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Title: Characterizing Pathogenic Pathways in TAF1- mutations related Intellectual Disability and Dysmorphic Features

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Abstract:

TATA-box binding protein associated factor 1 (TAF1) is an essential component of the basal transcription factor IID (TFIID) complex that coordinates pre-initiation of RNA polymerase II transcription. A syndrome of global developmental delay, intellectual disability, autistic behaviors, and dysmorphic facial features has recently been identified in nine families with different *TAF1* missense mutations. Peripheral blood monocytes from a family with a *TAF1* missense mutation were reprogrammed into induced pluripotent stem cells (iPSC) from which neural stem cells (NSC) were derived. My project is focused on trying to determine how TAF1 coding mutations could alter gene expression and cause developmental delay and intellectual disability.

Background:

The initiation of transcription by RNA polymerase II involves the activity of more than 70 factors and is coordinated by the basal transcription factor TFIID, which binds to the core promoter region of genes and promotes nucleation of the pre-initiation complex. TFIID consists of TATA-box binding protein (TBP) and more than ten TBP-associated factors (TAFs). TAF1 is the largest subunit of TFIID and binds to gene promoter sequences and other components of the TFIID complex.

Neuron specific isoforms of TAF1 have been identified and disruption in the *TAF1* gene is associated with the neurodegenerative disease X-linked Dystonia Parkinsonism. A distinct X-linked genetic syndrome of global developmental delay, intellectual disability, autistic features, facial dysmorphology, hypotonia, and an unusual gluteal crease has been described in nine patients from ten families with different *TAF1* missense mutations.

Specific forms of intellectual disability such as autism spectrum disorders (ASD) have a high degree of heritability. We hypothesize that *TAF1* missense mutations may cause intellectual disability with autistic features by altering the transcription of genes associated with ASD. In order to study this, our lab has derived NSCs from iPSCs from a family with two probands, who carry an isoleucine to threonine *TAF1* mutation, and an unaffected male family member.

Objective:

1) Determine if expression of autism associated genes is altered in *TAF1* mutant NSCs compared to control using quantitative PCR.

Resources:

1) TAF1 Variants Are Associated with Dysmorphic Features, Intellectual Disability, and Neurological Manifestations. **Am J Hum Genet**. 2015

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2) Developmental regulation of transcription initiation: more than just changing the actors. **Current Opinion in Genetics & Development**, 2010