Molecular genetic analysis in 14 czech kabuki syndrome patients is confirming the utility of phenotypic scoring.

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Abstract

Kabuki syndrome (KS) is a dominantly inherited disorder mainly due to de novo pathogenic variation in KMT2D or KDM6A genes. Initially, a representative cohort of 14 Czech cases with clinical features suggestive of KS was analyzed by experienced clinical geneticists in collaboration with other specialties, and observed disease features were evaluated according to the ‘MLL2-Kabuki score’ defined by Makrythanasis et al. Subsequently, the aforementioned genes were Sanger sequenced and copy number variation analysis was performed by MLPA, followed by genome-wide array CGH testing. Pathogenic variants in KMT2D resulting in protein truncation in 43% (6/14; of which 3 are novel) of all cases were detected, while analysis of KDM6A was negative. MLPA analysis was negative in all instances. One female patient bears a 6.6 Mb duplication of the Xp21.2-Xp21.3 region that is likely disease causing. Subjective KS phenotyping
identified predictive clinical features associated with the presence of a pathogenic variant in KMT2D. We provide additional evidence that this scoring approach fosters prioritization of patients prior to KMT2D sequencing. We conclude, that KMT2D sequencing, followed by array CGH, is a diagnostic strategy with the highest diagnostic yield.


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