

**Network: Obesity and Related Disorders****Project: Biostatistics, Genetic Epidemiological Methods and Data Management****Helmut Schäfer - Philipps University, Marburg - hsimbe@med.uni-marburg.de****Introduction**

The Institute of Medical Biometry and Epidemiology, University Marburg, has a long standing research focus on genetic epidemiological methodology and statistical genetics among other things within the former clinical research group on body weight regulation (Prof. Hebebrand, Dr. Hinney) since its start in 1995. Ever since we have successfully cooperated in many large scale studies. Moreover, we are part of the NGFN SMP platform for Genetic Epidemiological Methodology (GEM Marburg).

Within the network, the goal of this project is the application of statistical and epidemiological methods in search of candidate genes for obesity. In order to avoid artefacts e.g. resulting from multiple testing, a precise statistical evaluation is of major importance for the research pipeline. Concurrently, the identification of true genetic effects has to be ensured by means of maximized statistical power as subsequent studies of function and population genetics will focus on these candidates.

Our responsibilities, to name a few, cover the planning and statistical analysis (e.g. study design selection, criteria for marker and phenotype selection, sample size planning), the discussion or interpretation of the statistical results and the specification of follow-up confirmatory, replicate studies. Furthermore, we do statistical evaluations of published literature. The statistical methods for state of the art design and analyses of genetic epidemiological studies for complex diseases are available, such as genome-wide linkage and association analyses, haplotype estimation and analysis, case-control and family-based association analysis, methods for quantitative traits, complex segregation analysis, etc..

Besides biostatistical and data management service for the study groups within the network, we are doing research in advanced statistical methodology and development of statistical methods for the design and analysis of molecular genetic studies. Current research focuses in our group are statistical methods for estimation of genetic risks and population genetic parameters, statistical methods for the detection of genotyping errors, sequential and adaptive designs for sequentially recruiting studies with nuclear families and cases and controls as well as meta-analyses of genome-wide scans for linkage. Within the GEM Marburg our focus is on statistical methods for gene x environment interactions.

**Project Status**

Our group participated in numerous linkage and association studies, with a main focus on candidate genes. We refer to our contribution to several (recent) published articles of the cooperation partners [e.g. 1-3].

More specifically, within NGFN-2, we first contributed to the fine mapping and replication of several relevant candidate regions previously indicated by a genome scan for childhood and adolescent obesity. Within the network, we are currently involved in analysing data from the extended 10K SNP scan. Subsequent work will deal with the determination of allele

and genotype frequencies in large clinical sample and epidemiological samples.

At our routine conferences with partners in Essen and Marburg, we use the stimulating exchange with our clinical partners to provide them with information on recent methodological developments. Furthermore, we try to incorporate some of the ideas in new methodological developments which serve the special needs of our partners.

Consequently, we applied recently developed methods to our data sets. Furthermore, we implemented some of the methodological suggestions in macros e.g. tests for imprinting effects or exact HWE determinations.

**Outlook**

Given the recent advances in ultra-high-volume genotyping technology and the overwhelming growth of new statistical procedures, we assume that methodological expertise will become even more important within the network.

According to a recent review on methodological challenges in genetic epidemiology, Thomas [4] highlights e.g. the importance of multistage sampling designs in terms of expected efficiency gains.

Given both our contributions to research in advanced statistical methodology especially within the field of sequential and adaptive designs and the vivid exchange with our clinical partners, we hope to provide a solid and sound base facing the future requirements in genetic epidemiology.

*Lit.: 1. Wermter AK, Reichwald K, Buch T, Geller F, Platzer C, Huse K, Hess C, Remschmidt H, Gudermann T, Preibisch G, Siegfried W, Goldschmidt HP, Li WD, Price RA, Biebertmann H, Krude H, Vollmert C, Wichmann HE, Illig T, Sorensen TI, Astrup A, Larsen LH, Pedersen O, Eberle D, Clement K, Blundell J, Wabitsch M, Schäfer H, Platzer M, Hinney A, Hebebrand J. Mutation analysis of the MCHR1 gene in human obesity. Eur J Endocrinol. 2005 Jun;152(6):851-62. 2. Friedel S, Horro FF, Wermter AK, Geller F, Dempfle A, Reichwald K, Smidt J, Brönnner G, Konrad K, Herpertz-Dahlmann B, Warnke A, Hemminger U, Linder M, Kiehl H, Goldschmidt HP, Siegfried W, Remschmidt H, Hinney A, Hebebrand J. Mutation screen of the brain derived neurotrophic factor gene (BDNF): identification of several genetic variants and association studies in patients with obesity, eating disorders, and attention-deficit/hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet. 2005 Jan 5;132(1):96-9. 3. Heid IM, Vollmert C, Hinney A, Doring A, Geller F, Lowel H, Wichmann HE, Illig T, Hebebrand J, Kronenberg F; KORA Group. Association of the 1031 MC4R allele with decreased body mass in 7937 participants of two population based surveys. J Med Genet. 2005 Apr;42(4) 4. Thomas DC, Haile RW, Duggan D. Recent developments in genomewide association scans: a workshop summary and review. Am J Hum Genet. 2005 Sep;77(3):337-45.*