Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	*Pharmaco-epidemiology Unit* *Department of Epidemiology, Erasmus Medical Center, PO Box 2040, 3000 CA Rotterdam*
Project Title:	*Pharmacogenetics: finding effect modifiers for drug response*
Abstract:	*It is increasingly recognized that there is a large individual difference in response to pharmacotherapy which can be explained by genetic and epigenetic variation. This project will encompass finding new loci for drug response through hypothesis-free genome-wide association (GWA) studies, as well as hypothesis testing of candidate gene studies concerning drug metabolism, transport, and response. All analyses will be performed in the Rotterdam Study, a prospective population-based cohort study with extensive clinical information on cardiovascular, neurological, gastroenterological, respiratory, endocrinological, ophthalmological, and dermatological disease endpoints in almost 15,000 community-dwelling middle-aged and elderly participants with more than 20 years of follow-up. Clinical information comes from 5 cross-sectional measurements with an interview, laboratory investigations, ECG, and imaging procedures as well as from continuous follow-up of events such as stroke, myocardial infarction, and heart failure. DNA is available from the large majority of participants, and GWAs and exome sequencing data are ready for use. Automated pharmacy data on all prescribed drugs are obtained from all 7 pharmacies serving the region. During the past years, more than 500 papers were published by the Pharmaco-epidemiology Unit on drug safety and effectiveness, including pharmacogenetics. There is a very active participation in international networks of similar population-based genetic analyses such as the CHARGE consortium. The PhD-candidate will perform several analyses on cardiovascular and neurological drug effects, where these can be modified by genes.*
Requirements of candidate:	Background: candidate with medical, biological or molecular background with an interest in genetic studies Master degree: Yes IELTS Grade: 7.0 *(minimal 6.0 per component)* *or* TOEFL: *100 (minimal 20 per component)*

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Supervisor information:	*Prof. dr. B.H. Stricker* *Email address: b.stricker@erasmusmc.nl* *Recent publication list, preferably last 3-5 years (1-2 pages):* Arking DE, Pulit SL, Crotti L, et al. Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. Nat Genet 2014;46:826-36. Loth DW, Artigas MS, Gharib SA, et al. Genome-wide association analysis identifies six new loci associated with forced vital capacity. Nat Genet 2014;46:669-77. Kavousi M, Leening MJ, Nanchen D, Greenland P, Graham IM, Steyerberg EW, Ikram MA, Stricker BH, Hofman A, Franco OH. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. JAMA 2014;311:1416-23. den Hoed M, Eijgelsheim M, Esko T, et al. Identification of heart rate-associated loci and their effects on cardiac conduction and rhythm disorders. Nat Genet 2013;45:621-31. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects), Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants. Lancet 2014;383:970-83. Wilk JB, Shrine NR, Loehr LR, et al. Genome-wide association studies identify CHRNA5/3 and HTR4 in the development of airflow obstruction. Am J Respir Crit Care Med 2012;186:622-32**.** Ellinor PT, Lunetta KL, Albert CM, et al. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. Nat Genet 2012;44:670-5**.** Lucena MI, Molokhia M, Shen Y, et al. Susceptibility to amoxicillin-clavulanate-induced liver injury is influenced by multiple HLA class I and II alleles. Gastroenterology

	2011;141:338-47. Sotoodehnia N, Isaacs A, de Bakker PI, et al. Common variants in 22 loci are associated with QRS duration and cardiac ventricular conduction. Nat Genet 2010;42:1068-76. Eijgelsheim M, Newton-Cheh C, Sotoodehnia N, et al. Genome-wide association analysis identifies multiple loci related to resting heart rate. Hum Mol Genet 2010;19:3885-94. Pfeufer A, van Noord C, Marciante KD, et al. Genome-wide association study of PR interval. Nat Genet 2010;42:153-9. Benjamin EJ, Rice KM, Arking DE, et al. Variants in ZFHX3 are associated with atrial fibrillation in individuals of European ancestry. Nat Genet 2009;41:879-81. Vasan RS, Glazer NL, Felix JF, et al. Genetic variants associated with cardiac structure and function: a meta-analysis and replication of genome-wide association data. JAMA 2009;302:168-78. Teichert M, Eijgelsheim M, Rivadeneira F, et al. A genome-wide association study of acenocoumarol maintenance dosage. Hum Mol Genet 2009;18:3758-68. Aarts N, Akoudad S, Noordam R, Hofman A, Ikram MA, Stricker BH, Visser LE, Vernooij MW. Inhibition of serotonin reuptake by antidepressants and cerebral microbleeds in the general population. Stroke 2014;45:1951-7. Lubitz SA, Lunetta KL, Lin H, et al. Novel genetic markers associate with atrial fibrillation risk in Europeans and Japanese. J Am Coll Cardiol 2014;63:1200-10. Lahousse L, Vernooij MW, Darweesh SK, Akoudad S, Loth DW, Joos GF, Hofman A, Stricker BH, Ikram MA, Brusselle GG. Chronic obstructive pulmonary disease and cerebral microbleeds. Am J Respir Crit Care Med 2013;188:783-8. Sedaghat S, Pazoki R, Uitterlinden AG, Hofman A, Stricker BH, Ikram MA, Franco OH, Dehghan A. Association of Uric Acid Genetic Risk Score With Blood Pressure: The Rotterdam Study.

	Hypertension. 2014 Sep 2. pii: HYPERTENSIONAHA.114.03757. [Epub ahead of print] PubMed PMID: 25185132. Sinner MF, Tucker NR, Lunetta KL, et al. Integrating Genetic, Transcriptional, and Functional Analyses to Identify Five Novel Genes for Atrial Fibrillation. Circulation. 2014 Aug 14. pii: CIRCULATIONAHA.114.009892. [Epub ahead of print] PubMed PMID: 25124494. Rodenburg EM, Visser LE, Hoorn EJ, Ruiter R, Lous JJ, Hofman A, Uitterlinden AG, Stricker BH. Thiazides and the risk of hypokalemia in the general population. J Hypertens 2014;32:2092-7.