Erasmus University Rotterdam, the Netherlands
CSC PhD 2015 Project Description

School/Department:	Department of Forensic Molecular Biology and Department of Dermatology, Erasmus MC University Medical Center Rotterdam
Project Title:	Methodological approaches to Phenom-wide association studies with applications to skin traits and diseases
Abstract:	Nowadays, it is increasingly demanding for efficient and powerful methods to analyze high dimensional genome and phenotype data, or so-called Phenom-Wide Association Studies (PheWAS). Testing genetic association for millions of genetic markers with a high-dimensional vector of phenotypes remains a challenging task, with prospect of increased power to detect small effects. Some existing methods have rarely been compared to the extent of enabling assessment of their relative merits and setting up guidelines on which method to use, and how to use it. The proposed project aim to develop new methods for PheWAS using simulated data. The candidate will investigate whether sparse canonical correlation analysis has higher power than alternative methods, such as regression models with latent confounding factors, while remaining computationally tractable for routine use in the GWAS setting. The candidate will have opportunities to apply newly developed methods to real high dimensional data sets comprising dozens of highly correlated skin traits/diseases and approximately 15 million SNPs. The data set includes human pigmentation traits and a number of pigmentation related skin conditions/diseases, such as actinic keratosis, melanoma, nevi, freckling, age spots, and skin aging traits. These traits/diseases are highly interrelated via partially overlapping genetic pathways. Over recent years, the Department of Forensic Molecular Biology and the Department of Dermatology at Erasmus University Medical Center already began harvesting a number of SNPs showing significant association with some traits/diseases. These promising results provide a unique opportunity for the candidate to start with. Still, many causal DNA variants and the way they may functionally contribute to these traits/diseases remain to be discovered and illustrated. The successful candidate will work on extensive genomic and phenotypic data which have been collected by us in the Rotterdam Study (Netherlands) as well as by our close global collaborators such as in the TwinsUK Study (UK), the Brisbane Twin Nevus Study (Australia), the Nurses' health Study (USA), and the Health Professionals Follow-Up Study (USA). The existing large datasets (a dozen of thousands of samples) will ensure sufficient statistical power given the numbers of phenotypes and genotypes to be tested.

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	The successful candidate will be jointly supervised by the Department of Forensic Molecular Biology with expertise on genetics of human pigmentation traits and computational genomics and the Department of Dermatology with expertise on various skin disorders. The successful candidate is expected to obtain a PhD title in 4 years.
Requirements of candidate:	Master degree: Yes Essential requirements: The candidate is required to have background in in any of the following disciplines, at best more than one: biostatistics, bioinformatics, computer science, epidemiology, or public health. The candidate is required to have excellent programing and computing skills. Note that there will be an exam for this. Desired pluses: Knowledge in genetics and human disease; Experience in dealing with large datasets; Experience in software package development; Authorship on science citation indexed (SCI) publications. IELTS Grade: 7.0 *(minimal 6.0 per component)* *or* TOEFL: *100 (minimal 20 per component)*
Supervisor information:	*Assist.-Prof. Dr. Fan Liu* *Group Leader, Dept. of Forensic Molecular Biology, Erasmus MCP.O. Box 2040, 3000 CA Rotterdam, The Netherlands* *Visiting address: Wytemaweg 80, 3015 CN Rotterdam, The Netherlands, room Ee1067* *Phone: +31 10 70 429 96* *Email: f.liu@erasmusmc.nl* *www.erasmusmc.nl | www.erasmusmc.nl/fmb* *And* *Prof. Dr.Tamar Nijsten* *Head, Dept. of Dermatology* *P.O. Box 2040, 3000 CA Rotterdam, The Netherlands* *Visiting address: Burg s jacobsplein 51, 3015 CA, Rotterdam, The Netherlands* *Phone:+31 10 70 345 80* *Email: t.nijsten@erasmusmc.nl*

	Selected publications related to the topic last 5 years (1-2 pages) 1) Pasquali E, García-Borrón JC, Fargnoli MC, Gandini S, Maisonneuve P, Bagnardi V, Specchia C, **Liu F, Kayser M, Nijsten T**, Nagore E, Kumar R, Hansson J, Kanetsky PA, Ghiorzo P, Debniak T, Branicki W, Gruis NA, Han J, Dwyer T, Blizzard L, Landi MT, Palmieri G, Ribas G, Stratigos A, Council ML, Autier P, Little J, Newton-Bishop J, Sera F, Raimondi S; for the M-SKIP Study Group (2014) MC1R variants increased the risk of sporadic cutaneous melanoma in darker-pigmented Caucasians: a pooled analysis from the M-SKIP project. ***International Journal of Cancer***, Epub Jun 2014, doi: 10.1002/ijc.29018, **IF: 5.007, Ci: 0** 2) Jacobs LC, **Liu F**, Bleyen I, Gunn DA, Hofman A, Klaver CC, Uitterlinden AG, Neumann HAM, Bataille V, Spector TD, **Kayser M**, **Nijsten T** (2014) Intrinsic and extrinsic risk factors for sagging eyelids. ***JAMA Dermatology***, Epub May 2014, doi:10.1001/jamadermatol.2014.27, **IF: 4.306, Ci: 0** 3) Pośpiech E, Wojas-Pelc A, Walsh S, **Liu F**, Maeda H, Ishikawa T, Skowron M, **Kayser M**, Branicki W (2014) The common occurrence of epistasis in the determination of human pigmentation and its impact on DNA-based pigmentation phenotype prediction. ***Forensic Science International: Genetics***, 11:64-72, **IF: 3.202, Ci: 1** 4) **Liu F**, Hendriks AEJ, Ralf A, Boot AM, Benyi E, Sävendahl L, Oostra BA, van Duijn C, Hofman A, Rivadeneira F, Uitterlinden AG, Drop SLS, and **Kayser M** (2014) Common DNA variants predict tall stature in Europeans. ***Human Genetics***, 133(5):587-97, **IF: 4.522, Ci: 0** 5) Jacobs LC, Wollstein A, Lao O, Hofman A, Vingerling JR, Uitterlinden AG, **Nijsten T**, **Kayser M, Liu F** (2013) Comprehensive candidate gene study highlights *UGT1A* and *BNC2* as new genes determining continuous skin color variation in Europeans. ***Human Genetics***, 132:147–158, **IF: 4.522, Ci: 6** 6) Raimondi S, Gandini S, Fargnoli MC, Bagnardi V, Maisonneuve P, Specchia C, Kumar R, Nagore E, Han J, Hansson J, Kanetsky PA, Ghiorzo P, Gruis NA, Dwyer T, Blizzard L, Fernandez-de-Misa R, Branicki W, Debniak T, Morling N, Landi MT, Palmieri G, Ribas G, Stratigos A, Cornelius L, Motokawa T, Anno S, Helsing P, Wong TH, Autier P, García-Borrón JC, Little J, Newton-Bishop J, Sera F, **Liu F**, **Kayser M**, **Nijsten T**; GEM Study Group; M-SKIP Study Group (2012). Melanocortin-1 receptor, skin cancer and phenotypic characteristics (M-SKIP)

project: study design and methods for pooling results of genetic epidemiological studies. ***BMC Medical Research Methodology*** 12:116, **IF: 2.168, Ci: 0**

7) **Liu F**, van der Lijn F, Schurmann C, Zhu G, Chakravarty MM, Hysi PG, Wollstein A, Lao O, de Bruijne M, Ikram MA, van der Lugt A, Rivadeneira F, Uitterlinden AG, Hofman A, Niessen WJ, Homuth G, de Zubiceray G, McMahon KL, Thompson PM, Daboul A, Puls R, Hegenscheid K, Bevan L, Pausova Z, Medland SE, Montgomery GW, Wright MJ, Wickiing C, Boehringer S, Spector TD, Paus T, Martin NG, Biffar R, and **Kayser M** on behalf of the International Visible Trait Genetics (VisiGen) Consortium (2012) A genome-wide association study identifies five loci influencing facial morphology in Europeans. ***PLoS Genetics***, 8(9):e1002932, **IF: 8.167, Ci: 27**

8) **Liu F**, Struchalin MV, van Duijn K, Hofman A, Uitterlinden AG, Aulchenko YS, and **Kayser M** (2011) Detecting low frequent loss-of-function alleles in genome-wide association studies with red hair color as example. ***PLoS One***, 6(11):e28145, **IF: 3.534, Ci: 6**

9) Boehringer S, van der Lijn F, **Liu F**, Günther M, Sinigerova S, Birnbaum S, Ludwig KU, Herberz R, Klein S, Hofman A, Uitterlinden AG, Niessen WJ, Breteler MMB, van der Lugt A, Wurtz RP, Nöthen MM, Horsthemke B, Wieczorek D, Mangold E[+], **Kayser M**[+] (2011) Genetic determination of human facial morphology: links between cleft-lips and normal variation. ***European Journal of Human Genetics***, 19:1192-1197, **IF: 4.225, Ci: 17**

10) Branicki W, **Liu F**, van Duijn K, Draus-Barini J, Pośpiech E, Walsh S, Kupiec T, Wojas-Pelc A, and **Kayser M** (2011) Model-based prediction of human hair color using DNA variants. ***Human Genetics***, 129:443–454, **IF: 4.522, Ci: 31**

11) **Liu F**, Wollstein A, Hysi PG, Ankra-Badu GA, Spector TD, Park D, Zhu G, Larsson M, Duffy DL, Montgomery GW, Mackey DA, Walsh S, Lao O, Hofman A, Rivadeneira F, Vingerling JR, Uitterlinden AG, Martin NG, Hammond CJ, and **Kayser M** (2010) Digital quantification of human eye color highlights genetic association of three new loci. ***PLoS Genetics***, 6 (5):e1000934, **IF: 8.167, Ci: 43**

12) Flohil SC, van der Leest RJ, Arends LR, de Vries E, **Nijsten T** (2013) Risk of subsequent cutaneous malignancy in patients with prior keratinocyte carcinoma: a systematic review and meta-analysis. ***European Journal of Cancer***, 49: 2365-2375,

	IF:4.819, Ci: 2 13) Flohil SC, van der Leest RJ, Dowlatshahi EA, Hofman A, de Vries E, **Nijsten T** (2013) Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study. ***Journal of Investigative Dermatology***, 133: 1971-1978. **IF:6.372, Ci: 6** 14) Holterhues C, Vries E, Louwman MW, Koljenovic S, **Nijsten T** (2010) Incidence and trends of cutaneous malignancies in the Netherlands, 1989-2005. ***Journal of Investigative Dermatology*****,** 130: 1807-1812, **IF:6.372,Ci: 60** 15) Kiiski V, de Vries E, Flohil SC, Bijl MJ, Hofman A, Stricker BH, **Nijsten T** (2010) Risk factors for single and multiple basal cell carcinomas. ***Archives of Dermatology***, 146: 848-855. **IF:4.306, Ci: 34**
	Co-supervisor: Prof. Dr. M. Kayser Head, Dept. of Forensic Molecular Biology, Erasmus MC).