WHAT WAS THE RESEARCH ABOUT?

Due to advances in genetic sequencing and diagnostic procedures, the process of identifying genetic syndromes associated with neurodevelopmental disabilities—including intellectual disability (ID) and autism spectrum disorder (ASD)—has become easier in recent years. One of these genetic syndromes is dup15q syndrome, which is caused by duplications or multiple copies of the region called 15q11.2-q13.1 on chromosome 15. There are two primary types of multiplication that are known to occur. The first is an isodicentric chromosome 15 [idic(15)] that results in two or more copies of the region on an additional chromosome, and the second is an interstitial 15q multiplication [int(15)] where one or more copies of the region occurs on the same chromosome.

Children with dup15q syndrome typically have ID, language impairments, symptoms of ASD, and motor delays. Many individuals also have epilepsy that is resistant to treatment. No past studies have examined whether individuals with different subtypes of dup15q syndrome differ in terms of cognition and behavior or whether epilepsy status affects cognition and behavior.

WHAT DID THE RESEARCH TEAM DO?

Individuals with dup15q syndrome were assessed in 1- or 2-day visits at the UCLA Dup15q Clinic or at a Dup15q Alliance Family Conference. The battery included direct assessments of cognition and ASD symptoms completed with the child, as well as parent report
measures of epilepsy, challenging behavior, ASD symptoms, and adaptive behavior (i.e., the conceptual, practical, and social skills that individuals learn to function in daily life). The goals of the study were to 1) characterize behavioral and cognitive features of children with dup15q syndrome, 2) examine differences in these features based on genetic subtype and epilepsy status, and 3) assess the value of various tools for characterizing behavior and development in dup15q syndrome given the range of abilities in cognitive and language skills.

WHO WAS IN THE STUDY?

Sixty-two participants with a confirmed genetic diagnosis of dup15q syndrome between the ages of 30 months and 18 years were included in the study – 16 (26%) of these individuals had int(15) and 46 (74%) had idic(15). The average age of participants in the study was approximately 7.5 years. There was an equal number of males and females in the int(15) group, and a slightly higher number of males in the idic(15) group (26 males, 20 females). Overall, approximately 57% of the children in the idic(15) group had co-morbid epilepsy, whereas only 1 out of the 16 individuals in the int(15) group had a diagnosis of epilepsy.

WHAT DID THE RESEARCH TEAM LEARN?

**Cognitive functioning.** Scores of verbal and nonverbal cognitive skills were highly related across all participants. Nearly 3 out of 4 participants with idic(15) demonstrated severe impairment on tests of cognitive functioning, whereas those with int(15) were more evenly distributed across the impairment categories, with 40% of int(15) individuals in the normal or mild impairment range.
Adaptive functioning. Most participants with int(15) demonstrated adaptive functioning in the normal or mild impairment range, whereas most participants with idic(15) demonstrated mild to moderate impairment. Socialization and motor skills were strengths relative to communication and daily living skills, with communication being the most impaired adaptive functioning domain overall. Adaptive functioning scores were strongly related to cognitive scores, but adaptive functioning scores were higher on average compared to cognitive scores.

ASD symptoms. The majority of both idic(15) and int(15) participants met criteria for ASD on both direct (i.e., ADOS) and parent-report assessments (i.e., SRS-2). There were moderate associations found between these measures of ASD symptoms and cognitive functioning. Moderate associations were also found between parent report of ASD symptoms and challenging behavior.

Comparisons based on duplication type

Participants with int(15) had significantly higher cognitive and adaptive behavior scores compared to participants with idic(15). Additionally, parents of children with idic(15) reported more challenging behavior concerns in terms of social withdrawal and hyperactivity/noncompliance relative to parents of children with int(15), whereas there were no significant differences between the two groups in terms of irritability, stereotypic behavior, or inappropriate speech.

Comparisons based on epilepsy status

Because only one of 16 participants with int(15) had epilepsy, whereas 26 of 46 (57%) of participants with idic(15) had epilepsy, two comparisons of developmental and behavioral functioning were made: one comparison within in the idic(15) group for those with epilepsy vs. those without, and another comparison by duplication type for individuals without epilepsy.

Epilepsy status within the idic(15) group. Participants with epilepsy in the idic(15) group were significantly older than those without. Controlling for age, participants with epilepsy had lower cognitive and adaptive functioning scores compared to participants without epilepsy, except for scores in the socialization domain on the Vineland-2. ASD symptoms (as measured by both direct assessment and parent report) and challenging behaviors did not differ by epilepsy status.
Comparisons by duplication type for individuals without epilepsy. For participants without epilepsy, those with idic(15) had lower scores relative to those with int(15) across most cognitive and adaptive behavior domains. Verbal cognitive skills were no longer significantly different between the duplication type groups when participants with epilepsy were not included in the comparison. Again, there were no differences between the groups in terms of ASD symptoms as measured by either direct assessment or parent report, but parents of those with idic(15) reported greater concerns in terms of social withdrawal, stereotypic behavior, and hyperactivity/noncompliance.

Epilepsy characteristics

The average age of seizure onset was 33 months (range: 0-161 months). Parents reported a range of seizure types (mean = 2.2, range: 1-6), and the number of lifetime anti-epileptic medications used ranged from 1 to 15, with an average slightly below 4. Nearly half (48%) of participants had a history of infantile spasms and 56% of participants were still experiencing seizures at the time of assessment. Participants who had infantile spasms had significantly lower nonverbal and verbal cognitive scores, and more impaired motor skills, relative to those without.

Overall, these comparisons by duplication type and epilepsy status revealed a tiered pattern across cognitive and adaptive functioning: those with idic(15) and epilepsy experienced the greatest degree of impairment, those with int(15) without epilepsy experienced the least degree of impairment, and those with idic(15) and no epilepsy were in between.
WHAT DOES THIS MEAN FOR FAMILIES?

This study provides evidence that children with dup15q demonstrate a wide range of abilities in terms of cognitive and adaptive functioning, with children with int(15) typically having lower levels of impairment in skills relative to those with idic(15). Most children with dup15q demonstrate symptoms of ASD regardless of their duplication subtype or epilepsy status, and children with epilepsy—particularly those with infantile spasms—are likely to have a greater level of impairment in terms of cognitive and adaptive functioning relative to those without epilepsy. Identifying and controlling seizures early could be extremely beneficial for children with dup15q syndrome.

Full article by Dr. DiStefano and colleagues:

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