Exome sequencing unravels unexpected differential diagnoses in individuals with the tentative diagnosis of Coffin-Siris and Nicolaides-Baraitser syndromes.

Coffin-Siris syndrome (CSS) and Nicolaides-Baraitser syndrome (NCBRS) are rare intellectual disability/congenital malformation syndromes that represent distinct entities but show considerable clinical overlap. They are caused by mutations in genes encoding members of the BRG1- and BRM-associated factor (BAF) complex. However, there are a number of patients with the clinical diagnosis of CSS or NCBRS in whom the causative mutation has not been identified. In this study, we performed trio-based whole-exome sequencing (WES) in ten previously described but unsolved individuals with the tentative diagnosis of CSS or NCBRS and found causative mutations in nine out of ten individuals. Interestingly, our WES analysis disclosed overlapping differential diagnoses including Wiedemann-Steiner, Kabuki, and Adams-Oliver syndromes. In addition, most likely causative de novo mutations were identified in GRIN2A.
and SHANK3. Moreover, trio-based WES detected SMARCA2 and SMARCA4 deletions, which had not been annotated in a previous Haloplex target enrichment and next-generation sequencing of known CSS/NCBRS genes emphasizing the advantages of WES as a diagnostic tool. In summary, we discuss the phenotypic and diagnostic challenges in clinical genetics, establish important differential diagnoses, and emphasize the cardinal features and the broad clinical spectrum of BAF complex disorders and other disorders caused by mutations in epigenetic landscapers.