

## **KORA – a success story for genome-wide association studies**

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KORA (Collaborative Health Research in the Region of Augsburg) is a research platform based on a population-based cohort study of 18,000 adults from Southern Germany. Recruitment started in 1984/85 and was performed in 4 surveys, followed by repeated investigations in regular intervals. Phenotyping is very broad, with a focus on cardiovascular and metabolic diseases. Biosamples of most participants (whole blood, serum, plasma, DNA, urine) are available.

In recent years, we have implemented KORA-gen, which is the biobank of KORA. Meanwhile this biobank has been used in more than hundred national and international collaborations and is participating in consortia like MORGAM, ENGAGE, CARDIOGENICS, GIANT, IQWANA, MOLPAGE, DIAGRAM, CHARGE, NGFN (German National Genome Network).

The most impressive success was in the field of genome-wide association studies (GWAS), where KORA has provided cases of frequent diseases, quantitative traits, and controls.

Since 2005 about 100 publications on GWAS in refereed international journals with IF >5 based on KORA or using data from KORA have been published, some of them in journals like New England Journal of Medicine, Science, Nature Genetics Lancet etc. Especially the list of publications since 2008 is very impressive: It includes 84 papers in highly-ranked journals with IF > 5 (1 in Nature, 34 in Nature Genetics, 4 in the American Journal of Human Genetics, 7 in PLoS Genetics, etc, see list).

Scientificly, these successful collaborations are based on the quality of research and the openness to share data and ideas with colleagues.

Website: <http://epi.helmholtz-muenchen.de/kora-gen>

With respect to NGFNplus, KORA is used for health endpoints, quantitative traits or as control sample within the following projects:

- Genomics of Atherosclerosis (Schunkert)
- Genetics of Heart Failure (Katus)
- Molecular Mechanisms of Obesity (Hebebrand)
- Systematic Genomics of Chronic Inflammatory Barrier Diseases (Schreiber)
- Molecular Causes of Major Mood Disorders and Schizophrenia (Noethen)
- Functional Genomics of Parkinson (Gasser)
- Genetics of Alcohol Addiction (Spanagel)
- Epilepsy and Migraine Integrated Network (Kubisch)
- Gene Identification and Functional Analyses in Alzheimer's Disease (Riemenschneider)

The corresponding publications and collaborators are marked in yellow.

**Table: Highly-ranked publications from KORA 2008 - 2010 on GWAS (IF>5)**

<p><b>2008 (24)</b>  Döring et al. <b>Nat Genet</b> (2008)  Lettre et al. <b>Nat Genet</b> (2008)  Loos et al. <b>Nat Genet</b> (2008)  Schormair B et al. <b>Nat Genet</b> (2008)  Zeggini et al. <b>Nat Genet</b> (2008)  Lasky-Su et al. <b>Am J Hum Genet</b> (2008)  Luca et al. <b>Am J Hum Genet</b> (2008)  Gieger et al. <b>Plos Genetics</b> (2008)  Weidinger et al. <b>Plos Genetics</b> (2008)  Gibson et al. <b>Proc Natl Acad Sci</b> (2008)  Watanabe et al. <b>J Clin Invest</b> (2008)  Lao O et al. <b>Curr Biol</b> (2008)  Gretarsdottir et al. <b>Ann Neurology</b> (2008)  Gschwendtner et al. <b>Stroke</b> (2008)  Jacquemin et al. <b>J Am Coll Cardiol</b> (2008)  Lieb et al. <b>Circulation</b> (2008)  Schunkert et al. <b>Circulation</b> (2008)  Kolz et al. <b>Eur Heart J</b> (2008)  Sinner et al. <b>Eur Heart J</b> (2008)  Wiedmann et al. <b>Diabetes</b> (2008)  Brandstätter et al. <b>Diabetes Care</b> (2008)  Herder et al. <b>Diabetologia</b> (2008)  Weidinger et al. <b>J Allergy Clin Immunol</b> (2008)  Heid et al. <b>Am J Epidemiology</b> (2008)</p>	<p><b>2010 (48)</b>  Moffatt et al. <b>NEJM</b> (2010)  Int Stroke Genet Consort <b>NEJM</b> (2010)  Lango Allen et al. <b>Nature</b> (2010)  Eslovich et al. <b>Nature</b> (2010)  Anttila et al. <b>Nat Genet</b> (2010)  Dupuis et al. <b>Nat Genet</b> (2010)  Elks et al. <b>Nat Genet</b> (2010)  Ellinghaus et al. <b>Nat Genet</b> (2010)  Ellinor et al. <b>Nat Genet</b> (2010)  Franke et al. <b>Nat Genet</b> (2010)  Freatly et al. <b>Nat Genet</b> (2010)  Heid et al. <b>Nat Genet</b> (2010)  Hüffmeier et al. <b>Nat Genet</b> (2010)  Illig et al. <b>Nat Genet</b> (2010)  Köttgen et al. <b>Nat Genet</b> (2010)  Liu et al. <b>Nat Genet</b> (2010)  Mangold et al. <b>Nat Genet</b> (2010)  Meindl et al. <b>Nat Genet</b> (2010)  Pfeufer et al. <b>Nat Genet</b> (2010)  Repapi et al. <b>Nat Genet</b> (2010)  Saxena et al. <b>Nat Genet</b> (2010)  Sotoodehnia et al. <b>Nat Genet</b> (2010)  Speliotes et al. <b>Nat Genet</b> (2010)  Stuart et al. <b>Nat Genet</b> (2010)  Thorgeirsson et al. <b>Nat Genet</b> (2010)  Voight et al. <b>Nat Genet</b> (2010)  Yasuno et al. <b>Nat Genet</b> (2010)  Marzi et al. <b>PLoS Genet</b> (2010)  Naukkarinen et al. <b>PLoS Genetics</b> (2010)  Padmanabhan et al. <b>PLoS Genetics</b> (2010)  Segré et al. <b>PLoS Genetics</b> (2010)  Stark et al. <b>PLoS Genetics</b> (2010)  Eijgelsheim et al. <b>Hum Mol Genet</b> (2010)  Qi et al. <b>Hum Mol Genet</b> (2010)  Barbalic, et al. <b>Hum Mol Genet</b> (2010)  Kettunen et al. <b>Hum Mol Genet</b> (2010)  Perry et al. <b>Hum Mol Genet</b> (2010)  de Kovel et al. <b>Brain</b> (2010)  Schnabel et al. <b>Blood</b> (2010)  Smith et al. <b>Circulation</b> (2010)  Blankenberg et al. <b>Circulation</b> (2010)  Lubitz et al. <b>Circulation</b> (2010)  Markus et al. <b>J Am Coll Cardiol</b> (2010)  Kestenbaum et al. <b>J Am Soc Nephrol</b> (2010)  Fernández-Santiago et al. <b>Neurobiol Aging</b> (2010)</p>
<p><b>2009 (42)</b>  Kong et al. <b>Nature</b> (2009)  Aulchenko et al. <b>Nat Genet.</b> (2009)  Benjamin et al. <b>Nat Genet.</b> (2009)  Erdmann et al. <b>Nat Genet.</b> (2009)  Esparza-Gordillo et al. <b>Nat Genet.</b> (2009)  Ganesh et al. <b>Nat Genet.</b> (2009)  Gudbjartsson et al. <b>Nat Genet.</b> (2009)  Hallmayer et al. <b>Nat Genet.</b> (2009)  Harold et al. <b>Nat Genet.</b> (2009)  MI Genetics Consort <b>Nat Genet.</b> (2009)  Newton-Cheh et al. <b>Nat Genet.</b> (2009)  Pfeufer et al. <b>Nat Genet.</b> (2009)  Prokopenko et al. <b>Nat Genet.</b> (2009)  Simón-Sánchez et al. <b>Nat Genet.</b> (2009)  Soranzo et al. <b>Nat Genet.</b> (2009)  Trégouët et al. <b>Nat Genet.</b> (2009)  Van Es et al. <b>Nat Genet.</b> (2009)  Willer et al. <b>Nat Genet.</b> (2009)  Soranzo et al. <b>Blood</b> (2009)  Landi et al. <b>Am J Hum Genet</b> (2009)  Meisinger et al. <b>Am J Hum Genet</b> (2009)  Chio et al. <b>Hum Mol Genet</b> (2009)  Kettunen et al. <b>Hum Mol Genet</b> (2009)</p>	

Org et al. **Hum Mol Genet** (2009)  
Perry et al. **Hum Mol Genet** (2009)  
Heid et al. **PLoS Genet.** (2009)  
Hicks et al. **PLoS Genet.** (2009)  
Kolz et al. **PLoS Genet.** (2009)  
Lindgren et al. **PLoS Genet.** (2009)  
Richards et al. **PLoS Genet.** (2009)  
Peters et al. **Am J Respir Crit Care Med** (2009)  
Vasan et al. **JAMA** (2009)  
Freilinger et al. **Stroke** (2009)  
Schlachter et al. **Neurology** (2009)  
Gschwendtner et al. **Ann Neurol** (2009)  
Huth et al. **Ann Med** (2009)  
Linsel-Nitschke et al. **Atherosclerosis** (2009)  
CAD Consortium **Art Thromb Vasc Biol** (2009)  
Kääb et al. **Eur Heart J** (2009)  
Laumen et al. **Diabetes** (2009)  
Achenbach et al. **Diabetologia** (2009)  
Luotola et al. **J Clin Endocrinol Metab.** (2009)  
Ljungman et al. **Environ Health Perspect** (2009)  
Salanti et al. **Am J Epidemiology** (2009)

Lücking et al. **Neurobiol Aging** (2010)  
Bergboer et al. **J Invest Dermat** (2010)  
Landi et al. **Lancet Oncology** (2010)

## Appendix

**Name of study:** KORA Study Augsburg

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**Primary aim:** Assessment of risk factors for chronic complex diseases with a focus on coronary heart disease and diabetes and their related quantitative traits in adults.

### Summary of design:

KORA is a population-based cohort study that recruited randomly subjects from the general population age 25 to 74 years (N= 18,079 subjects) in Augsburg, Germany and the two adjacent counties between 1984 and 2001. The recruitment of subjects was as follows:

	Survey 1984/85	Survey 1989/90	Survey 1994/85	Survey 1999/01
Men	2023	2482	2405	2090
Women	1999	2458	2451	2171

The baseline examination included an assessment of traditional risk factors and subclinical disease measures, based on questionnaire information including information on socio-demographic variables, utilization of the medical health care system, smoking, nutrition, physical activity, medication use, family history, women specific variables, self-reported health status, and psychosocial variables. More extended subclinical measures were taken in the re-examinations of S3 in 2004 to 2005 (N=3006, F3) and re-examination of S4 in 2006 to 2008 (N=3080, F4); these included for example fasting blood (F4), bioelectrical Impedance Analysis (BIA), 12-lead resting ECG, daily 1-lead ECG, echocardiography (S3/F3), oral glucose tolerance test (S4/F4), endothelial dysfunction (F4), thyroid sonography (F4), skin examination (S3/F3, S4/F4), spirometry, and exhaled NO (F4). Events follow-up for incident cardiovascular clinical events, diabetes and mortality was performed in 1998 and 2002. It is currently being updated for mortality as of end 2007 and morbidity in 2008.

**Phenotypes available for genetic analyses:** CVD risk factors, including blood pressure, BMI, height, weight, body fat, lean body mass, fasting glucose and lipids, oral glucose tolerance test, insulin, Hba1c, smoking, nicotine, alcohol, CRP, fibrinogen, IpPAL2, MCP-1, leptin, adiponektin, uric acid, liver enzymes, Fe, BNP, kidney function, type A, type D, cognitive function, dementia, and medication use; measures of subclinical disease, including electrocardiography (QT, PQ, QRS), carotid ultrasound, echocardiography, pulmonary function tests, ankle-brachial index, Holter monitoring, pulse pressure, endothelial function; cardiovascular events, focusing on myocardial infarction and stroke, diabetes and mortality; and other measures, including depression, restless legs. For more details see Wichmann et al. 2005 and recent publications listed below.

**Whole-genome data (type and date available):** Whole-genome data genotyped with Affymetrix 500K on 1644 participants from S3 who participated in the follow-up examination and with Affymetrix 1000K on approximately 2000 subjects from S4 who participated in the follow-up examination. In 80% of the GWAS, Sequenom I-plex technology has been used for replication.

### Design paper:

H. E. Wichmann, C. Gieger, and T. Illig. KORA-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen* 67 Suppl 1:S26-S30, 2005.

## Publications

### KORA GWAS 2010 (Jan – Dez) (IF>5)

- Moffatt, M.F., ..., Cookson, W.O.C.M., for the GABRIEL consortium with **Heinrich, J.**: A Large-Scale, Consortium-Based Genomewide Association Study of Asthma. N Engl J Med 363(13), 1211-1221 (2010) – Impact Factor: 47,1
- International Stroke Genetics Consortium, with **Klopp, N., Wichmann, H.E.**: Failure to Validate Association between 12p13 Variants and Ischemic Stroke. N Engl J Med 362(16), 1547-1550 (2010) – Impact Factor: 47,1
- Lango Allen, H., ..., **Heid, I., ..., Albrecht, E., ..., Müller, M., ..., Illig, T., ..., Gieger, C., ..., Wichmann, H.E., ..., Hirschhorn, J.N.**: Hundreds of variants clustered in genomic loci and biological pathways affect human height. Nature 467, 832-838 (2010) – Impact Factor: 34,5
- Teslovich, T.M., ..., **Wichmann, H.E., ..., Heid, I.M., ..., Gieger, C., ..., Döring, A., ..., Kathiresan, S.**: Biological, clinical, and population relevance of 95 loci mapped for serum lipid concentrations. Nature 466, 707-713 (2010) – Impact Factor: 34,5
- Anttila, V., ..., **Wichmann, H.E., ..., Palotie, A.**, on behalf of the International Headache Genetics Consortium: Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1. Nat Genet 42(10), 869-873 (2010) – Impact Factor: 34,3
- Dupuis, J., ..., **Grallert, H., ..., Gieger, C., ..., Meisinger, C., ..., Wichmann, H.E., Illig, T., ..., Barroso, I.** for the MAGIC investigators: New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nat Genet 42(2), 105-116 (2010) – Impact Factor: 34,3
- Elks, C.E., ..., **Albrecht, E., ..., Döring, A., ..., Illig, T., ..., Wichmann, H.E., ..., Murray, A.**: Thirty new loci for age at menarche identified by a meta-analysis of genome-wide association studies. Nat Genet 42(12), 1077-1085 (2010) – Impact Factor: 34,3
- Ellinghaus, E., ..., **Gieger, C., Wichmann, H.E., ..., Franke, A.**: Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2. Nat Genet 42(11), 991-995 (2010) – Impact Factor: 34,3
- Ellinor, P.T., ..., **Müller, M., ..., Wichmann, H.E., ..., Käab, S.**: Common variants in KCNN3 are associated with lone atrial fibrillation. Nat Genet 42(3), 240-244 (2010) - Impact Factor : 34,3
- Franke, A., ..., **Gieger, C., Wichmann, H.E., ..., Karlsen, T.H., Schreiber, S.**: Genome-wide association study for ulcerative colitis identifies risk loci at 7q22 and 22q13 (IL17REL). Nat Genet 42(4), 292-294 (2010) – Impact Factor: 34,3
- Freathy, R.M., ..., **Chen, C.M., Tiesler, C., Heinrich, J., ..., McCarthy, M.I.** for the Early Growth Genetics (EGG) Consortium: Variants in ADCY5 and near CCNL1 are associated with fetal growth and birth weight. Nat Genet 42(5), 430-435 (2010) – Impact Factor: 34,3
- **Heid, I.M., ..., Lamina, C., ..., Grallert, H., ..., Illig, T., ..., Wichmann, H.E., ..., Lindgren, C.M.**: Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet 42(11), 949-960 (2010) – Impact Factor: 34,3

- Hüffmeier, U., ..., **Gieger, C., Wichmann, H.E.**, ..., Reis, A.: Common variants study at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis. Nat Genet 42(11), 996-999 (2010) – Impact Factor: 34,3
- **Illig, T., Gieger, C.**, ..., **Wang-Sattler, R.**, ..., **Wichmann, H.E.**, ..., Suhre, K.: A genome-wide perspective of genetic variation in human metabolism. Nat Genet 42(2), 137-141 (2010) – Impact Factor: 34,3
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- Liu, J.Z., ..., **Wichmann, H.E.**, ..., **Lamina, C.**, ..., Marchini, J.: Meta-analysis and imputation refines the association of 15q25 with smoking quantity. Nat Genet 42(5), 436-440 (2010) – Impact Factor: 34,3
- Mangold, E., ..., **Wichmann, H.E.**, ..., Nöthen, M.M.: Genome-wide association study identifies two susceptibility loci for nonsyndromic cleft lip with or without cleft palate. Nat Genet 42(1), 24-26 (2010) – Impact Factor: 34,3
- Meindl, A., ..., **Wichmann, H.E.**, ..., Schmutzler, R.K., Hanenberg, H.: Germline mutations in breast and ovarian cancer pedigrees establish RAD51C as a human cancer susceptibility gene. Nat Genet 42(5), 410-414 (2010) - Impact Factor: 34,3
- Pfeufer, A., ..., **Müller, M.**, ..., **Sauter, W., Gieger, C.**, ..., **Wichmann, H.E.**, ..., Heckbert, S.R.: Genome-wide association study of PR interval. Nat Genet 42(2), 153-160 (2010) - Impact Factor: 34,3
- Saxena, R., ..., **Grallert, H.**, ..., **Illig, T., Wichmann, H.E.**, ..., Watanabe, R.M. for the MAGIC investigators: Genetic variation in GIPR influences the glucose and insulin responses to an oral glucose challenge. Nat Genet 42(2), 142-148 (2010) - Impact Factor: 34,3
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- Stuart, P.E., ..., **Gieger, C., Wichmann, H.E.**, ...Elder, J.T.: Genome-wide association analysis identifies three psoriasis susceptibility loci. Nat Genet 42(11), 1000-1004 (2010) – Impact Factor: 34,3
- Thorgeirsson, T.E., ..., **Gieger, C.**, ..., **Döring, A.**, ..., **Nitz, B.**, ..., **Wichmann, H.E.**, ..., Stefansson, K.: Sequence variants at CHRN3-CHRNA6 and CYP2A6 affect smoking behaviour and risk of lung cancer. Nat Genet 42(5), 448-453 (2010) - Impact Factor: 34,3
- Voight, B.F., Scott, L.J., ..., **Huth, C.**, ..., **Grallert, H.**, ..., **Gieger, C.**, ..., **Klopp, N.**, ..., **Petersen, A.K.**, ..., **Thorand, B.**, ..., **Wichmann, H.E.**, ..., **Illig, T.**, ..., McCarthy, M.I.: Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis. Nat Genet 42(7), 579-589 (2010) – Impact Factor: 34,3
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