The effect of SNPs on gene regulation and metabolic processes in autism

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Autism is a common cognitive disorder affecting brain functions. Many studies determined a large number of genetic variants linked to the disorder, each having a small effect. Our understanding of how these variations interact and affect biological processes within tissues and cells leading to autism is still limited. Changes in gene expression regulation and metabolic processes could be among the potential effects of the autism-associated genetic variants. In this work, we investigated the effect of autism-associated variants on these two mechanisms: (i) activity of enzymes in metabolic pathways and (ii) genome architecture mediated gene regulation.

To address the first question, we integrated metabolome, lipidome, transcriptome and autism GWAS data with protein structures and molecular interaction networks to estimate the effect of autism-associated variants on metabolite binding. We found several candidate genes with significant changes in metabolite binding and protein folding properties caused by autism-associated SNPs affecting composition of metabolite binding sites. Analysis of autism transcriptome and metabolome data confirmed that for one of these genes (GSTP1) these protein changes result in metabolic changes in disease. Although this gene was not found in the autism-associated gene database, literature mining indicated its involvement in the disease.

To answer the second question, we integrated data on chromatin contacts (Hi-C) with transcriptome and autism GWAS data to study gene expression regulation in autism mediated by the relationship between spatial chromatin organization and locations of autism risk variants. We found that the number of forebrain enhancers linked to autism-associated genes was significantly higher than the number of enhancers linked to the other protein-coding genes. Furthermore, forebrain enhancers had contacts with significantly higher number of different autism-associated genes per enhancer than with the other protein-coding genes. Notably, forebrain enhancers containing at least one autism-associated SNP have significantly higher ratio of contacts per enhancer with autism-associated genes to contacts per enhancer with control genes.

In summary, we found the effect of autism-associated variants on both gene regulation and changes in molecular phenotype. These results lay foundation for further research.

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References

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