Mutations

Landmarks of interest around participants’ heads were registered in conormgm@uw.edu However, past age = 11.33

Data were collected using a 3dMDhead System as part of an = .02; left = .01; subject = .04); both measurements were below population averages for probands.

All other Wilcoxon sign–rank tests were performed to compare Z-scores between probands and each biological parent, assessing familial genetic influence on observed dysmorphologies (Earl et al., 2017).

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RESULTS:

• Outercanthal width in probands was significantly different from both biological parents (subject-mother Z = -2.67, p = .01; subject-father Z = -2.55, p = .01) and significantly smaller than average.

• Palpebral fissure lengths significantly differed between probands and fathers (right Z = -2.43, p = .02; left Z = -2.07, p = .04); both measurements were below population averages for probands.

• All other Z-scores did not significantly differ between parents and probands. P values were not corrected for multiple comparisons due to small sample size, which represents a limitation of this study.

CONCLUSIONS:

Facial morphology of individuals with DYRK1A mutations significantly differs from the general population and unaffected parents when examining eye regions. This bolsters the link between DYRK1A and genes that code for craniofacial development (e.g., DCAF7). The absence of other significant discrepancies between parent and proband measurements suggests the facial phenotype associated with DYRK1A mutations may be more variable and nuanced than expected, presenting challenges for clinical assessment. Our future analyses will extend to non-white participants. Additional research should examine how DYRK1A interacts with genes that code for eye regions and possible differences in dysmorphism between sexes.

BACKGROUND:

• Disruptive mutations to DYRK1A, located in the Down Syndrome critical region of chromosome 21, are associated with autism spectrum disorder, intellectual disability, and medical comorbidities (Courcet et al., 2012; Earl et al., 2017; Guedj et al., 2012).

• Previous literature suggests facial anomalies in children with DYRK1A mutations, predominantly around the eyes, nose, and chin (Oegema et al., 2010; Van Bon et al., 2016).

• Studies of DYRK1A’s regulatory functions confirm its role in the expression of several genes, with DCAF7, DYRK1A’s highest predicted functional partner, directly involved in craniofacial development (Park et al., 2009; String Consortium, 2020).

• However, past DYRK1A studies have not quantitatively assessed the nature and severity of dysmorphic facial features.

OBJECTIVE:

To determine if quantitative differences in facial features exist between children with DYRK1A mutations and the general population, including unaffected parents.

METHODS:

From a sample of 28 children with de novo DYRK1A mutations, analyses focused on nine white non-Hispanic children (M age = 11.33 years, 77.78% male) and their unaffected biological parents due to the availability of facial norms.

• Data were collected using a 3dMDhead System as part of an ongoing genetics-first study (Aldridge et al., 2005).

• Landmarks of interest around participants’ heads were registered in 3D and measurements between landmarks were calculated using 3DMVultus software.

• FaceBase’s 3D Facial Norms for European Caucasians were used as a control group, and Z-scores were calculated for all complete measures using FaceBase norms (Brinkley et al., 2016).

• Six measures—intercanthal width, outercanthal width, palpebral fissure lengths, cranial base width, and philtrum width—were selected for analysis based on Van Bon et al., (2011).

• Wilcoxon sign–rank tests were performed to compare Z-scores between probands and each biological parent, assessing familial genetic influence on observed dysmorphologies (Earl et al., 2017).

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