Genome-wide Association Studies (GWAS)

Principal Investigator: Claudia Lamina and Florian Kronenberg

History

In 2005 eleven collaborators founded a consortium headed by H.-Erich Wichmann and Thomas Meitinger at the Helmholtz-Center Munich to perform genome-wide association studies (GWAS) within the KORA cohorts F3 and F4. Each of the partners is responsible for a certain phenotype group. The Innsbruck group around Florian Kronenberg was selected for lipid-related phenotypes. However, we are also involved in several other phenotypes of interest. With the move of Claudia Lamina from the Helmholtz-Center Munich to our research group in 2009, our team became more intensively involved in data analysis. Besides data analyses, our laboratory team from the "Sequencing & Genotyping Unit" contributes to many GWAS by performing de-novo genotypings in replication samples as well as bioinformatic analysis of detected gene regions.

GWAS on Lipids

After carrying out a GWAS on HDL cholesterol **[1]**, we and the field came to realize that very large sample sizes are required to have the statistical power to identify new genes and pathways involved in lipid metabolism. Therefore, we joined the European ENGAGE consortium with 16 population-based cohorts including up to 22.000 study participants. This initiative observed 22 genetic loci associated with serum lipid levels, 6 of which were newly identified. A score of risk alleles for lipids found associations of these alleles with carotid intima-media thickness as well as coronary heart disease incidence **[2]**. Since these 22 genetic loci still explained only up to 4.8% of lipid levels, we joined the "Global Lipids Genetics Consortium" with far more than 100 000 individuals investigated. This study finally identified 95 (59 new) genetic loci associated with serum lipids levels. These mapped variants explained 10-12% of each trait which corresponds to about a quarter of the variance for each trait expected to be explained by genes. Many of these genes were not previously implicated in lipoprotein metabolism and they contribute not only to normal variation in lipid traits but also to extreme lipid phenotypes and lipid traits in multiple ethnic populations **[3]**.

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GWAS on Adiponectin

Plasma adiponectin is strongly associated with various components of metabolic syndrome, type 2 diabetes and cardiovascular outcomes. Concentrations are highly heritable and differ between men and women. We therefore aimed to investigate the genetics of plasma adiponectin in men and women.

Together with Iris M. Heid from the University of Regensburg we organized a GWAS consortium for adiponectin plasma concentrations. We combined genome-wide association scans of three population-based studies including 4659 persons (Erasmus Rucphen Family Study, KORA-F3 and the MICROS Study). The replication stage included 13795 subjects from the studies CoLaus, Framingham, GEMS, ALSPAC, TWINS UK, InChianti and BLSA. We demonstrated that the ADIPOQ gene is the only major gene for plasma adiponectin, which explains 8.7% of the phenotypic variance **[4]** and which we had already studied intensively in earlier times **[5]**. We further found that neither this gene nor any of the known metabolic syndrome loci explained the sex differences observed for plasma adiponectin levels **[4]**.

To increase the power of this GWAS study to find further genes which have an influence on adiponectin concentrations, our entire consortium joined the ADIPOGEN consortium which currently analyses the data of more than 20.000 subjects.

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GWAS on Metabolites

Serum metabolite concentrations provide a direct readout of biological processes in the body and mirror an individual's metabolic capacities. They are associated with disorders such as cardiovascular and metabolic diseases. Our group was involved in the first combination of two hypothesis-free approaches by combining a GWAS with a wide spectrum of metabolites. It was argued that knowledge of the "genetically determined metabotypes" in the human population is key to identifying the contributions and interaction of genetic and environmental factors in the etiology of complex diseases. Serum concentrations of 163 metabolites covering a wide panel of amino acids, sugars, acylcarnitines, and phospholipids, were determined by electrospray ionization tandem mass spectrometry (ESI-MS/MS) with commercially available metabolomics kit technology. Most of the identified loci in this GWAS were located in or near enzyme or solute carrier coding genes, where the associating metabolic traits match the proteins' function. The most important observation was that the use of metabolite concentration ratios as proxies for enzymatic reaction rates reduces the variance and yielded robust statistical associations with p-values between 10^{-43} and 10^{-178} **[6,7]**. In contrast to most GWAS with clinical endpoints, it appears that for metabolic traits most of the associations are linked to genetic variants in genes with a matching metabolic function.

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GWAS on Body Size Measurements

Claudia Lamina is involved in the GIANT consortium (Genetic Investigation of ANthropometric Traits), which performs genome-wide meta-analyses on body size measurement such as body mass index (BMI) or waist-hip-ratio (WHR).

The first big step into unraveling the genetic basis of central obesity and fat distribution has been made in 2009. A meta-analysis of 16 genome-wide association studies (N=38,580) followed by replication in further studies (additional N=70,689) revealed two loci which were associated with waist circumference and one locus (near *LYPLAL1*) associated with Waist-Hip-Ratio (WHR) **[8]**. The effect of the latter was found to have higher effects in women than in men and was also found to be independent from general obesity, as defined by the Body Mass Index (BMI). This sexual dimorphism of the genetic basis of fat distribution could be confirmed in the following round of GIANT, which focused on WHR **[9]**: By doubling the sample size (32 GWAS, N=77,167 + 29 replication studies, N=113,636 subjects), 13 new loci could be identified and the already known locus at *LYPLAL1* replicated. 7 of these loci exhibit marked sexual dimorphism, all with a stronger effect on WHR in women than men.

Another study within the GIANT consortium looked for genetic determinants of Body Mass Index (BMI) **[10]**. Data from 46 studies involving nearly 124,000 people were combined and replicated by additional studies including almost 126,000 individuals. 14 known obesity susceptibility loci were confirmed and 18 loci newly identified. The effects of each individual variant were found to be modest and can explain only a small fraction of the overall variation in obesity. Nevertheless, the findings are very important, since they may provide new insights into the underlying biology of human body weight regulation. Some of these loci, for example, map near key hypothalamic regulators of energy balance and may affect appetite.

The GIANT consortium effort is still going on and thus will contribute to the understanding of genetic contribution to obesity and fat distribution.

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GWAS on Ankle-Brachial-Index

Asymptomatic peripheral arterial disease can be diagnosed by means of the Ankle-Brachial-Index (ABI), defined as the ratio of Doppler-recorded systolic blood pressures in the lower and upper extremities, a standardized, non-invasive, simple diagnostic tool. ABI-values of 0.9 or lower indicate the presence of peripheral arterial disease with a sensitivity of 95% and specificity of 100%. A low ABI may be a relevant indicator of atherosclerotic burden and is associated with increased CVD morbidity and mortality.

We contributed our data on ABI from 1581 and 1407 persons from the KORA F3 and KORA F4 Study, respectively to two internationally acting GWAS consortia for ABI (CARE and CHARGE) for a meta-analysis. In the meanwhile the number of investigated persons from the entire consortium adds up to more than 30.000. We are currently in the stage of meta-analyzing the data.

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GWAS on other Phenotypes

Our group is involved in the following GWAS either in data analysis, genotyping or bioinformatic analysis:

- Uric acid concentrations **[11,12]**
- Kidney function or chronic kidney disease (CKDGen consortium) **[13]**
- Smoking quantity **[14]**

Team members:

Claudia Lamina, Stefan Coassin, Barbara Kollerits, Anita Kloss-Brandstätter, Margot Haun, Gertraud Erhart, Monika Summerer, Doreen Dähnhardt

Main collaborators:

- H.-Erich Wichmann, Thomas Illig, Norman Klopp, Annette Peters, Angela Döring, Konstantin Strauch, Christian Gieger, Karsten Suhre (Helmholtz Center Munich, D)
- Iris M. Heid and Carsten Böger (University of Regensburg, D)
- Caroline S. Fox (Framingham Heart Study, USA)
- Bernhard Paulweber (Paracelsus Private Medical University Salzburg)
- KORA Study Group, SAPHIR Study, Utah Obesity Case-Control Study, Bruneck Study, CoLaus Study, SHIP Study, ERF Study, MICROS Study, Rotterdam Study and many others

Selected Publications:

1. Heid IM, Boes E, Müller AM, Kollerits B, Lamina C, Coassin S, Gieger C, Döring A, Klopp N, Frikke-Schmidt R, Tybjærg-Hansen A, Brandstätter A, Luchner A, Meitinger T, Wichmann HE, Kronenberg F: Genome-wide association analysis of high-density lipoprotein cholesterol in the population-based KORA Study sheds new light on intergenic regions. ***Circulation: Cardiovascular Genetics*** 1:10-20, 2008. [Pub-Med]
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