Schizophrenia Research 243 (2022) 214–216

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the Editor

Multimorbidity landscape of schizophrenia: Insights from meta-analysis of genome wide association studies

ARTICLE INFO

Keywords
Schizophrenia
Comorbidity
meta-analysis
SNP
Disease enrichment analysis

To the Editors

Schizophrenia (SCZ) is a neuropsychiatric disorder with a prevalence rate of 1% causing severe disability. Although several genetic and environmental causative factors are implicated for SCZ, the high heritability of nearly 80% emphasizes the role of the genetic component. Being a multigenic disorder, individuals with SCZ often present with several comorbidities that are diagnosed at varied stages of disease progression. The timely diagnosis of these comorbidities will help in improving treatment outcomes, quality of life and reducing mortality in SCZ.

Genome wide association (GWA) studies data mining can aid in identifying the risk of comorbidity in SCZ due to shared gene-disease associations. We performed gene and disease enrichment analysis on GWAS Catalog (Buniello et al., 2019) (https://www.ebi.ac.uk/gwas) data, downloaded upto 16/05/2021, and screened for studies that had individuals with SCZ (and no other comorbidities) as case group and healthy individuals as control group. We found 22 GWA studies and 654 single nucleotide polymorphisms (SNPs) (P Value $<5 \times 10^{-8}$) that qualified for the disease enrichment-analysis (Supplementary Table S1A). All the entries were verified by manually reviewing the publications describing subject selection and recruitment of individuals. The ethnicity distribution of the 22 GWA studies included Asian (5), European (5), Ashkenazi Jews (1) and mix of east Asian, European and others (11). SNPs were labelled as "coding" or "non-coding" based on context information available in GWAS catalog. SNPs with context as "missense" and "synonymous" were marked as "coding" SNPs; and context as "5′ or 3′ UTR", "intragenic", "intron", "regulatory region" and "non-coding transcript exon" were marked as non-coding SNPs. These coding and non-coding SNPs were used to identify quantitative trait loci (QTL) i.e. loci that influences the expression of another gene (eQTL); or alterations in DNA methylation (mQTL) or protein expression (pQTL). The SNPs present in GWAS Catalog were of GRCh38.p13 form which were converted into GRCh37 (hg19) for the mapping of tissue specific (brain related tissues) QTL from QTLbase (Zheng et al., 2020) (http://www.mulinlab.org/qtlbase). The target genes with P Value of <0.05 (Supplementary Table S1B) were subjected to disease enrichment analysis using GeDiPNet (http://gedipnet.bicnirrh.res.in), an in-house developed knowledgebase of genes, diseases and pathway networks.

The results of disease enrichment analysis revealed that 53 diseases were significantly enriched and the most enriched parent disease terms were related to cellular proliferation (18%), immune (15%) and nervous system diseases (13%; Fig. 1A; Supplementary Table S2). We validated these observations by comparing the findings to the clinical phenotypes reported for SCZ individuals. Breast cancer featured as the top enriched disease and this observation is in accordance with clinical reports of increased risk of breast cancer observed in women with SCZ (Lu et al., 2020). Apart from breast cancer, SCZ has been clinically associated with colorectal cancer, carcinomas, lung cancer, and colon cancer (Nordentoft et al., 2021). These cancers are identified by the SNP enrichment analysis (Fig. 1B). Many epidemiological studies have identified a positive association between SCZ and autoimmune disorders such as lupus erythematosus (Tiosano et al., 2017), psoriasis (Eaton et al., 2010); hearing loss (Molina et al., 2021) and Crohn's Disease (Bernstein et al., 2019). Alzheimer's disease also featured amongst the top enriched diseases. Several clinical studies have reported that white matter deficit is a phenotype shared amongst Alzheimer's and SCZ; and individuals with SCZ have an elevated risk for Alzheimer's disease (Kochunov et al., 2021). Eight genes identified from SNP analysis of SCZ individuals were associated with 10 or more diseases (Fig. 1C). These eight genes were *CYP21A2* (chromosome 6), *NOTCH4* (chromosome 6), *POLG* (chromosome 15), *MECP2* (X chromosome) and the remaining four genes belonged to *HLA* locus (chromosome 6).

Since the observations from disease enrichment analysis were in accordance with clinical and epidemiological reports, the data generated from this analysis was compiled to create an online tool that can aid in predicting the risk of multimorbidity in SCZ individuals presenting with one or more comorbid conditions. For e.g., using the tool, it is predicted that an individual presenting with SCZ, seizures and bipolar disorder may likely be harboring *MECP2* variants and will have a high risk for breast cancer; as compared to SCZ individual with celiac disease wherein the predisposing gene may be one of the *HLA* genes and such individuals will have higher risk for morbidities such as lymphoma and Crohn's disease (Fig. 1C). These predictions concur with clinical

https://doi.org/10.1016/j.schres.2022.03.013
Received 22 March 2022; Received in revised form 25 March 2022; Accepted 26 March 2022
Available online 20 April 2022

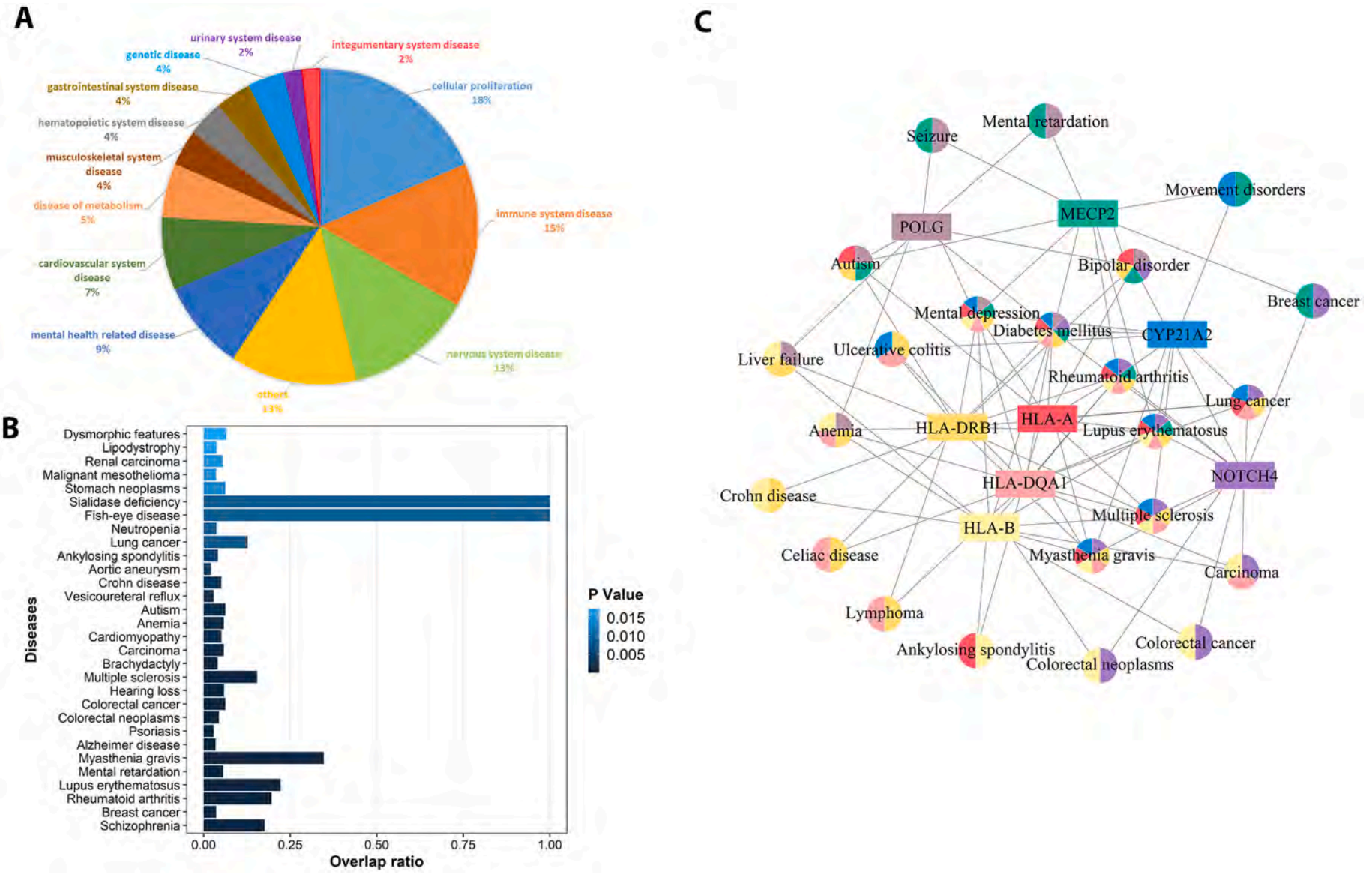

Fig. 1. A) Pie chart depicting the distribution of parent disease terms for morbidities associated with SCZ; B) bar plot depicting top 30 diseases associated with SCZ. The x-axis and y-axis represent gene-overlap ratio and associated diseases respectively; C) network of genes associated with ten or more diseases. Square and circular nodes represent the genes and diseases respectively. Edge represents a gene-disease association. The circular node is segmented into colored pies to illustrate the associated genes with each disease. Diseases associated with a single gene are not displayed in the network.

phenotypes observed for SCZ individuals (Cunningham et al., 2015). This multimorbidity risk prediction tool for SCZ (MRPS) is freely accessible at http://www.mrps.bicnirrh.res.in.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.03.013.

Role of the funding source

The funders had no role in study design, data collection, and analysis, decision to publish, or preparation of the manuscript.

CRediT authorship contribution statement

SIT conceptualized the study and methodology, supervised the work and reviewed the manuscript. DKD was involved in the conceptualization of study and reviewed the manuscript. UG and PH performed the data curation and analysis. UG was involved in data visualization. SIT, KD, UG, and BRS wrote the manuscript. RSB developed the multimorbidity risk prediction tool for schizophrenia (MRPS). All authors contributed to data interpretation. All authors read and approved the final manuscript.

Ethics approval

Exemption from ethics review was approved by the ICMR-NIRRCH Ethics committee for clinical studies (D/ICEC/Sci-32/35/2022).

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgment

Authors are grateful to Dr. Debangana Chakravorty and Ms. Indra Kundu for help with data curation.

Funding

This work [RA/1227/03-2022] was funded by Indian Council of Medical Research (ICMR), and Department of Biotechnology (DBT), India [BT/PR40165/BTIS/137/12/2021].

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