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Mapping the genetic and phenotypic landscape of neonatal C3 and C4 protein concentrations

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The complement system is crucial for innate immunity and has been linked to autoimmune and psychiatric disorders. Borbye-Lorenzen et al.[1] perform GWASs and PheWASs of neonatal C3/C4 protein concentrations, finding multiple genome-wide significant loci, and identify sex-specific associations between C3 protein concentration and C4 copy number with risk for schizophrenia.

The complement system is composed of multiple proteins that function to initiate the body's immune response in order to eliminate damaged cells and fight against infection.[2] In the brain, complement proteins facilitate neuroimmune signaling by tagging synapses for elimination by microglia.[3] Earlier work has identified the complement component 4 (*C4*) gene as a risk factor for both autoimmune disease and schizophrenia, with greater effects in males relative to females.[4,5] In humans, C4 is encoded by *C4A* and *C4B* genes. Previous observations suggest that greater *C4A* gene copy number and high *C4A* genetically regulated expression is associated with human brain size, risk for schizophrenia, and multiple autoimmune diseases.[4–7] Yet there has been limited research investigating how common genetic variation may drive C3/C4 protein concentration or the relationship between neonatal C3/C4 protein levels and later psychiatric and immune-related outcomes.

In this issue of *Cell Genomics*, Borbye-Lorenzen et al.[1] perform a large-scale investigation of the genetic and phenotypic correlates of neonatal complement protein concentration. Using data from 68,768 participants in the population-based iPSYCH2012 case-cohort study, the authors leveraged C3/C4 protein concentrations measured from neonatal dried blood spots to perform genome-wide association studies (GWASs), summary-data-based Mendelian randomization (SMR), and phenome-wide association studies (PheWASs) with over 1,000 longitudinal behavioral and immune-related traits. Analyses were performed in males and females separately, enabling the identification of sex-specific associations between complement proteins and risk for immune and psychiatric illness.

The authors find that neonatal complement protein concentrations are significantly heritable, suggesting that genetic variation accounts for a sizable proportion of variability in circulating neonatal C3/C4 protein concentrations. Partitioned heritability estimates were calculated to identify the contribution of genetic variants on the same vs. different chromosomes (chr) from *C3*/*C4* genes (i.e., *cis*-chr and *trans*-chr single-nucleotide polymorphisms [SNPs]). For C4, *cis*-chr SNPs accounted for a greater proportion of variance relative to *trans*-chr SNPs, indicating that genetic variants located proximal to the *C4* gene account for more variability in C4 concentration levels compared to distal genetic variants. The team follow up on these heritability estimates by calculating genetic correlations between neonatal C3/C4 protein concentrations. Here, the authors find a genetic correlation of r_g= 0.38; notably, this estimate increases to $r_g > 0.70$ when limited to *trans*-chr SNPs, indicating that the genetic correlation is not predominantly due to SNPs proximal to C3 and C4 coding genes. Neither heritability nor genetic correlations differed as a function of sex, suggesting that neonatal C3 and C4 protein expression has a similar genetic architecture in males and females.

Having established significant SNP-based heritability of C3/C4 protein concentrations, Borbye-Lorenzen et al. next performed the largest GWAS of complement protein concentrations published to date. The C4 GWAS revealed 30 genome-wide significant (GWS) loci located near the *C4* gene, as well as six additional loci on other chromosomes. A majority of the GWS SNPs discovered in the C4 GWAS were located in the major histocompatibility complex (MHC) on chromosome 6, a region of the genome known to harbor many genes involved in immune-related processes, including the C4 locus. The authors noted that several of the C4 GWS loci outside of the MHC showed remarkable face validity, including a SNP in the complement component 4 binding protein alpha (*C4BPA*) locus on chromosome 1, a SNP on chromosome 7 in the interleukin 6 (*IL6*) locus, and a SNP on chromosome 12 located near two genes that encode for the complement subcomponent C1. The C3 GWAS identified seven GWS loci including one association with the MHC region. Here, the authors replicated an association between neonatal C3 protein concentration and the complement factor H (*CHF*) gene on chromosome 1, which was previously reported in a smaller GWAS of C3/C4 levels in the Chinese population.[8]

Overall, these findings identify common genetic variants driving neonatal complement protein expression and showcase the considerable impact of MHC variants on C3/C4 protein levels. Importantly, the GWAS findings reported by Borbye-Lorenzen et al. are limited to individuals of European ancestry as the iPSYCH2012 dataset had a limited

number of individuals from other ancestry groups. However, recent work indicates that genetic variants detected in European populations may not translate equitably to other ancestry groups.[9] Thus, future research will be needed to perform large-scale GWASs of C3/C4 protein concentrations in diverse ancestries.

Finally, the authors examined the relationship between phenotypic and genetic correlates of C3/C4 with psychiatric and autoimmune disorders. Surprisingly, no significant associations were detected between C3/C4 neonatal protein concentrations, *C3/C4* genotypes, or imputed *C3/C4* brain gene expression with any of six common psychiatric disorders (schizophrenia, bipolar disorder, depression, autism spectrum disorder, attention deficit hyperactivity disorder, and anorexia nervosa) in the combined male and female iPSYCH sample. However, the team reported several sex-specific associations: in females, higher neonatal C3 concentration was associated with lower risk of schizophrenia, while in males, higher *C4A* copy number was linked to a higher risk of schizophrenia. To assess the impact of polygenic scores for neonatal C3/C4 protein levels on a broad range of phenotypes, PheWASs were performed using data from the UK Biobank. Results indicated robust associations between C4 polygenic scores and autoimmune phenotypes; these findings were confirmed by SMR analyses, which suggested a causal relationship between neonatal C4 protein levels and later autoimmune disease. Importantly, however, no significant PheWAS associations were detected for polygenic scores of either C3 or C4 protein concentration with psychiatric phenotypes.

This comprehensive examination of the impact of neonatal C3 and C4 protein concentration on psychiatric and immune-related outcomes provides a valuable resource to the research community and a scaffold for future studies of the complement system. Many questions remain; for example, what is the biological mechanism of the observed sex-specific effects of C3 and C4 on schizophrenia? Do the same genetic variants that influence neonatal C3/C4 protein concentrations also exert their effects throughout the lifespan? How might the complement system interact with other co-expressed genes and networks to regulate psychiatric and autoimmune phenotypes? Further studies are needed to investigate these questions, and it will be critical to explore the clinical relevance of these findings in diverse populations.

DECLARATION OF INTERESTS

The author declares no competing interests.

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