Title: Depressive Symptoms and DNA Methylation in People with Mosaicism for Down Syndrome

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Introduction: Down syndrome (Ds) is the most common genetic cause of intellectual disability (ID) (Canfield et al., 2014). The physical and medical phenotypes associated with trisomy 21 are the focus of a wide and ongoing area of study (Capone, 2001; Dierssen, 2012). However, the research on mental health phenotypes, such as internalizing disorders, lag far behind despite evidence that people with Ds are more prone to depression and anxiety when compared to the general population and people with other forms of ID (Dykens, 2007; Walker, Dosen, Buitelaar, & Janzing, 2011). Assessment of internalizing symptoms in people with Ds is challenging due to limited language and cognitive abilities associated with trisomy 21, thus research on assessment strategies is critical to addressing the mental health needs of this population. Evidence that epigenetic modifications, such as telomere attrition and DNA methylation, may reveal the biological embedding of psychiatric disorders has resulted in growing interest in the use of these modifications as biomarkers to provide more objective means to detect and treat psychiatric illness (Klengel, Pape, Binder, & Mehta, 2014; Schmidt, Shelton, & Duman, 2011; Uddin et al., 2011). The development of biomarker panels may facilitate assessment of people from populations that are challenging to diagnosis due to language and cognitive deficits. To explore this possibility, we examined depression symptoms in a sample of people with mosaicism for Down syndrome (mDs). The higher cognitive functioning and language abilities in people with mDs compared to those with complete trisomy 21 provides a “window” into the experience of people with Ds (Papavassiliou, Charalsawadi, Rafferty, & Jackson-Cook, 2015) that may prove helpful in validating assessments for future research with people with Ds. This present study examined the prevalence of depressive symptoms in a sample of people with mDs and compared DNA methylation in a subsample with the highest and lowest depressive symptoms.

Method: All study procedures were approved by the university Institutional Review Board. Participants were recruited to participate at the International Mosaic Down Syndrome Association annual Research Retreat. The study participants completed self-report (n = 17) and caregiver-report (n = 21) measures of internalizing symptoms using the Glasgow Depression Scale (GDS) (Cuthill, Espie, & Cooper, 2003) and Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1999). Participants also provided a blood sample for DNA analysis.

Three probands with high levels of depressive symptoms (cases; ages 16 - 35) and two with low levels (controls; ages 24 and 33) on both the GDS and SDQ were examined for DNA methylation. DNA was extracted from the cells using standard methods. Following bisulfite conversion of the DNA, the methylation patterns of 485,764 targets (including CpG islands, shores, “open sea”) were determined using the 450K HumanMethylation Chip (Illumina) according to the vendor’s protocol. Probes containing any SNPs within 10 bases of the target site were excluded, leaving 395,833 CpG sites for statistical analysis. Statistical analyses were performed on the peak corrected logit transformed β values.

Results: Rates of clinically significant internalizing symptoms ranged from 21 – 80% according to self-report, and 25 – 52% according to parent-report. Preliminary analyses revealed that 19 CpG sites were differentially methylated using an FDR of .10 between the 3 cases and 2 controls. More detailed analyses are ongoing and final results will be presented at the meeting.

Discussion: Findings suggest that youth and adults with mosaic DS, like people with other forms of ID, experience high rates of internalizing symptoms, and increased research is warranted. Discrepancies between self and caregiver report and between SDQ and GDS scores will be discussed. Although underpowered, the results of the DNA methylation study are promising in that they provide preliminary proof of concept that will be followed up in future planned research with people with complete trisomy 21. If successful, the use of DNA methylation may help to identify people with Ds suffering from depression, or may aid in the differential diagnosis between depression and other medical conditions such as dementia.
References/Citations: