Co-expression Network Analysis of the Developing Human Brain Implicates Synaptogenesis and Mitochondrial Function as Central Mechanisms in Autism

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Summary

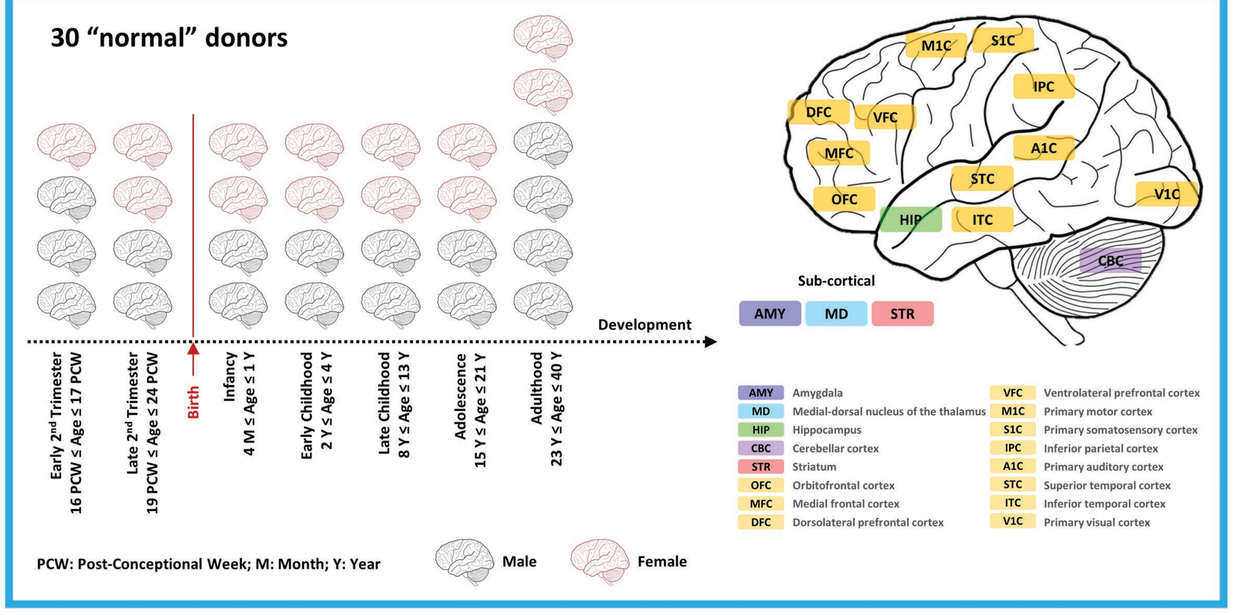
We analyzed the spatial-temporal co-expression relationships of 455 genes previously implicated in Autism spectrum disorder (ASD) using the BrainSpan transcriptome atlas. Understanding how the heterogenous set of ASD-related genes contribute to normal brain development helps identifying cellular/molecular processes which are commonly disrupted in ASD.

First, we discovered modules among ASD candidates with biologically relevant temporal co-expression dynamics. These modules were related to the processes of synaptogenesis, apoptosis, and the neurotransmitter γ-aminobutyric acid (GABA).

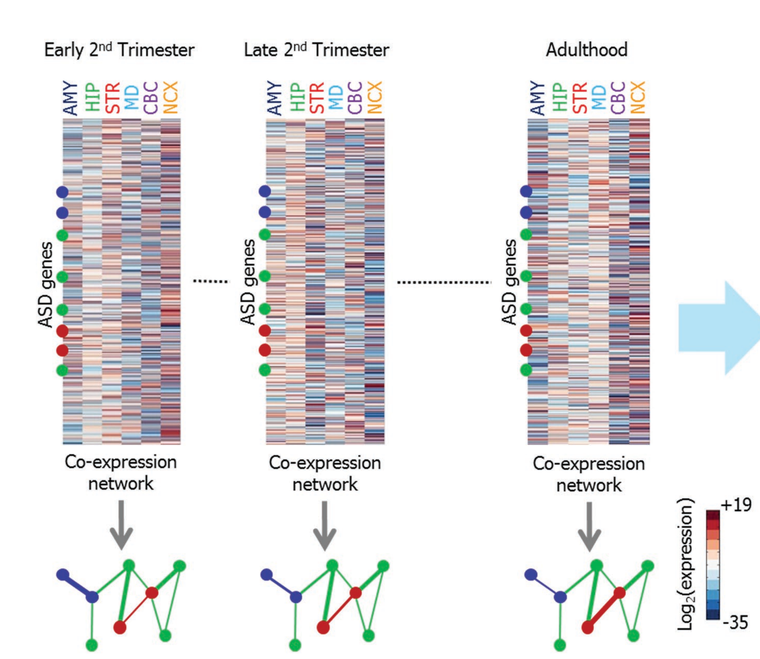
Second, we created a transcriptome-wide co-expression network to discover significant Molecular Interaction Modules, and demonstrated that ASD candidate genes are enriched in modules related to the processes of synaptogenesis, mitochondrial function, protein translation, and ubiquitination.

Finally, we identified hub genes within the ASD-enriched Molecular Interaction Modules, which may serve as additional ASD candidate genes, potential biomarkers, or therapeutic targets.

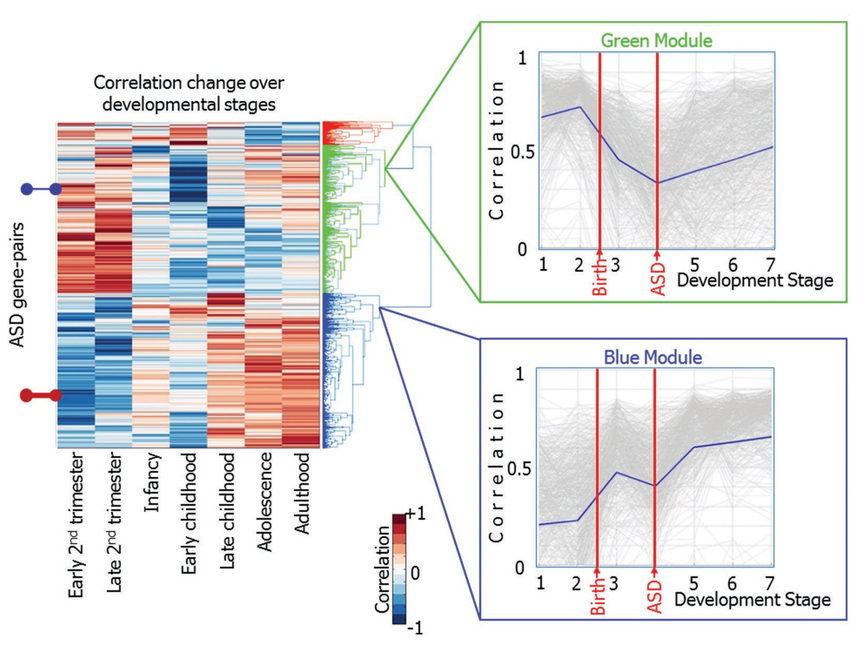
BrainSpan Atlas



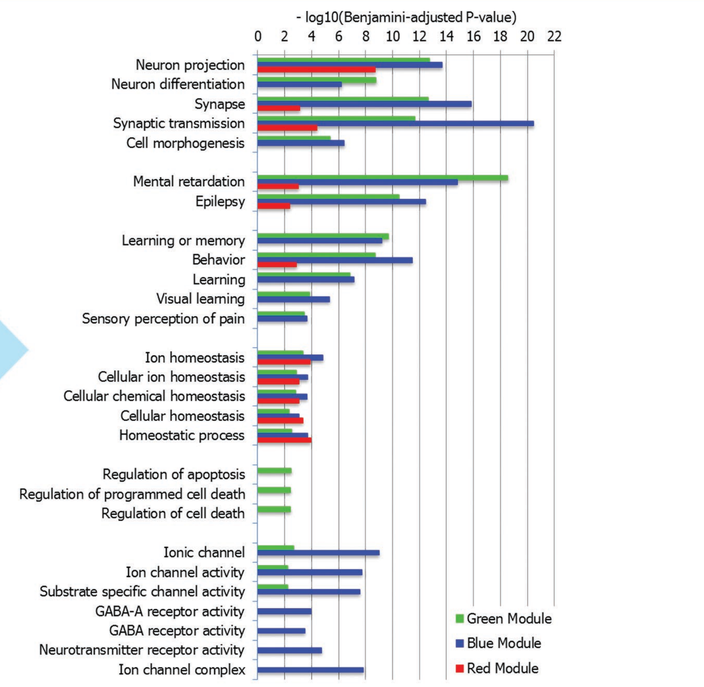
Co-expression Networks of Autism Genes



A co-expression network of ASD-related genes is constructed at each developmental stage.

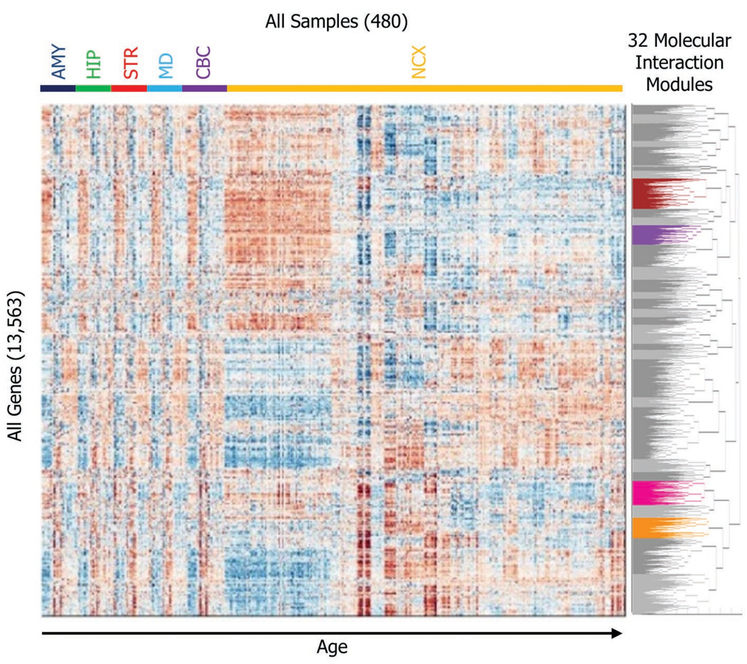


Patterns of correlation change —for ASD gene-pairs— are hierarchically clusterded into three modules.

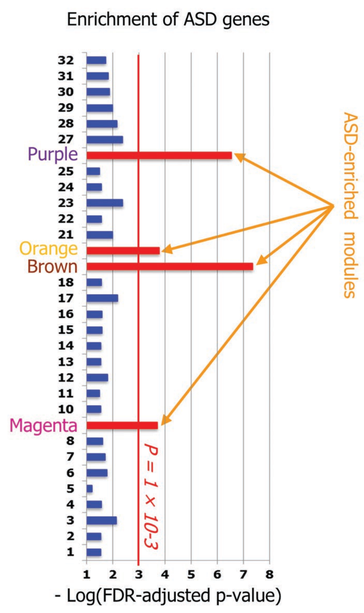


GO enrichment analysis of the ASD co-expression modules identifies common and unique functional pathways between neurodevelopmental transcriptional modules.

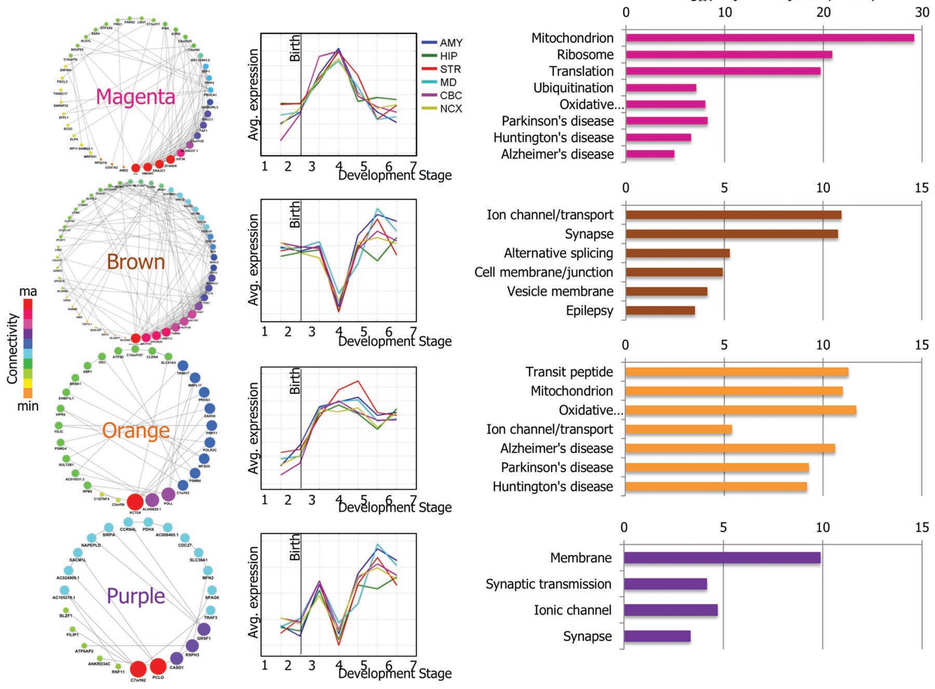
Transcriptome-wide Molecular Interaction Network



A transcriptome-wide co-expression network is constructed by hirarchially clustering all genes (13,563) based on the correlation between their expression profile across all samples (480).



The resulting Molecular Interaction Modules are tested for enrichment of ASD genes.



GO enrichment analysis of the ASD-enriched modules shows that the disruption of synaptogenesis in autism is related to basic cellular processes: *alternative splicing, protein translation, and ubiquitination*. Hub genes of each ASD-enriched modules provide potential additional high-yield ASD candidates.

Conclusion

We analyzed the transcriptional co-expression networks of autism candidate genes throughout the developing human brain. We identified ASD modules with enrichment for synaptogenesis, apoptosis, and GABA-ergic signaling, suggesting that pathways previously independently implicated in autism are related to each other through shared neurodevelopmental transcriptional networks. We demonstrated shared relationships between ASD-enriched transcriptome-wide Molecular Interaction Modules and *mitochondrial function, splicing, and protein turnover* presenting a firsthand attempt to integrate the various pathways implicated in autism into a broader functional framework. Our analysis of this multi-dimensional expression data suggests pathways previously independently implicated in autism are related to each other through shared neurodevelopmental transcriptional networks.

References

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Kang H, Kawasawa Y, Cheng F, Zhu Y, Xu X, Li M, Sousa AM, Pletikos M, Meyer K, Sedmak G et al. 2011. Spatio-temporal transcriptome of the human brain. Nature 478(7370): 483-489.

BrainSpan: Atlas of the Developing Human Brain [Internet]. Funded by ARRA Awards 1RC2MH089921-01, 1RC2MH090047-01, and 1RC2MH089929-01. © 2011. Available from: http://developinghumanbrain.org.

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