A Patient with Beaulieu-Boycott-Innes Syndrome, Illustrating the Utility of Whole Exome

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A 19-year-old female, initially identified with developmental delays and anatomic abnormalities at infancy, presented for re-consideration. Her features include cleft palate, corpus callosum dysplasia, developmental delays, bilateral hearing deficit, hypothelorism, lordosis, retrognathia, and ventriculomegaly; this constellation of features was considered “non-syndromic,” not fitting any currently identified syndromes. Previously, routine karyotype and subtelomere FISH had revealed a normal variant 2q deletion. Comparative genomic hybridization later revealed a 163 kb deletion at 10q21.3, which was shown to be of maternal origin but has uncertain clinical significance. A literature search had been performed (using London Dysmorphology Database) to identify candidate syndromes, without success. DNA was extracted from lymphocytes and subjected to whole exome sequencing in search of diagnostic insights; five mutations were found. Two significant novel mutations were found in the THOC6 gene. One was a missense mutation causing a protein change T250P and the other was a nonsense mutation of R87 (stop codon). Other notable mutations were in the genes ATR, FANCD2 and NIPBL; while they might have clinical importance, they are not thought to have any significance to the patient’s phenotype since each is heterozygous and the conditions with which they are associated are autosomal recessive. Mutations of THOC6 have been associated with Beaulieu-Boycott-Innes Syndrome (BBIS), an autosomal recessive condition (OMIM #613680); all four previously published cases were homozygous for Q46R inherited in an extended pedigree characterized by consanguinity. Comparing our patient’s phenotype with previously reported patients, we note some overlap in features including intellectual disability, microcephaly, and retrognathia. Other features in our patient, such as brain anomalies found by MRI, submucous cleft palate, short stature, hypothyroidism, bilateral hearing deficit, strabismus and low-set ears, were not observed in previously reported patients. Mutations found in this patient are novel and likely causative of her adverse phenotype. Her divergence from previously observed phenotypes may be due to the differential effects of the specific mutations. We are in the process of obtaining follow-up information about the previously reported patients, seeking insight for this patient’s optimum management.