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 postsynaptic density (PSD) genes (Goin-Kochel et al., under review).
- PSD genes play a role in regulating synaptic function in human neocortex (Bayés 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.

Objectives

The objectives are:

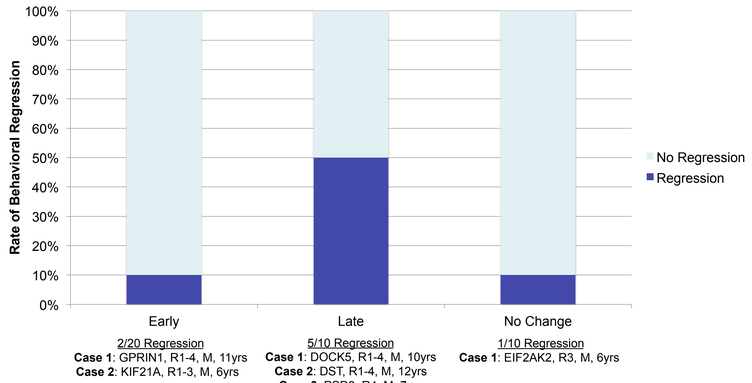
- To explore the relationship between gene expression timing and presence of behavioral regression in individuals with ASD who have PSD gene disruptions
- To explore regional differences in the relationship between gene expression timing and presence of behavioral regression in individuals with ASD who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



2/20 Regression
Case 1: GPRIN1, R1-4, M, 11yrs
Case 2: KIF21A, R1-3, M, 6yrs

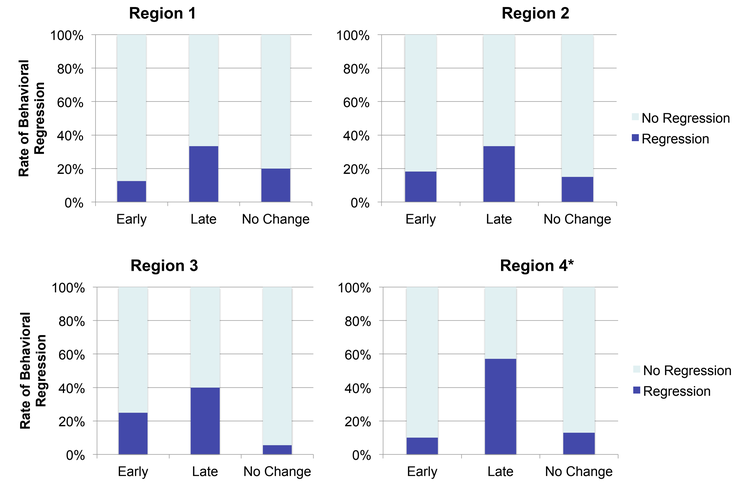
5/10 Regression
Case 1: DOCK5, R1-4, M, 10yrs
Case 2: DST, R1-4, M, 12yrs
Case 3: PSD3, R4, M, 7yrs
Case 4: RIMS1, R1-4, M, 13yrs
Case 5: SORBS1, R3, M, 17yrs

1/10 Regression
Case 1: EIF2AK2, R3, M, 6yrs

Brain Regions (as identified by Willsey et al., 2013)

Region 1	Region 2	Region 3	Region 4
Posterior inferior parietal cortex	Primary somatosensory cortex	Striatum	Mediodorsal nucleus of the thalamus
Primary auditory cortex	Primary motor cortex	Hippocampus	Cerebellar cortex
Primary visual cortex	Orbital prefrontal cortex	Amygdala	
Superior temporal cortex	Dorsolateral prefrontal cortex		
Inferior temporal cortex	Medial prefrontal cortex		
	Ventrolateral prefrontal cortex		

Rates of Regression by Brain Region



Results Continued

- For cases with gene disruptions in genes typically expressed in higher levels prenatally than postnatally, two cases (10%) reported loss, and 18 cases (90%) did not report loss.
- For cases with gene disruptions in genes typically expressed in similar levels prenatally and postnatally, one case (10%) reported loss, and nine cases (90%) did not report loss.
- For cases with gene disruptions in genes typically expressed in greater levels postnatally than prenatally, five cases (50%) reported loss, and five cases (50%) did not report loss.
- Non-parametric analysis examining the relationship between the timing of gene expression levels and the presence of regression revealed differences in rates of loss: χ^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).

Discussion

- The observed relationship between behavioral regression and period of maximum gene expression in individuals with likely gene-disrupting mutations to PSD genes suggests the importance of gene expression timing in symptom expression timing.
- Previous mouse model studies demonstrate preferential expression of PSD genes in different phases of synaptic development (Swulius et al., 2010); these findings suggest that the differential phases of expression can impact symptom onset.
- Specifically, our results suggest that differential timing of gene expression in the thalamic and cerebellar region may have an increased impact on rate of regression. Better understanding of the normal developmental timing of gene expression in genes disrupted in individuals with ASD may aid in explaining the phenotypic variability regarding symptom onset among children with ASD.

References

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