Young Adults with Down Syndrome have Increased Levels of Soluble TREM2 and Inflammatory Markers

Weber et al.

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Alzheimer's disease (AD) is a devastating neurodegenerative disorder, and currently lacks a blood-based biomarker of neuroinflammation. Triggering receptor expressed on myeloid cells 2 (TREM2) regulates inflammation in the periphery; TREM2 genetic variants have been shown to increase risk for AD and other neurodegenerative disorders. The cleaved, soluble form (sTREM2) circulates in the periphery and its function is not well understood, but believed to be different than the membrane- bound form. Most individuals with Down syndrome (DS) have trisomy 21, resulting in three copies of amyloid precursor protein (APP). APP is processed into amyloid beta (Aβ), of which there are normal and pathologic forms. The extra copy of APP in DS causes accelerated Aβ deposition in the brain and the nearly universal development of AD. Few studies to date have examined TREM2 in individuals with DS. We hypothesized that there is a relationship between sTREM2 and other immune factors in DS, prior to the development of dementia symptoms. We investigated this hypothesis in a pilot study of young adults with DS pre-dementia (n=15, mean age 30.0 years) compared to neurotypical, age- matched controls (n=16, mean age 29.0 years). AD biomarkers, sTREM2, and immune factors were measured in plasma using the Luminex platform. DS and control groups were compared using Fisher's exact test, unpaired t-tests, and Pearson's correlation. Principal component analysis and hierarchical clustering were performed with the bioinformatician blinded to disease groups. Data were analyzed utilizing GraphPad Prism 8.1.1, SPSS version 22, and Rstudio version 3.6. Young adults with DS displayed an altered immune profile compared to neurotypical controls, with increased levels of plasma sTREM2 and immune factors. sTREM2 strongly correlated with many of the immune factors in DS, but not in controls. Participants with DS clustered together based on their immune factors when analyzed by principal components and hierarchical clustering. sTREM2 clustered with pro-inflammatory cytokines based on hierarchical clustering of all participants, which supports the hypothesis that its function is altered in the cleaved form.

This pilot study provides a basis for future studies investigating sTREM2 and the development of AD in adults with DS.