Genome-wide sequencing analysis of multiple cohorts to identify candidate causative genes for enchondromatoses and related malignant tumors.

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Ollier disease (OD) and Maffucci syndrome (MS) are newly recognized cancer susceptibility syndromes. Our recent work shows that ~50% of patients with these syndromes develop a malignancy. Most commonly chondrosarcomas (~30%), gliomas (~10%), and, in patients with MS, vascular malignancies (~7%). Additional shared clinical features include enchondromas with resulting bone deformities, and other skeletal abnormalities. In addition, patients with MS have vascular overgrowth anomalies. As part of the Gabriella Miller Kids First Pediatric Research Program and of the Baylor-Hopkins Center for Mendelian Genomics, we performed germline WGS or WES for 96 unrelated individuals with OD or MS. Somatic gain-of-function variants in isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) genes were identified in enchondromas, vascular anomalies, and chondrosarcomas of ~80% of patients with OD and MS, however, the complete germline and somatic mutational landscape in the majority of patients with OD or MS remains unknown. We hypothezised that OD and MS are caused by a combination of germline/early post-zygotic variants and tumor-specific variants in genes that affect few connect pathways yet to be discovered and that these pathways are also affected in a subset of patients with isolated chondrosarcomas and gliomas. To test this hypothesis, through the Gabriella Miller Kids First Pediatric Research Program Data Resource Center and CAVATICA, we accessed tumor (and corresponding non-tumor tissue) WGS data from 816 patients from the Pediatric Brain Tumor Atlas. Using the CAVATICA platform we are performing a burden analysis aimed to identify the genes that have germline variants (missense, nonsense, stop loss, and splice site single nucleotide variants (SNVs) with MAF <1% in gnomAD) at a higher rate among the patients with OD/MS and the patients with gliomas as compared to the controls. A contingency table containing the number of patients presenting the qualified SNVs will be built for each of the ~20,000 genes. The p-value will be determined by Fisher's exact test (FET) and corrected by Benjamini and Hochberg method (False Discovery Rate - FDR). FDR of <5% will be considered statistically significant.