Expansion and further delineation of the phenotype of *SETD5*

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Introduction: The SET domain containing 5 gene (*SETD5*) encodes the SET domain-containing protein 5 and has been reported to be associated with intellectual disability (ID), language delay, and dysmorphic features. Previously reported individuals with *SETD5* alterations have been described with psychiatric/behavioral anomalies such as autism (ASD) and stererotypic behaviors, gastrointestinal abnormalities. Craniofacial abnormalities such as low posterior hairline, nasal abnormalities, upslanting/ downslanting palpebral fissures, long and smooth philtrum, thin upper lip, and ear abnormalities have also been described.

Methods: Herein we report 13 unrelated affected individuals with pathogenic alterations in *SETD5* detected by Diagnostic Exome Sequencing (DES).

Results: We identified 9 males and 4 females ranging from ages 18 months to 20 years. Common features included intellectual disability (ID) (92.3%) and dysmorphic features (92.3%). Twelve alterations are *de novo*, while one was inherited from a partially affected mother. The proband and his mother have similar craniofacial features and polydactyly. However, the mother did not have the ID/DD present in her son. Four individuals have a *de novo* c.2347-7A>G alteration that was previously reported in a patient with West syndrome, is predicted to affect splicing, and shown damaging by functional studies (Kobayashi, 2016). Only one of these individuals had seizures, and additional features varied. Previously undescribed features include neuroimaging abnormalities (38.5%), synophrys (23.1%), pectus deformity (23.1%), polydactyly (23.1%), submucous cleft palate/cleft palate (15.4%), and scoliosis (15.4%). Additional findings

in one individual included hearing loss, gingival hyperplasia, and coarse hair. Of the individuals with dysmorphic features, most (92.3%) did not have the previously reported features such as low hairline, nasal abnormalities, abnormal palpebral fissures, or thin upper lip.

Conclusion: Herein we report the largest group of individuals with *SETD5* alterations identified by DES. These cases demonstrate the phenotypic variability of *SETD5* cases, both within a recurrent alteration and within one family. Interestingly, not all of our patients with *SETD5* alterations had dysmorphic features nor intellectual disability. Additionally, musculoskeletal findings were more common and more varied than previously reported. This report identifies a recurrent splice site alteration and provides new information about the variability of the clinical phenotype associated with *SETD5* alterations. Such information may be useful in the clinical recognition of affected individuals and for early identification of associated features.