Abstract for general public

Congenital heart disease (CHD) is an abnormality of the heart which is present at birth caused by errors in the process of heart development. It is one of the most common type of birth defect, affecting nearly 1% of newborns with mild to severe disease spectrum. CHD could lead to devastating impact on health and, in severe cases, early death. Despite advances in medical science, the genetic cause of CHD is still not fully understood. Small alterations within the genomic sequences known as single nucleotide polymorphism (SNPs) are found to be associated with CHD. Population-based whole genome investigations to study the genetic basis of CHD has revealed that ~90% of the CHD-associated SNPs fall within the fraction of the genome that does not code for protein, referred to as non-coding regions. However, due to the lack of sufficient understanding of the non-coding genome, it is currently challenging to understand the mechanism by which these SNPs could lead to CHD. Several studies have reported that disease-associated SNPs could affect a type of non-coding regulatory element called enhancers. Enhancers comprise unique binding sites for a class of proteins called transcription factors which act to regulate the expression of genes. The presence of SNPs within enhancers is thought to interrupt these transcription factor binding sites, thereby preventing their ability to activate their crucial target genes. Here we propose to elucidate the contribution of non-coding genomic SNPs towards the mechanism of heart development and CHD. We hypothesize that SNPs might affect the function of enhancers, resulting in mis-regulation of genes important for early heart development. We plan to apply state-of-the-art single cell epigenomics analysis in the zebrafish (*Danio rerio*), an established model organism for studying human development and disease, to identify enhancers important for heart development. We will then combine this with computational analysis of publicly available genomic data on human CHDs to systematically identify genome-wide CHD-associated enhancers. The power of this integrative approach lies in the complimentary information it will provide: while the zebrafish single cell analyses will provide an unbiased information on enhancers associated with heart development, the analysis of publicly available human genomics data will allow us to pinpoint those enhancers which are clinically relevant to CHD. Finally, we will biologically validate the regulatory functions of these enhancer candidates in heart development *in vivo* using the zebrafish, which permits easy and rapid genetic modifications. The zebrafish heart exhibits remarkable similarities with the human heart in terms of structure and function, which ensures the translatability of zebrafish-obtained results to human biology. Moreover, the zebrafish shares more than 70% of genes with humans, making it feasible to perform genetic comparisons. Taken together, our study promises to reveal novel CHD-causing genetic factors and mechanisms and contribute critical insights into understanding the mechanism of non-coding genetic variants in the pathogenesis of CHD.