PERIPHERAL BLOOD BIOMARKERS AS PREDICTORS OF PHENOTYPES RELATED TO BRAIN SPECIFIC CHANGES IN ANGELMAN SYNDROME

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Angelman syndrome (AS) is a severe neurodevelopmental disorder usually associated with hypomethylation of the 15q11-q13 imprinted locus, with brain specific loss of UBE3A expression. While mouse models have implicated loss of UBE3A expression in the brain to specific deficits in AS, expression changes in UBE3A and other genes within the 15q11-q13 imprinted locus have not been well characterised in human peripheral tissues. We recruited and assessed 76 individuals aged between 9 months and 45 years with chromosome 15 (C15) imprinting disorders (28 with AS as well as 34 with Prader-Willi syndrome [PWS] and 14 with chromosome 15 duplication syndrome [Dup15q] which are also caused by abnormal imprinting at the 15q11-q13 locus). The Mullen Scales of Early Learning or an age appropriate Wechsler Intelligence Scale and the Autism Diagnostic Observation Schedule-2nd Edition were used to assess intellectual functioning and autism features, respectively. Venous blood samples were collected from C15 participants and 23 controls. Gene expression analysis of the C15 imprinted region included quantification of UBE3A, SNORD116, NDN and MAGEL2 mRNA using droplet digital PCR (ddPCR). A set of internal control genes was determined that were stably expressed across the C15 disorders from a panel of 12 genes, using the geNorm software. Both SNORD116 and UBE3A mRNA were increased in AS (n=16), compared to PWS (n=22) and controls (n=23; p<10^{-5}). Increased UBE3A mRNA in blood was correlated with increased fine motor skills (p=0.025; n=15) and receptive language skills in AS (p=0.001; n=15). There were also strong associations between NDN mRNA and receptive language (p=0.004; n=15) and fine motor scores (p=0.034; n=15) in AS. The findings demonstrate that novel human peripheral blood biomarkers, based on gene expression analysis using ddPCR, may provide an indication of phenotypes related to brain specific changes in C15 imprinting disorders, though validation in larger independent cohorts is required.