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Extended Abstract

Understanding the Pathophysiology and Searching for Biomarkers for Rare Genetic Developmental Diseases †

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Opitz C syndrome (OCS, MIM #211750) is an extremely rare genetic disorder characterized by multiple malformations (e.g., trigonocephaly, congenital heart defects) and variable intellectual and psychomotor delay. In a cohort of 15 families with patients clinically diagnosed as OCS, mutations in 10 different genes were identified as disease-causing by whole exome sequencing (WES). Thus, OCS turned out to be a genetically heterogeneous clinical phenotype. In this project, we aim to functionally characterize two of these causal genes whose de novo mutations were identified in different patients by studying patients' fibroblasts.

De novo heterozygous missense variants in *TRAF7* have been recently associated with CAFDADD syndrome (MIM #618164), whose encoded protein is an E3 ubiquitin ligase involved in different signaling pathways mediated by TNFα. While no significant differences in cell viability were observed between fibroblasts from patients and controls, RNAseq results yielded differentially expressed genes belonging to pathways related to axonal guidance, synapsis, and cardiac hypertrophy.

De novo truncating mutations in *MAGEL2*, a gene included in the Prader–Willi region (15q11–q13), have been associated with SHFYNG syndrome (MIM #615547). MAGEL2 is an essential component of the retromer, involved in endosome to trans-Golgi retrograde transport, and alteration of VPS35 (a MAGEL2 partner) leads to alterations in APP transport from endosomes. In this line, we have found a significant decrease in excreted amyloid $B_{1\text{-}40}$ (Ab) in patients' fibroblasts when compared with controls, making Ab a promising biomarker for SHFYNG syndrome.

Results so far confirm a pathogenic role of these mutations. These data together with future experiments will allow us to determine trustable biomarkers for each disease that could help to better understand its pathophysiology and to monitor the effect of therapeutic drugs.