Functional characterization of mutations in the Runt domain of RUNX2 in Polish patients with Cleidocranial Dysplasia

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Introduction: Cleidocranial Dysplasia (CCD) is an autosomal dominant disorder occurring 1 in a million births. The most common phenotypic manifestation of CCD includes hypoplastic or absent clavicles, failure of cranial suture closure and dental anomalies. These defects were linked to mutations in the RUNX2 (Runt-related transcription factor 2), a master regulator of osteoblast differentiation, cartilage, and bone development. Although the gene is known, novel variants are constantly being discovered. The purpose of the study was the functional characterization of six mutations found in Polish patients with CCD.

Methodology & Theoretical Orientation: Members of 11 Polish families were genotyped for variants in the RUNX2 gene. Then to assess the pathogenicity of 6 variants functional studies were carried out, including tests for transactivation potential of RUNX2 mutants and subcellular localization.

Findings: All of the found variants are present in the Runt domain of RUNX2 and are associated with the presence of supernumerary teeth among all patients. What is more, three variants are newly reported missense changes. Furthermore, we showed a significant decrease in the RUNX2 transactivation activity of all mutants, and although only two variants are within Nuclear Localization Signal (NLS), and other two affect the putative NLS, all investigated mutants localize to the cytoplasm.

Conclusion & Significance: The report brings functional evidence on the pathogenicity of found mutations which have a detrimental effect on the RUNX2 and trigger the CCD phenotype. These data not only increase our knowledge about the function of RUNX2 domains but also add to the clinical description and the phenotype/genotype correlation in the patients with these mutations.

Biography

Ewa Hordyjewska-Kowalczyk is a young scientist focusing her interest on human genetics and the development of limbs. She has been studying mutations linked to monogenic diseases (Cleidocranial Dysplasia, IFAP syndrome) as well as a complex disorder – Clubfoot.

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