The normal skull development begins around 23-26 day of gestation. This process involves mesenchymal cell proliferation and endochondrial ossification at the cranial base. The main function of developing skull is a brain protection. The premature closure of the cranial sutures, craniosynostosis, is a disorder leading to abnormal head shape and as a consequence, to blindness, deafness, epileptic seizures orhigh intracranial pressure. Craniosynostosis, in a significant proportion of cases is caused by genetic factors. Despite recent progress of the knowledge on human genetics and constant improvement of genetic diagnostic methods, the molecular cause of craniosynostosis remains unidentified in about 40-70% of the cases. For several subtypes of craniosynostosis (i.e. metopic, lambdoid, and sagittal) genetic origin is almost entirely unknown. In addition, a subset of craniosynostosis results from small segmental changes within the genome (known as copy-number variations, CNVs), which usually represent regulatory mutations. Genome-wide interaction studies by chromosome conformation capture-based approaches (f. e. Hi-C or 4C) revealed that mammalian genome is partitioned into topologically associated domains (TADs). Disruption of TADs can change the long-range regulatory landscape of a locus leading to misregulation of developmental genes and consequently to various pathological phenotypes. For these reasons, we are going to study a cohort of children affected by craniosynostosis in two steps: **1)** a custom, unique next-generation sequencing-based genes panel screening **2)** implementation of high-resolution array comparative genomic hybridization (array CGH) approach combined with bioinformatic tools. As a product of this project, it is expected to:

[A] identify novel *loci*, genes, rare single nucleotide polymorphisms, disease-causing CNVs associated with craniosynostosis,

[B] identify novel regulatory elements responsible for the formation of the cranial sutures,

[C] gain insight into the molecular mechanisms of normal and abnormal skeletal (especially cranial) embryonic development.