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Altered Genetic Expression Disrupts Facial Ontogenetic Trajectory in Down Syndrome and *DYRK1A* Haploinsufficiency

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Abstract

The development of the human face is a complex, dynamic and coordinated process. Disruptions to this ontogenetic process through genetic and/or environmental factors can lead to altered patterns of growth and development, causing facial dysmorphogenesis. The Dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 1 A (*DYRK1A*) is a gene located in HSA21, which over- or under-expression is associated with cognitive impairment, facial and bone dysmorphologies, as those of Down syndrome (DS) and DYRK1A haploinsufficiency syndrome (DYRK1A). In this study, we assessed facial postnatal development and morphological variation using Geometric Morphometric methods, in a cross-sectional sample of 373 children between 0 and 18 years old, including individuals diagnosed with DS (n=62) and DYRK1A (n=14), as well as control individuals (n=297). Three-dimensional facial images were obtained using a multi-camera system and further characterization of facial shape was performed recording the 3D coordinates of 21 anatomical landmarks. Results showed a clear separation of DS, DYRK1A and control groups based on their facial shape across all stages, showing a phenotypic continuum from reduced to increased levels of DYRK1A expression. Facial differences were already present at infancy (0-5 years old) and involved changes in facial retraction, mandibular protrusion, as well as changes in the relative position of the mouth, nose and eyes. Sexual dimorphism was a significant factor after adolescence within the control group (P-value<0.001), as well as within the DS (P-value=0.04) and DYRK1A groups (P-value=0.03). Euclidean Distance Matrix Analysis (EDMA) showed that

74.7% of facial traits were significantly different in individuals with DS. These localized facial traits causing differences in DS changed over postnatal development until the adult facial phenotype was achieved. Finally, multivariate regression analysis of facial shape on age (% predicted=13.26%; P-value<0.0001) showed differences in the intercept and slope of the ontogenetic slopes of the three groups. These results highlight the processes by which these genetic syndromes significantly alter normal facial postnatal growth, increasing facial differences already established before birth. Our study suggests that changes in heterochrony can drive modifications in the rate or timing of facial development and produce morphological variation.