

Summary for the general public

Congenital malformations of the human skeletal system represent the second most frequent group of inborn developmental defects. Proper embryonic development of the skeleton depends on the precisely regulated interplay between numerous developmental genes and their regulatory sequences that orchestrate their action. The regulatory sequences switch on and off their target gene(s) in a spatio-temporal manner, i.e., in a particular embryonic site and developmental time point. This project proposal focuses on the identification of novel, previously unreported genetic variants contributing to the development of selected skeletal defects in human individuals. Specifically, we are going to study the structural defects of the vertebral column and its bony structures, i.e., vertebrae. The studies will deal with deciphering the molecular basis of Klippel-Feil syndrome, hemivertebrae, butterfly vertebrae, vertebral fusions, and other structural vertebral defects.

The progress in the field of DNA and RNA sequencing methods allows nowadays for the analysis of the entire genomes of single patients. With the advent of modern high-throughput next generation sequencing (NGS) techniques, the discovery of novel causes of human hereditary disorders and congenital malformations is indeed less challenging and feasible even if a single individual in a family is affected. Recent advances in human genetics of skeletal malformations suggest that structural osseous defects, including vertebral column ones, are predominantly caused by mutations located in the non-coding parts of DNA.

Identification of novel genetic factors (either coding or non-coding mutations) responsible for embryonic vertebral column formation will represent an important contribution to the field of clinical genetics, molecular biology, and developmental genetics. The results will broaden the knowledge on human congenital malformation phenotypes, as well as provide an insight into the processes of gene regulation, and skeletogenesis in humans and other vertebrates. To conclude, better delineation of the genetic etiology of analyzed congenital defects, in addition to marked input into basic science, will undoubtedly contribute to better diagnostics, prognosis, treatment, and genetic counseling in this highly heterogeneous group of developmental abnormalities.