beta=0.1041, p=0.2016; AT-PRS x recent stress: beta=19.82, p=0.05811; AG-PRS x recent stress: beta=0.3169, p=0.6661).
Conclusions: Our present results show that while there is an overlap in the genetic background of depression and some autoimmune or inflammatory conditions, current stressors may not have an interacting role in this relationship. Our results need replication in larger samples, and should be extended to investigate polygenic scores for other conditions and other types of stress.
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EPP308

COX-2 gene rs689466 polymorphism and nicotine dependence among schizophrenia patients

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Introduction: In addition to play a key role in the generation of the inflammatory response, cyclooxygenases (COXs) are involved in a variety of other physiological processes, including dopaminergic signaling, and the skin flush response to the water-soluble B vitamin niacin. Patients with schizophrenia frequently exhibit abnormal signaling of dopamine and other neurotransmitters and attenuated niacin skin flush response. Clinical studies reported beneficial effects of selective cyclooxygenase-2 (COX-2) inhibitors on the simptom expression of schizophrenia, as measured by the Positive and Negative Syndrome Scale (PANSS). Several studies investigated potential correlations between functional rs689466 polymorphism (A/G polymorphism) of the COX-2 gene and etiology of schizophrenia, but the results have not been consistent. While we did not find evidence that the COX-2 polymorphism was associated with an elevated risk of schizophrenia risk in a Croatian population, we observed that the COX-2 polymorphism contributes to attenuated niacin skin flushing in patients with schizophrenia.
Objectives: To the best of our knowledge, no studies have investigated the potential associations between any COX-2 gene polymorphisms and the etiology of nicotine dependence. Based on the elevated smoking rate observed consistently in patients with schizophrenia and the possible relevance of COX-2 genes in schizophrenia and nicotine dependence via dopaminergic signaling, we investigated whether the risk of nicotine dependence among patients with schizophrenia is associated with the COX-2 gene rs689466 polymorphism. Given evidence suggesting that smoking influences the severity of schizophrenia, we also hypothesized that an interaction between smoking and the COX-2 polymorphism may contribute to the age of schizophrenia onset and/or PANSS psychopathology.
Methods: Polymerase chain reaction analysis/restriction fragment length polymorphism analysis was used to genotype 190 chronically ill schizophrenia patients treated with antipsychotic medications (104 males/86 females).
Results: There were no significant differences in the distribution of COX-2 genotypes and alleles in male or female schizophrenia patients who were stratified based on their smoking status and no COX-2 genotype-smoking interaction on PANSS psychopathology ($P > 0.05$). We revealed a significant COX-2 genotype-smoking interaction on the time of disease onset among female patients ($P < 0.05$). An earlier onset, observed for female smokers carrying the G-allele in their COX-2 genotypes (COX-2-GG homozygous and COX-2-AG heterozygous), in comparison to nonsmoking COX-2-G allele carriers, contributed mostly to this finding.
Conclusions: Our results indicate no COX-2 gene polymorphism's effect on the risk of nicotine dependence, but they suggest that COX-2 genotype-smoking interaction might be of relevance in disease onset, in a gender-specific fashion.

Disclosure of Interest: None Declared

EPP310

Quantitative Co-expression and Pathway Analysis Reveal the Shared Biology of Intellectual Disabilities

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Introduction: Intellectual disabilities(ID) are heterogeneous conditions, where mutations in more than 1000 genes are associated with ID. In the Genomic England gene panel, at least 1399 genes have sufficient evidence to be deemed diagnostic grade. The cellular pathways in some of these genes function remain ill-defined.
Objectives: Identification of molecular pathways or upstream regulators common across multiple intellectual disability genes would increase our understanding of the pathophysiological mechanisms and potentially identify therapeutic targets. Quantitative network analysis, using large datasets, is a potentially robust way to identify functional pathways, yet it has not been applied to ID genes at scale.
Methods: We have used co-expression analysis to identify functional modules of genes co-expressed with 1399 causative ID gene in human brain tissues. Specifically, we optimised existing large-scale transcriptomic data from three separate human brain data sets (>1,000 samples), one of which is neocortex (Kang *et al.* Nature 2011; 478 483–489, Trabzuni *et al. Nat Commun*2013; 4, 2771). Optimisation included reannotation, signal filtering, data scaling and then application of Multiscale Embedded Gene Co-expression Network Analysis (MEGENA) framework (Song W-M, Zhang B PLoS Comput Biol 2015; 11 11), to define robust network structures. Gene ontology was carried out using Metascape (Zhou Y *et al.* Nat Commun. 2019 Apr 3;10(1):1523).
Results: Following validation steps, we have confirmed our strategy produced valid co-expression modules for genes with known biology. For example, OXPHOS genes were detected in the same module (Image 1). Moreover, for modules containing ID genes,

that have been extensively studied, ontology analysis of the module identified terms related to their known function. A sunburst plot was generated to map intellectual disability genes against co-expression modules (Image 2). The most ID gene enriched neocortex module underwent gene ontology (Image 3) consisting of twelve ID genes, gene ontology was consistent with neuronal cell biology including "trans-synaptic signaling" and "brain development".

Image 1:

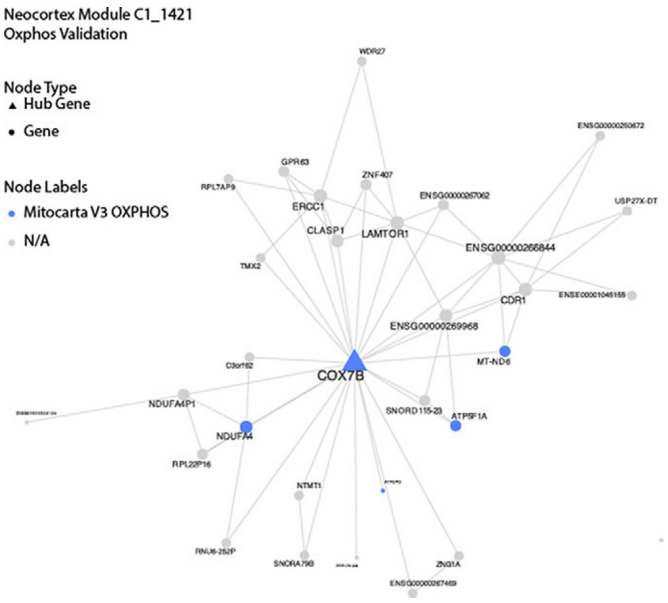


Image 2:

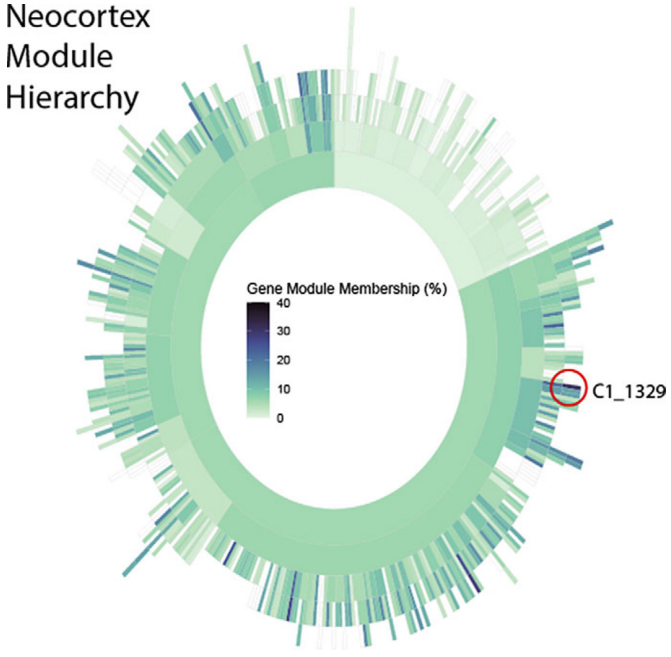
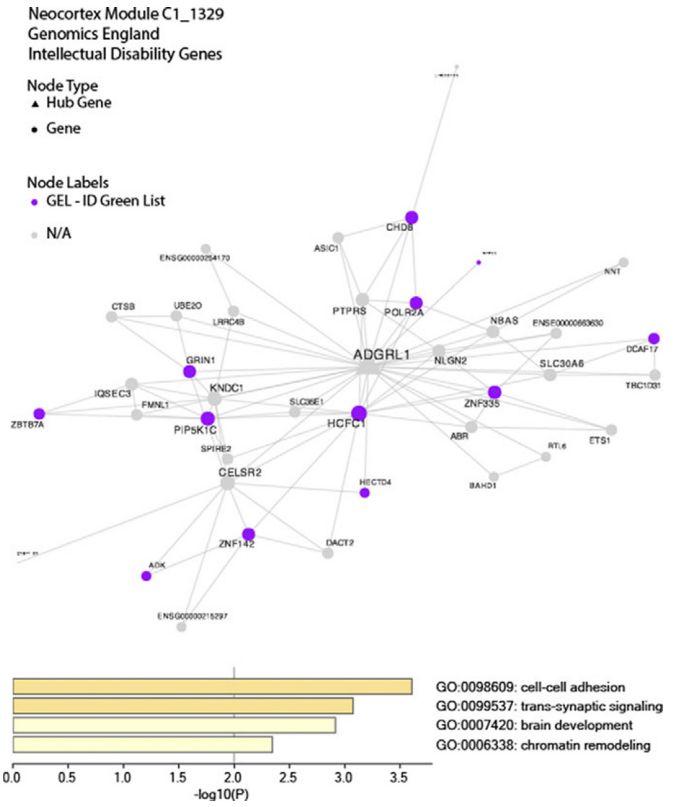


Image 3:



Conclusions: We have identified functional modules of genes that co-expressed with causative ID genes in human brain. The genes HCFC1, ZNF355, GRIN1, POLR2A and PIP5K1C in neocortex module C1_1329 are associated with microcephaly and ID (Koufaris C *et al.*Biomed Rep. 2016, Stouffs K *et al.* Clin Genet. 2018;, Platzer K *et al.* GeneReviews 2019, Haijes HA *et al.* Am J Hum Genet. 2019, Morleo M *et al.* Am J Hum Genet. 2023). Defining ID gene co-expression modules provided new insights into their underlying biology, revealing novel molecular links between different intellectual disability genes. This should improve molecular classification of these diseases as well as highlight therapeutic targets, facilitating drugs discovery and repositioning for rare causes of intellectual disabilities.

Disclosure of Interest: None Declared