**Network: Systematic Gene Identification and Functional Analyses in Common CNS Disorders**

# Project: Population Based Assessment of Genetic Risk Factors for Parkinson Disease (PD)

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## Introduction

The definition of disease genes in specialized populations is accompanied by incertainty about their impact at the population level. Currently available population samples have been designed to investigate the course of diseases prospectively. While it may be possible to assess the impact of general risk factors on this basis, incidence rates will generally be too low to allow the evaluation of polygenic disease markers. In contrast, precise estimates of population-specific genotypic risks can be obtained efficiently though the complete ascertainment of patients in a geographically confined region. The PopGen project represents an example of such a pursuit.

With most complex diseases, the recruitment of samples for gene finding studies has focused upon cases of a particularly pronounced phenotype, or of strong familiarity. This strategy of extreme sampling reflects the expectation that genetic variants involved in the aetiology of severe or strongly heritable phenotypes represent so-called “major genes”. Major genes are rare but their marginal effects are likely to be strong. Therefore, extreme sampling is generally thought to maximise the chance of detecting a disease-associated genetic variant at all. The clinical impact of a newly found disease marker is however only made by the implementation in an unselected (i.e. “normal”) population of marker-based diagnostic and therapeutic algorithms. For such purposes, covariate-adjusted absolute and relative genotypic disease risks are the parameters of interest, but these figures can only be estimated from representative population samples. Furthermore, in order to be able to evaluate the relative disease risk of a given genetic variant, its background frequency in the same population has to be known. Unbiased sampling of patients is best achieved at the population level by defining a confined geographical catchment area in which all clinically overt cases with the disease in question are recruited. A population-representative sample requires that no systematic and uncontrolled “escape” of patients occurs from the recruitment area. In this respect, Northern Schleswig-Holstein provides an almost paradigmatic test case since its tight geographical borders and low density of treatment facilities set stringent limits to patients seeking treatment outside its confines. Northern Schleswig-Holstein, an area that is home to approximately 1.1 Million people, is enclosed by the Danish border (North), the Atlantic Ocean and Elbe River (West), the Baltic Sea (East), and the Kiel Canal (South) (Fig. 1).

The Popgen infrastructure is used to carry out a combined genetic/epidemiologic population-based study for Parkinson’s disease (PD). Parkinson’s disease is one of the key phenotypes in the NeuroNet with disease gene definitions forthcoming. It is one of 12 frequent diseases that are examined in this geographically well-defined population within the framework of Popgen. A large sample of unselected control individuals from the population of interest has already been recruited and can be used for the PD project. Parkinson`s disease has a prevalence around 100-200 per 100.000 with an age related increase. It is estimated that about 250.000 people in Germany presently suffer from PD. The annual incidence is around 5-24 per 100.000. Genetic factors in PD have been identified so far mainly in the subgroup of young onset patients. Approximately 10% of all PD patients have a young onset of the disease but it is known that genetically determined PD can occur as late as in the 7$^{th}$ decade. Within the Popgen population of 1,1 Mio. people it is expected to identify 1100 to 2500 PD patients.

The diagnosis of PD is a clinical diagnosis defined by the presence of akinesia and one of the following symptoms: rigidity, rest tremor, postural instability. 75% of the patients with such a Parkinsonian syndrome suffer from PD and 25% from other conditions (Multisystem Atropy, Normal Pressure Hydrocephalus, etc.). The British Brain Bank Criteria are used to diagnose PD and a short list of key criteria to exclude patients with other Parkinsonian syndromes (developed by the Kompetenznetz Parkinson).

Objectives of this project are the evaluation and exact clinical characterization of all PD cases in the regional defined population, registration of a representative selection of PD cases in a prospective follow-up program, definition of genotype-phenotype associations and investigation of interaction of genetic and environmental factors in PD. This combined genetic/epidemiologic approach for the key phenotype PD shall help to translate molecular findings in population relevant data.

## Results/Project Status

Patients with PD will be selected and recruited in a two step procedure. In the first step patients will be recruited by contacting all active neurologists and psychiatrists in the Popgen area which will be around 70 including 4 hospitals. The patients will be identified by searching the registers of the board certified physicians. It cannot be excluded that some patients with PD are treated by general physicians only and, thus would escape the catchment algorithm of this study. Therefore, the second step is a cross-sectional study of a reference population of 40.000 people older than 60 years that will be screened for PD.

In the first year an address database will be constructed, the PD phenotype has been defined; a patient and a screening questionnaire for PD have been developed. Four hospitals and 36 neurologists / psychiatrists have been contacted, so far. All hospitals and 31 of the contacted physicians have agreed to participate in this study. Up to now, 505 PD patients have been identified and contacted. 156 patients gave their informed consent (response rate: 31%) and returned the patient questionnaire and the blood samples. For the cross-sectional study a positive ethical vote was obtained. At present, the recruitment of 40.000 people from the database of the inhabitant registry has been initiated.

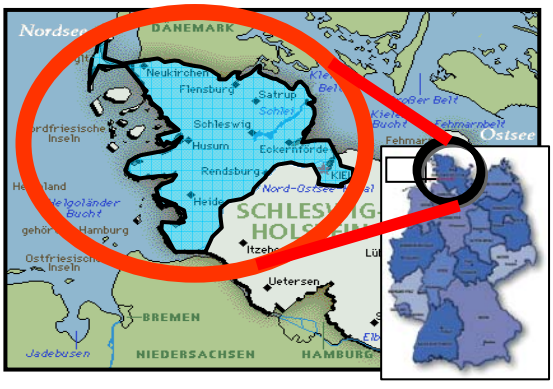


***Fig 1:*** *Popgen area with 1,100,000 inhabitants, 4 hospitals with a neurologic department and 70 neurologists.*

NGFN Nationales Genomforschungsnetz

GEFÖRDERT VOM Bundesministerium für Bildung und Forschung

Within the second year of the study phenotype extraction and blood work will be done. Home visits are planned in samples to validate diagnosis of idiopathic PD and exclude atypical Parkinson-syndromes. Within the cross-sectional study a sample of negatively screened individuals will be examined to test the quality of the screening questionnaire. For the third year is the completion of phenotype ascertainment and collection of blood planned. Furthermore the follow-up scheme will have been completely conducted and the first follow-ups will be carried out.

## Outlook

The Popgen-project is linking various disease-related nets together by providing material according to common principles on a population-based for the core diseases within the NGFN. It has therefore a necessary bridging function and opens the research field for environment disease-interactions, which can only be studied on the basis of population-based data. The qualification of phenotype data that are obtained from specialized and sub-specialized health care providers for each patient is a key feature of Popgen. Therefore Popgen will be a population-based project offering in-depth, specialized phenotype information together with detailed follow-up information. Popgen resources for PD are made available in international collaborations through the NeuroNet.

The availability of a population sample for key phenotypes will be of pivotal importance for the NeuroNet to generate understanding of the medical importance of disease genes. This information will be crucial to understand gene-gene and gene-environment interactions. The understanding of the medical importance and the interaction with trigger factors is necessary to deliver the promise of gene-based medicine in the future.