Temporal gene expression profiles and behavioral regression in children with ASD with post-synaptic density gene disruptions

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Background

- Approximately one-third of children with an autism spectrum disorder (ASD) experience developmental regression within the first three years of life. However, the mechanisms underlying this behavioral phenotype remain unknown.
- Our group has identified higher rates of developmental regression in language and social engagement skills in children with de novo gene disrupting mutations to post-synaptic density (PSD) genes (Goin-Kochel et al., under review).
- PSD genes play a role in regulating synaptic function in human neocortex (Bayles et al., 2011) and show differential timing in expression, with some genes preferentially expressed during synaptic formation and others during synaptic remodeling and differentiation (Swulius et al., 2010).
- Thus, disruptions in PSD genes preferentially expressed later in synaptic development may lead to normal initial behavioral development followed by onset of abnormal development and/or behavioral regression.
- Understanding the relationship between developmental gene expression timing and phenotypic ASD profiles may elucidate mechanisms of behavioral regression in ASD.

Objective

The objectives are:
- To explore the relationship between gene expression timing and presence of behavioral regression in individuals with ASD who have PSD gene disruptions.
- To explore regional differences in the relationship between gene expression timing and presence of behavioral regression in individuals with ASD who have PSD gene disruptions.

Methods

- Participants were 40 children from the Simons Simplex Collection and The Autism Simplex Collection with PSD gene disruptions (as defined by Iossifov et al., 2014) who met strict criteria for ASD.
- Timing of typical maximum expression for each PSD gene was extracted from the BrainSpan transcriptome exon microarray data (http://www.brainspan.org).
- Expression data over three years post-birth was removed.
- For each gene, a t-test was performed to determine presence of significant differences between prenatals and postnatal expression levels.
- Genes were categorized in three groups based on changes in expression levels:
  - Early: Prenatal expression was significantly greater than postnatal expression.
  - Late: Postnatal expression was significantly greater than prenatal expression.
  - No Change: Prenatal and postnatal expression levels were not significantly different.
- Eight children with parentally reported history of developmental regression in language and social engagement skills were compared to 32 children without regression.

Results

- Rates of regression in individuals with gene disruptions in PSD genes with differential typical expression (Wilksley et al., 2013)
- Brain regions as identified by Wilksley et al., 2013

Discussion

- The observed relationship between the timing of gene expression and the presence of regression revealed significant differences in rates of loss: \( \chi^2 (2, N = 40) = 7.500, p = 0.02 \).
- When brain regions were examined separately, rates of loss remained significantly different only in Region 4, composed of the thalamus and cerebellum \( (p = 0.04) \).

References


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