UNITY THROUGH KNOWLEDGE FUND

UKF CONNECTIVITY PROGRAM - "Gaining Experience" Grant 2A: Establishing novel genetic loci for eating disorder-related traits, brachial circumference and sex

Project Leader: Vesna Boraska, vboraska@mefst.hr

Co-applicant: Dr. Eleftheria Zeggini, Wellcome Trust Sanger Institute, Eleftheria@sanger.ac.uk

Associate: Professor Igor Rudan, MD, PhD

Project duration: 23 January 2011 – 20 May 2011

Institutions involved in the project: University of Split School of Medicine & Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK, http://www.sanger.ac.uk/

Total financial value: 81,364 HRK (11,066 EUR)

UKF funding: 66,660 HRK (9066 EUR)

Co-funding (Wellcome Trust) : 14,704 HRK (2000 EUR)

Abstract & Results:

I was privileged to obtain training and develop my analytical skills in one of the strongest groups for statistical genetics in Europe supervised by dr. Eleftheria Zeggini, at the Wellcome Trust Sanger Institute (WTSI). During my stay at WTSI I have been the lead analyst of three large-scale, high-profile collaborative studies with the aim of gaining insights in some of the important biological mechanisms underlying health and disease. Studies I have been involved in focus on three phenotype groups of interest: brachial circumference, differences between males and females, and eating disorder-related traits. Two of these projects incorporate data from the 10,001 Dalmatians project, a set of Croatian population-based cohorts with genome-wide association scan data (GWAS).

This project adds value beyond the set scientific goals. It helps in establishing stronger bonds and empowers technology and knowledge transfer between MEFST and the WTSI, which boasts high-throughput genotyping, next generation sequencing and computing facilities and is a worldwide centre of excellence in the field of human genetics.

Brachial circumference (BC): BC can be used as an indicator of muscle mass and fat tissue, which are differently distributed in men and women. Analysis of anthropometric measures of peripheral fat distribution such as BC could shed light into the biological pathways involved in fat deposition and body shape which can further help in understanding complex phenotypes such as obesity and cardiometabolic diseases. The purpose of this study is to identify genetic variants associated with BC through a large-scale GWAS meta-analysis. To identify sex-specific effects underlying BC we used fixed-effects meta-analysis to synthesise summary results from 14 GWAS on 8,961 males, 9,792 females and on the combined set of 18,753 individuals. In our discovery dataset we have identified promising signals and selected 24 SNPs for replication, which is currently underway.

Differences between males and females: The male to female sex ratio at birth is very constant across world populations with an average of 1.06 for populations of European descent. In the present study we test if common variant genetic effects at least partly underlie the observed male-to-female sex ratio at birth. To address this, we investigate the presence of autosomal variant differences between males and females across 114,863 individuals (61,094 females and 53,769 males) through large-scale genome wide association study (GWAS) meta-analysis. We performed fix and random-effects meta-analysis to synthesize summary statistics results across 51 studies. Overall 2,555,483 directly genotyped and imputed SNPs were included in the meta-analysis. We did not detect differences at autosomal common SNPs between males and females (at the genome-wide significance level of $5x10^{-8}$). In addition, we are conducting a simulation study to investigate the lack of evidence for systematic sex differences in autosomal allelic frequencies. Forward simulations under the demographic model for the European population are currently underway. Our main results indicate that there are no genetic differences at common loci between males and females. However, the results of our study will have significant implications for the future design of genetic association studies, especially in the terms of usage of mixed controls for gender-biased traits i.e. traits that predominantly affect females (for example anorexia nervosa) or males (such as prostate cancer). This is highly-collaborative study with ~120 authors deriving from ~100 world institutions. By the number of analysed samples this meta-analysis is one of the largest to be carried out to date.

Eating disorder-related traits: It is postulated that EDRTs share similar genetic background with eating disorders (EDs) such as anorexia and bulimia nervosa. EDs are complex and genetically heterogeneous phenotypes that may be genetically dissected by analysing less complex EDRTs. Therefore, an insight in the genetic architecture of EDRTs may help in understanding the biological processes and mechanism leading to EDs. Six EDRTs derived from standardized self-report instruments (the drive for thinness, bulimia nervosa, body dissatisfaction, childhood obsessive compulsive personality disorder, weight fluctuation and breakfast skipping questionnaires) have been analysed across 283,744 SNPs in the discovery dataset of ~2000 individuals from the British TwinsUK cohort. Our preliminary-results, based on meta-analysis of discovery and *in silico* replication datasets, suggest the involvement of several biologically interesting genes in the etiology of EDRTs. On the basis of these results we have selected 30 SNPs for *de novo* follow-up, which is currently underway.

Presentations: „Genome-wide meta-analysis of brachial circumference“ submitted to 7th ISABS Conference in Forensic, Anthropologic and Medical Genetics and Mayo Clinic Lectures in Translational Medicine, Bol, Island of Brač, Croatia, June 20-24, 2011. Authors: Vesna Boraska, for the brachial circumference meta-analysis group.

Publications: in preparation

Lectures: to be held

Additional financial support: The National Foundation for Science, Higher Education and Technological Development of the Republic of Croatia, BRAIN GAIN- Postdoc