A human neurodevelopmental model for Williams syndrome.

Journal: Nature

Publication Year: 2016

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PubMed link: 27509850

Funding Grants: Developing a drug-screening system for Autism Spectrum Disorders using human neurons , A drug-screening platform for autism spectrum disorders using human astrocytes

Public Summary:
This publication describe a human model for Williams syndrome (WS) using iPSC. People affected by WS have a hyper social phenotype but the genes related to this behavior are unknown. We postulated that one of the genes in the WS deletion region, FZD9, could be implicated in the phenotype. Cortical progenitor cells from WS individuals have a high level of apoptosis compared to controls. We showed that FZD9 is responsible for this observation. The progenitor cells that survive form cortical neurons from layer V/VI that are far more complex than controls. WS networks is also more active and with early burst synchronization. We validate these observations by MRI and showed that WS subjects have reduced cortical surface. We also validated the morphometric observations from the iPSC in postmortem tissues. Our data indicates a strong cell autonomous neuronal phenotype that is kept during WS neurodevelopment. This is the first work where iPSC were used to generate insights about a neurodevelopmental disorder and will help us to understand the molecular and cellular basis of the human social brain capacity.

Scientific Abstract:
Williams syndrome is a genetic neurodevelopmental disorder characterized by an uncommon hypersociability and a mosaic of retained and compromised linguistic and cognitive abilities. Nearly all clinically diagnosed individuals with Williams syndrome lack precisely the same set of genes, with breakpoints in chromosome band 7q11.23 (refs 1-5). The contribution of specific genes to the neuroanatomical and functional alterations, leading to behavioural pathologies in humans, remains largely unexplored. Here we investigate neural progenitor cells and cortical neurons derived from Williams syndrome and typically developing induced pluripotent stem cells. Neural progenitor cells in Williams syndrome have an increased doubling time and apoptosis compared with typically developing neural progenitor cells. Using an individual with atypical Williams syndrome, we narrowed this cellular phenotype to a single gene candidate, frizzled 9 (FZD9). At the neuronal stage, layer V/VI cortical neurons derived from Williams syndrome were characterized by longer total dendrites, increased numbers of spines and synapses, aberrant calcium oscillation and altered network connectivity. Morphometric alterations observed in neurons from Williams syndrome were validated after Golgi staining of post-mortem layer V/VI cortical neurons. This model of human induced pluripotent stem cells fills the current knowledge gap in the cellular biology of Williams syndrome and could lead to further insights into the molecular mechanism underlying the disorder and the human social brain.