. However, follow up studies should be conducted to obtain better correlation. The results showed that TRS was heritable trait (1%-4%).

In this study, TRS had a small but detectable heritability associated with common risk alleles. The polygenic validation through the PRS method, showed that the contribution of these alleles were similar across incidence and prevalence samples.

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