Background

• Identifying the etiology of neurodevelopmental disorders (NDD) is challenging due to genetic heterogeneity and the clinical variability of these disorders. Trio-based exome sequencing (ES), which compares data from an affected proband to both parents, has been established as an effective tool for identifying the genetic etiology in patients with NDD, particularly when due to a de novo event in the proband.

• Using our analytical pipeline to evaluate a data set consisting of 10,259 probands referred for clinical exome sequencing for NDD, we identified by trio-based ES de novo ARID4A variants in five unrelated individuals. The ARID4A gene plays a role in the epigenetic regulation of genomic imprinting at the Prader-Willi/Angelman syndrome domain.\(^1\) To date, no sequence variants have been published in the ARID4A gene. However, a de novo 14q23.1q23.3 deletion including ARID4A was reported in an individual with developmental delay, hypoplasia of the corpus callosum, epilepsy, and neuroblastoma,\(^2\) suggesting a haploinsufficiency mechanism.

Methods

• Exome sequencing was performed on exon targets isolated by capture using the Agilent SureSelect Human All Exon V4 (50 Mb) or Clinical Research Exome kit (Agilent Technologies, Santa Clara, CA).

• The sequencing methodology and variant interpretation protocol has been previously described.\(^4\)

Results

• Five unrelated individuals were found to harbor de novo variants in ARID4A. One frameshift and four missense variants were identified, none of which were observed in large population cohorts (Table 1).

• Patients range in age from 6 to 28 years. All five individuals had developmental delays, and 3/5 experienced developmental regression. Intellectual disability was reported in three individuals, and IQ was not assessed in the remaining two.

• All but one individual had a diagnosis of autism. Other psychiatric concerns were also reported in this cohort, including obsessive-compulsive behavior (3/5), anxiety (2/5), and bipolar disorder (1/5).

• Two out of four individuals tested by brain MRI had brain anomalies (thin corpus callosum, absent septum pellucidum, and holoprosencephaly in one, pontocerebellar atrophy in another).

• Only one patient was reported to have dysmorphic features including mild hypotelorism, upslanting palpebral fissures, bulbous nasal tip, mild micrognathia, hypoplastic ear lobules, bilateral bradydactyly, and nearly complete right 1-2 toe syndactyly.

Table 1. Patients with ARID4A variants

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Variant</th>
<th>De novo/ Inherited</th>
<th>Developmental Delay</th>
<th>Developmental Regression</th>
<th>Autism</th>
<th>Intellectual Disability</th>
<th>Other Psychiatric Concerns</th>
<th>Brain Anomalies</th>
<th>Additional Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27yo</td>
<td>F</td>
<td>c.1717 T&gt;G</td>
<td>p.C573G</td>
<td>De novo</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>UNK</td>
<td>Bipolar disorder, obsessive-compulsive behavior, anxiety, hyperactivity</td>
<td>Normal brain MRI</td>
</tr>
<tr>
<td>2*</td>
<td>17yo</td>
<td>M</td>
<td>c.2051 C&gt;G</td>
<td>p.S684C</td>
<td>De novo</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Aggressive behavior</td>
<td>Agenesis of the corpus callosum, holoprosencephaly, optic nerve hypoplasia</td>
</tr>
<tr>
<td>4</td>
<td>6yo</td>
<td>F</td>
<td>c.3716 G&gt;A</td>
<td>p.G1239E</td>
<td>De novo</td>
<td>Yes</td>
<td>UNK</td>
<td>Yes</td>
<td>UNK</td>
<td>No</td>
<td>UNK</td>
</tr>
<tr>
<td>5**</td>
<td>13yo</td>
<td>M</td>
<td>c.1602dupA</td>
<td>p.Q535X5</td>
<td>De novo</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>UNK</td>
<td>Obsessive-compulsive disorder, depression</td>
<td>Normal brain CT</td>
</tr>
</tbody>
</table>

UNK = Unknown, N/A = Not Applicable

\(^1\) Also heterozygous for a maternally inherited pathogenic variant in the FGFR1 gene.

\(^2\) Also homozygous for a deletion at 17q13 involving the NPHP1 gene.

Conclusions

• Trio-based ES is an effective tool for the discovery of novel causes of molecularly heterogeneous conditions such as neurodevelopmental disorders.

• Our data suggest that de novo variants in ARID4A are associated with a unique neurodevelopmental disorder characterized by a spectrum of overlapping clinical features including developmental delay, intellectual disability, autism, and brain anomalies.

• We propose a haploinsufficiency mechanism of disease, given the previous report of a microdeletion involving the ARID4A gene being associated with an NDD phenotype and the observation of a frameshift variant in our cohort. Additional research is needed to further explore the association between variants in ARID4A and any resultant neurodevelopmental phenotype.

References