Quantitative 3D Analysis of Craniofacial Dysmorphia in *DYRK1A* Mutations

Conor M. Miles, Eva C. Kurtz-Nelson, Caitlin M. Hudac, Evan E. Eichler, Raphael A. Bernier, & Rachel K. Earl
University of Washington, Center on Human Development and Disability, Seattle

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 3dMDvultus 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).

FIGURE 1: Example 3dMD Head scan (Raphael Bernier)

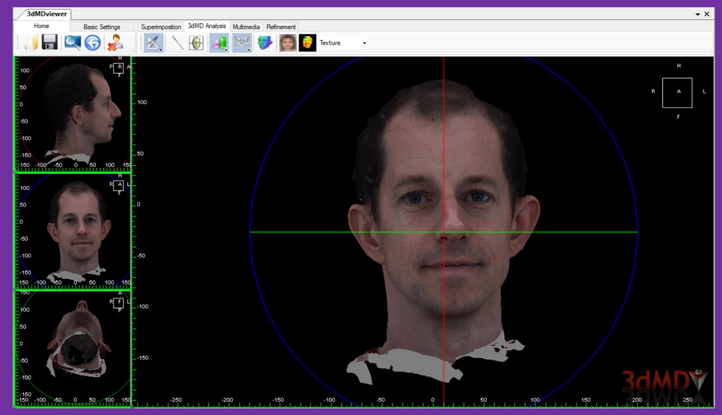
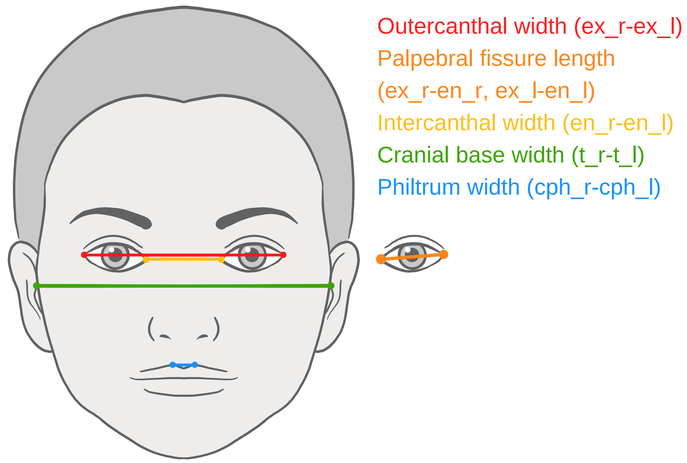


FIGURE 2: Targeted measurements of interest



bernierlab.uw.edu conormgm@uw.edu

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.

Proband-Mother Wilcoxian Results

	ex_r-ex_l	ex_r-en_r	ex_l-en_l	en_r-en_l	t_r-t_l	cph_r-cph_l
Z	-2.666	-1.718	-1.955	-0.889	-1.461	-0.178
Asymp. Sig. (2-tailed)	0.008	0.086	0.051	0.374	0.144	8.59

Proband-Father Wilcoxian Results

	ex_r-ex_l	ex_r-en_r	ex_l-en_l	en_r-en_l	t_r-t_l	cph_r-cph_l
Z	-2.547	-2.429	-2.073	-1.599	-1.095	-0.734
Asymp. Sig. (2-tailed)	0.011	0.015	0.038	0.11	0.273	0.463

Note: Z scores calculated from Wilcoxian Signed Ranks Tests based on positive ranks except for Proband-Father cph_r-cph_l, which was based on negative ranks.

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 dysmorphology between sexes.