ESC First Contact Initiative Grant report

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Dear council members,

I would like to thank the European Society of Cardiology for awarding me the First Contact Initiative Grant.

The grant provided by the ESC has allowed me to visit the group of Dr. Newton-Cheh at the Broad Institute of Harvard and MIT and Massachusetts General Hospital/Havard Medical School. Under the supervision of Dr. Newton-Cheh I have had the opportunity to learn how to use cutting edge statistical tools for genetic quality control and genetic association studies to identify genetic loci associated with quantitative and dichotomous traits in the general population (see **Table 1**). This training introduced me to the field of population genetics, epidemiology and genetic statistical analyses using the UK Biobank cohort study.

The UK biobank is a prospective cohort study that has recruited ~500,000 individuals from the United Kingdom aged 40-69 years between 2006 and 2010. To assess the role of genetic variation in blood pressure we used the 500,000 UK Biobank participants with available genotype and phenotype data. During my stay, I was trained in how to perform quality control on genotype data using PLINK2 and QCtool2. I performed principal component analysis in the UK Biobank genetic data using flashPCA2 and learned how to perform both common as well as rare variants genetic association analysis in BOLT-LMM, PLINK and SNPTEST. Furthermore, I performed gene-based analyses in Rvtest and RareMETALS and learned how to process and manage large genetic datasets.

The skills and knowledge that I have acquired during this traineeship will be used further in a large QT-interval GWAS meta-analysis that includes amongst others the UK Biobank participants. The extent of QT-interval prolongation, an electrocardiographic measure reflecting myocardial repolarization, is a risk factor for ventricular arrhythmias and sudden cardiac death (SCD). The QT-interval GWAS will also allow us to identify the role of common genetics variants in the Long-QT syndrome (LQTS) using data from the international LQTS GWAS consortium. With this project, we hope to find additional common genetic factors that modulate the extent of QTc-interval prolongation and occurrence of arrhythmia in LQTS patients in addition to the primary disease-causing mutation. The opportunity to combine

these datasets will also help us to answer the question of whether there is an overlap in common genetic variation modulating QT-interval in the LQTS and the general population.

In conclusion, this traineeship has allowed me to gain knowledge that can be implemented at our department of Experimental Cardiology in the AMC and has strengthened the relationship among our respective research groups. From the results generated during my UK Biobank analyses at the Broad Institute I expect a publication in a genetics journal. Furthermore, this project has also helped me to strengthen my professional network and will hopefully help me to establish my dream of combining genetic research in large datasets in parallel with treating a unique single patient in the clinic as a cardiologist.

Yours sincerely,

Najim Lahrouchi

Table 1. Tools used during my stay at the Broad Institute of Harvard and MIT and Massachusetts General Hospital/Harvard Medical School

Software tools	**Source**
flashpca2	(Abraham and Inouye, 2014) https://github.com/gabraham/flashpca
R	version 3.3 (R Core Team, 2014) https://www.r-project.org/
data.table	The R Foundation https://cran.r-project.org/web/packages/data.table/index.html
dplyr	The R Foundation https://cran.r-project.org/web/packages/dplyr/index.html
stringr	The R Foundation https://cran.r-project.org/web/packages/stringr/index.html
PLINK	PLINK v1.9 (Chang et al., 2015) https://www.cog-genomics.org/plink2
BOLT-LMM	(Loh et al., 2015) https://data.broadinstitute.org/alkesgroup/BOLT-LMM/
RareMETALS	https://genome.sph.umich.edu/wiki/RareMETALS
Rvtests	version 20171010 https://github.com/zhanxw/rvtests/
QCtool	version 2 http://www.well.ox.ac.uk/~gav/resources/
SNPTEST	https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html