MZ-PARENTAL CONTROL-DISCORDANT DESIGN STUDY OF COPY NUMBER VARIATION IN 50 MZ TWINS CONCORDANT AND DISCORDANT FOR ATTENTION PROBLEMS

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Introduction

Copy Number Variations have been proposed as a possible contributing factor to a number of neuropsychiatric conditions such as Autism Spectrum Disorder, Schizophrenia, and Bipolar Disorder. Although the proposed etiopathologic mechanism of large copy number variations leading to a mis- or dis-function of the human genome is an intoxicating proposition, much work needs to be done to determine how CNVs contribute risk. The MZ-Parental Control Discordant Design is one such approach.

Sample

Subjects were fifty monozygotic (MZ) twin pairs selected from the Netherlands Twin Registry and for whom longitudinal information was available on attention problems. 22 concordant affected (CA), 17 concordant unaffected (CU), and 11 discordant pairs participated. Whole genome Copy Number Variation Scans were performed using Affy 6.0 CNV/SNP Chip.

Measures

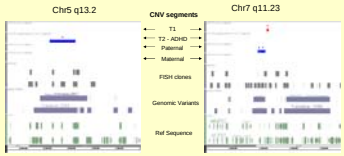
The Child Behavior Checklist (CBCL) Attention Problems (AP) scale was completed by parents at ages 7, 10 and 12. Individuals were selected as affected if they had a T-score > 65 for AP on at least one occasion ***and*** a T-score > 60 for AP ***at all three time points.***

Analyses

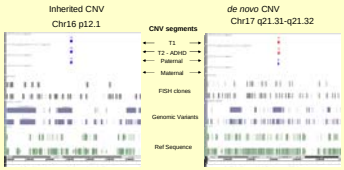
In a sample of 50 MZ pairs and their parents we will determine the concordance and discordance of inherited CNVs in cross twin and cross standard (using Affymetrix cross baseline data set) comparisons in twins who both have longitudinal persistent CBCL attention problems (AP) (N= 17), in pairs in which neither have attention problems (N= 22) and in discordant pairs in which one member of the pair has AP (N= 11). Parental CNV scans will be used to determine whether or not conservation of CNVs across pedigree is found.

CNV Scans

***de novo* CNVs**



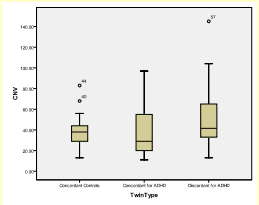
Family 0150
CNV Analyses of an MZ Discordant Twin Pair and Parents



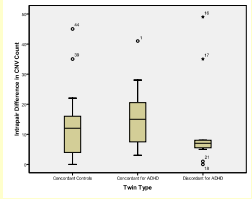
Results

	Total CNVs	Average # of CNVs	*N*	Std. Dev.
MZ Pairs Concordant Controls	1606	37.35	43 (21.5 pairs)	13.61
MZ Pairs Concordant for ADHD	1206	37.69	32 (16 pairs)	23.26
MZ Pairs Discordant for ADHD	1123	51.05	22 (11 pairs)	30.97

Total CNVs vs. MZ group



Intrapair Differences in CNV Totals vs. MZ group



The majority of CNVs were seen in the telomeres and centromeres as predicted, however, many differences were identified in the discordant twin pairs not seen in either the concordant for AP or concordant control pairs.

When compared to the Affymetrix CNV standard, 98% of the novel CNVs found in the discordant pairs were associated with gains in CNVs (in some cases very large 22454 KB).

A one-way ANOVA revealed a trend suggesting that the mean number of total CNVs was not equal across MZ groups (F (2, 94) = 2.98, p = .055). Collapsing across MZ groups, number of CNVs did not significantly differ as a function of affection status (F (1, 95) = .016, p = .90). Prior to analyses, a square root transformation was performed on total CNV data in order to correct for positive skew.

Individual CNVs associated with specific genes will be presented. These CNVs were found in association with both known and novel candidate regions for attention problems.

Conclusions

Future Analyses will include:
1. PBAT CNV Analyses in Golden Helix using ADHD Status as the dependent variable.
2. Within the discordant pairs we will do paired comparisons of intensity by affection status across twins.