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Scientific abstract – **A functional genomics approach to teleost musculoskeletal homeostasis**

It is well recognized that most key regulatory skeletal genes are conserved in mammals and fish, however, many essential genes controlling bone formation and maintenance remain unknown. This has important implications not only as it prevents a comprehensive understanding of the molecular control of vertebrate skeletal diversity, but also aspects of human bone diseases, and skeletal malformations in commercially-farmed fish. The main premise of this proposal is that bones do not develop, function, or age in isolation. Mounting evidence shows that bone strength and muscle mass share genetic determinants; therefore, genes with potentially-pleiotropic effects exist and have to be functionally validated. We aim to develop an innovative evolution-based approach in teleost fish models to functionally characterize novel bone relevant genes that were earlier identified by the Israeli PI in a multi-trait genome-wide association study (GWAS) for pleiotropic musculoskeletal (MSK) factors.

Teleosts show remarkable morphological variations and physiological adaptations, most obviously for musculoskeletal morphology. Teleost fish have become popular models for studying both evolutionary bone biology and to mimic human bone diseases. We will use three fish models, zebrafish, medaka and spotted gar, which have been extensively studied by the PIs and are encompassing the spectrum of ray-finned fish evolution. The chosen fish models offer unique opportunities for gene modification by CRISPR/Cas9 technologies followed by gross morphological and live imaging of dynamic bone cell behavior.

Our innovative approach will not only allow to identify novel key players involved in teleost bone homeostasis but will also provide important new insight into the roles these genes play in human bones in norm and disease. By identifying commonalities as well as differences in the genetic control of bone formation, we will obtain important insight into the functional conservation or divergence of regulatory pathways.

Our joint project is significant, as it will bring together complementary expertise from the partners in Israel (human GWAS studies) and Singapore (fish models) in order to identify novel regulators of musculoskeletal homeostasis, which are important for bone formation in vertebrates and diseases in humans. Such synergism can only be achieved by joint funding through an Israel-Singapore program.

Abstract

Disruption of the normal structural or physiological function of the skeleton has profound consequences. As we age, the skeleton is severely affected leading to increased rate of fracture and fragility. Genome-wide association studies (GWAS) have identified genetic loci linked to the propensity for fracture and bone fragility. In several of these associated regions, the causal genes for bone fragility have been identified and confirmed through analysis in animal models as well as identification of phenotypes of patients with congenital skeletal defects. However, for many loci, the affected gene(s) have not been identified leaving a large component of our understanding of skeletogenesis undefined. This ambiguity, even with increased resolution of mapping, is primarily due to multiple genes being present at a locus confounding the identification of the underlying cause. We hypothesize that these genetic loci contain genes necessary for regulation of bone growth or homeostasis, identification of which will reveal novel pathways underlying susceptibility to skeletal disease. Here, we have developed an innovative high throughput screening approach to refine characterization of particular loci and models to functionally characterize genes previously identified by GWAS analyses. We will use multiplexed deletion screening in the zebrafish, to systematically assess the function of a broad class of genes. Our innovative approach, bringing together complementary expertise from the partners in Israel and the USA, will allow for the identification of novel key players involved in bone homeostasis to provide important new insight into the roles these genes play in human bones and skeletal disease.