General public summary

Human skeleton is the result of a very carefully orchestrated process of cellular proliferation, migration and differentiation. At the end of that process an organ is created that provides the vertebrates with a structural framework for muscle attachments, movement, protects organs, and maintains calcium homeostasis. The process is regulated by genetic and epigenetic factors. This proposal focuses mainly on the genetic component. Research into hereditary diseases is an attractive strategy to discover the molecular basis of tissue formation, organogenesis, and the disease process itself.

The progress of the next Generation Sequencing methods makes it less challenging to identify mutations, their functional characterization is however lagging behind. Specifically, we frequently do not have a good understanding of the mechanism that translated a mutation into a particular phenotype.

Additionally, current technologies revealed that diseases (including skeletal) are frequently caused by mutations in noncoding parts of the genome.

We will focus on two hereditary skeletal disorders, clubfoot (CF) and cleft palate disorders (CLP). We have identified several families with these conditions and the preliminary work suggests that the mutations causing the phenotype are located in the non-coding regions of the genome.

We plan to identify these regions and using in vitro and in vivo studies explain why these mutations cause this particular phenotype. This work will contribute to building our general knowledge about skeleton formation as well as give clinicians an additional tool in patient diagnosis and genetic counseling.