News from NGFN-Plus and NGFN-Transfer

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New Clue About Language Development

In an extensive screening program NGFN scientists found a first genetic clue about language development in humans. They investigated a mouse model carrying a part of the human Foxp2 gene, which is thought to be a key gene for language development. In order to identify effects of the human Foxp2 gene NGFN researchers from the German Mouse Clinic screened over 300 physiological parameters of the model mice such as vision, hearing, bone density as well as metabolic- and neurological functions. In the brains of the mice the researchers found alterations which may be closely linked to speech and language development. Their analyses comprise part of an international study led by the Leipzig Max Planck Institute for Evolutionary Anthropology.

A Novel Type of Cardiac Insufficiency and Its Mechanism

The heart is one of the especially hard working organs of the human body - and its integrity is of major importance for health. NGFN scientists now demonstrated that mutations in the protein Nexilin are causative for a new type of heart failure. This protein is an important structural element of the heart muscle as it stabilizes the muscle fibers. Using the zebrafish as a model organism the researchers demonstrated that a dysfunction of Nexilin or its absence directly lead to chronic cardiac insufficiency. The analysis of patients with heart failure confirmed these findings. 9 of 1,000 participants of the study revealed pathological changes of Nexilin, which led to their disease. Hence, patients showing a Nexilin dysfunction could benefit from an optimized therapy applied early in course of the disease thus preventing them from developing chronic cardiac insufficiency.

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Genome-wide Association Studies - a Research Approach With Guaranty for Success

In genome-wide association studies (GWAS) geneticists identify disease-associated genes and their variants that contribute to an increasing risk of developing a disease. With this approach NGFN scientists identified nine new gene variants that predispose for changes in the heart rhythm and atrial fibrillation. It was already assumed that genetic differences make some people more vulnerable to atrial fibrillation being one of the major risk factors for suffering a stroke. Now these differences could be located in the genome, which might help elucidating the molecular basis of atrial fibrillation and understanding its causalities. This knowledge provides insights into atrial disease and lead to new opportunities for prevention and therapy of atrial fibrillation.

International Projects

1000 Genomes

The implementation of new sequencing technologies allows a detailed characterization of the genome of single individuals in a very short time. Using those technologies, the genomes of more than 1,000 people will be sequenced within the international **1000 Genomes Project** in order to provide a detailed catalogue of human genetic variations. With the Max-Planck-Institute for Molecular Genetics in Berlin Germany is partner in this international consortium. The German Federal Ministry of Education and Research (BMBF) is funding this contribution with about 6.9 million Euros.

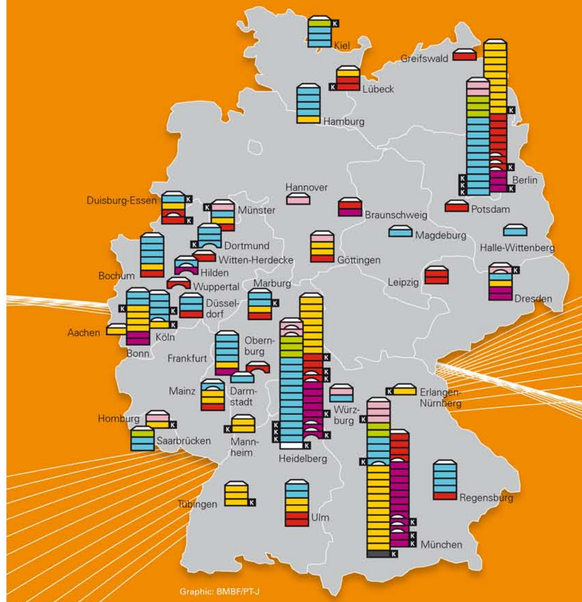
SPONSORED BY THE
Federal Ministry of Education and Research
ANR AGENCE NATIONALE DE LA RECHERCHE

The German Federal Ministry of Education and Research (BMBF) and the French Agence Nationale de La Recherche (ANR) set up a joint funding program in the field of **Genomics and Physiopathology of Cardiovascular and Metabolic Diseases.** Scientists from both countries are cooperating with the common purpose of improving diagnosis and therapy for these diseases. As resources regarding patient and control collectives are limited on a national level, these projects are feasible due to the international collaboration.

International Cancer Genome Consortium

To date, the **International Cancer Genome Consortium (ICGC)** is the most comprehensive international cancer genome project referring human genome research. By combining top-class research expertise from all over the world, the analysis of genetic changes in tumors aims to provide better diagnosis, therapy and prevention of cancer. The German ICGC contribution started in December 2009 with the **PedBrain Tumor-Project** (Coordination at the German Cancer Research Center (DKFZ), Heidelberg). In June 2010 Germany´s contribution was extended by the new projects **Prostate Cancer** (Coordination at the DKFZ, Heidelberg) and **Malignant Lymphomas** (Coordination at the Christian-Albrechts-University, Kiel).

Locations of NGFN-Plus and NGFN-Transfer



Graphic: BMBF/PT-J

- NGFN-Plus location
- NGFN-Plus coordination site
- NGFN-Transfer location
- NGFN-Transfer coordination site
- NGFN Management Office
- Technology Transfer Competence Center

Main focus of research

- Infection / Inflammation
- Diseases due to environmental factors
- Cancer
- Diseases of the nervous system
- Cardiovascular / Metabolic diseases
- Reaching across different diseases

NGFN Management Office

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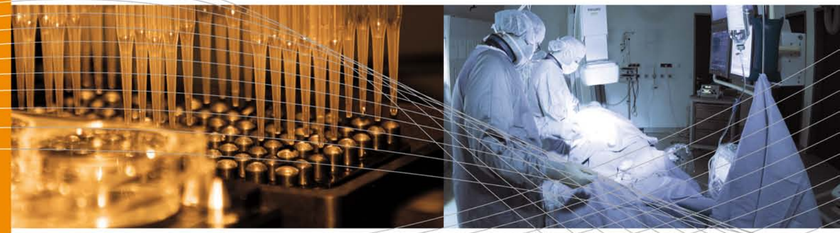
NGFN
National Genome Research Network



NGFN-PLUS AND NGFN-TRANSFER
IN THE PROGRAM OF MEDICAL GENOME RESEARCH

SPONSORED BY THE
Federal Ministry of Education and Research

NGFN-Plus and NGFN-Transfer in the Program of Medical Genome Research

The successful sequencing of the human genome was the first major milestone in human genome research. Since then particularly the genetic diversity between different people as well as the transfer of the findings into medical application arouse public interest. In order to utilize the full potential of medical genome research an intensive networking between the national researchers is essential. For this purpose the National Genome Research Network (NGFN) was launched in 2001. In order to sustain Germany's high impact in science, research and development, the German Federal Ministry of Education and Research (BMBF) is funding this close cooperation of experts from multiple disciplines, including physicians and molecular scientists, in the NGFN. With the newly established Program of Medical Genome Research the NGFN has entered its third period of funding that started by mid-2008. The program consists of two harmonized areas, one is investigating the functions of disease-associated genes (NGFN-Plus) and the other focusing on the rapid transfer of the results into improving diagnosis and therapy (NGFN-Transfer). For the period of sponsorship from 2008 to 2011 153 million Euros have been earmarked by the BMBF. Hence, the BMBF creates decisive space for continuation and enhancement in the advanced field of medical genome research and is strengthening the international competitiveness of German science and research.

NGFN-Plus – Seeking for the Causes and the Curability of Diseases

Widespread diseases such as cancer, obesity, neurological- and cardiovascular disorders are complex phenomena. The disease-oriented research of NGFN-Plus is applying functional genomics and proteomics to extend the fundamental understanding about these diseases. By its clinical orientation NGFN-Plus promotes new strategies and initial points for the development of innovative methods and products for diagnosis and therapy. The NGFN research groups utilize the latest high-throughput technologies for the sequencing of whole genomes and search for disease-associated gene variants. Moreover they analyze the function of the identified genes and their products by manifold experimental methods. Thus they contribute to a better understanding of the molecular causes of diverse diseases and the complex molecular interactions in the human body, which will be crucial for a specific prevention and for the development of effective therapies.

NGFN-Transfer – Application is the Paramount Objective

The rapid and efficient transfer of results from medical genome research into medical application is the objective of NGFN-Transfer, encouraging cooperations of academic research and the business community. Thus in this part of the Program of Medical Genome Research universities, research institutes and biomedical enterprises are closely collaborating in order to develop marked-relevant and transfer-suitable innovations together. Moreover the improvement of existing medications and the optimization of the drug safety are research topics of NGFN-Transfer aiming a personalized and targeted medicine, which spotlights the individual patient.

PD Dr. Stefan Wiemann
Spokesperson for the Project Committee

"Elucidating the molecular causes of diseases and setting the course for optimized therapies"

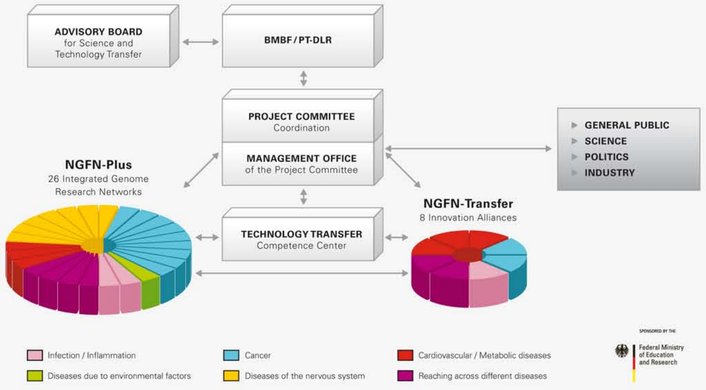
"In the NGFN scientists of diverse disciplines at hospitals, universities and in research institutes are working together on the highest scientific and medical level following a common aim: Utilizing genome research to elucidate the molecular causes as well as setting the course for optimized therapies of widespread diseases. This unique research program makes Germany a competitive player in the international science community. Thus the NGFN contributes substantially to the positioning of the business location Germany in a front rank of the biomedical field."

Prof. Dr. Hugo A. Katus
Spokesperson for the Project Committee

"Transferring the results from human genome research into the medical application"

"The scientists of the NGFN benefit from the overall infrastructure and the expertise of the genome research network. Because of the distinct interconnectedness of the NGFN an enhanced collaboration of academic and industrial research partners is possible, enabling the transfer of the results from human genome research into the medical application. The resulting innovations will contribute to economic growth and the creation of highly qualified jobs in Germany."

The Structure of the NGFN



Graphic: NGFN

In most diseases hereditary factors play an important role and are thus in the focus of medical genome research. Numerous scientific groups in the NGFN are working to identify modifications of genes, which are relevant for the development of various diseases. This knowledge offers the basis for sustained optimization of diagnosis and therapeutic strategies.

Diseases of the nervous system

Neurological diseases are very complex and are often not yet completely understood. In the NGFN the following different disease patterns are investigated:

- Alzheimer's disease
- Parkinson's disease
- Huntington's disease
- epilepsy and migraine
- schizophrenia
- mental retardation
- alcohol addiction

Cancer

Almost any human cell can become a tumor cell. Beside the general basics of tumor development NGFN scientists are studying the following cancer types:

- breast cancer
- colon cancer
- pancreatic cancer
- prostate cancer
- brain tumors
- leukemia
- neuroblastoma

Cardiovascular / Metabolic diseases

Among the risk factors for developing cardiovascular and metabolic diseases are hereditary predispositions as well as environmental components such as smoking, overweight and lack of physical exercise. NGFN researchers are analyzing:

- heart failure
- atherosclerosis
- adiposity
- cardiovascular disorders in kidney disease

Infection / Inflammation

Since more and more pathogens are becoming resistant to drugs the need for further research regarding causes, development and treatment of infectious diseases is obvious. NGFN scientists are working on questions about:

- Herpes virus infections
- malaria
- HIV

Diseases due to environmental factors

The aim of the researchers is to unscramble the interrelation between genetic and environmental factors in the genesis of for instance chronic inflammatory diseases. Within the scope of the NGFN are diseases of the barrier organs such as:

- asthma bronchiale
- inflammatory bowel disease
- dermatologic diseases

Reaching across different diseases

The development of latest technologies for highly parallel analyses is a further broad field of NGFN research.

- systems genomics
- disease pathways (DiGtoP)
- German Mouse Clinic
- MHC sequencing
- subgenome fractionation
- amplification methods for biobanks

News from NGFN-Plus and NGFN-Transfer

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Migraine Risk Factor Identified

Migraine is an episodic neurological disorder with a complex pathophysiology. In a NGFN-funded study researchers now succeeded in identifying a first genetic risk factor that is associated with migraine. Based on genome data from 50,000 persons they discovered a correlation between the risk to suffer from migraine and a specific DNA variant next to the genes PGCP and MTDH/AEG-1 on chromosome 8. These two genes are known regulators of EAAT2 which plays an important role in the glutamate clearance in nerve cells. Thus this polymorphism is directly associated with the metabolism of glutamate, an important neurotransmitter in the human brain. This discovery delivers the first clear genetic connection between the accumulation of glutamate in the nerve cells of the brain and the pathogenesis of migraine, making it a possible target for migraine therapy.

Smoking: Altered Brain Structure in Smokers

In a comparative study NGFN scientists have shown a reduced thickness of the medial orbitofrontal cortex in smokers in contrast to persons who have never smoked. Interestingly the affected brain region plays a role in decision making, reward and impulse control. In this trial a clear correlation was shown between the cortex thickness and the number of cigarettes consumed per day as well as with the life span the test persons have been smoking for. Yet it is still unclear whether this alteration of the brain structure is caused by nicotine consumption or if it is a predisposition that promotes taking up smoking. Although it is known that nicotine has a destructive impact on nerve cells, future studies have to clarify the causal relationship of the findings.

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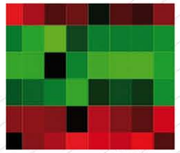
Improved Treatment Stratification for Neuroblastoma Patients

Neuroblastoma is a malignant tumor of early childhood that affects 8 % of the pediatric cancer patients. The course of disease is remarkably different for individual patients ranging from spontaneous regression to a deadly outcome. Therefore accurate risk estimation is very important to prevent avoidable cases of recurrence as well as unnecessary treatments. Scientists of the NGFN succeeded in developing a gene expression-based classifier for neuroblastoma. This 144-gene PAM classifier expands the current neuroblastoma classification system and reliably distinguishes patients with contrasting clinical courses. The highest potential clinical impact of the classifier lies in the early identification of patients currently considered non-high-risk but who require more intensive treatment.

Breast Cancer Cells Get Thwarted by miRNAs

Regulatory micro-RNAs of the miR-200 family are often down regulated during tumor growth. NGFN scientist could now demonstrate that miR-200 family members differentially regulate EGF (Epidermal Growth Factor)-driven invasion, viability, apoptosis and cell cycle progression of breast cancer cells. They divided the miRNA-200 family into two distinct sequence-based clusters, miR-200bc/429 and miR-200a/141, that acted mechanistically different. For example one of the genes that were down regulated by miR-200bc/429 and not by miR-200a/141 turned out to be relevant for the EGF-driven mobility and mitosis of the breast cancer cells. Thus a direct relationship between the miR-200 family and tumor progression in breast cancer seems obvious, making it a potential target for future therapies.



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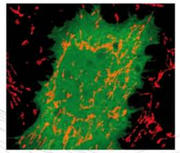

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New Insights into the Pathogenesis of Parkinson's Disease

NGFN scientists from the Hertie Institute for Clinical Brain Research in Tübingen showed for the first time, that and how the removal of damaged mitochondria is directed by the two proteins PINK1 and Parkin. A defect in this mechanism might be crucial for the pathogenesis of Parkinson's disease. The mechanism plays a very important role in cell integrity since mitochondria are the power plants of the cell. Damaged mitochondria lead to oxidative stress in the cells and ultimately to programmed cell death (apoptosis). The researchers showed that the two proteins PINK1 and Parkin in fact work hand-in-hand to label defective mitochondria for degradation by tagging a channel on their surface with the small protein Ubiquitin. This tag is a signal for degradation of damaged mitochondria. Mutations in the proteins PINK1 and Parkin are thus responsible for a breakdown of the mitochondria degradation process.