Genome Scan

From Complex Genomics to Trial-Ready Stratification:

a GBA1 Case Study

Using Next Generation Sequencing to detect *GBA1* variants in Parkinson's disease patients.

A case study involving GenomeScan's genomic analysis and Centre for Human Drug Research's (CHDR) clinical research infrastructure.

CHDR
Centre for Human Drug Research

Introduction

Parkinson's disease is increasingly recognized as a genetically heterogeneous disorder, requiring genetically informed approaches to patient selection and clinical trial design. Among the numerous genetic contributors to Parkinson's disease, variants in the *GBA1* gene represent the most common genetic risk factor, influencing disease risk and progression.

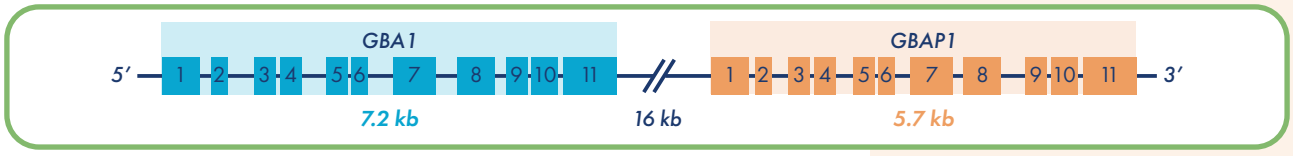
This case study describes how high complexity *GBA1* genotyping was integrated into CHDR's monocenter clinical research model, supported by GenomeScan's genomic expertise. This enabled genetically informed patient stratification and helped accelerate the path from genomic insight to targeted clinical trials.

Background

Although *GBA1* variants are well established as a major genetic risk factor to Parkinson's disease, comprehensive analysis of the full *GBA1* gene remains technically challenging. The gene shares a high degree of homology with its nearby pseudogene (*GBAP1*), making conventional sequencing approaches prone to false positives and false negatives. As a result, accurate detection of rare, complex, and population-specific variants requires specialized laboratory and bioinformatics strategies.

At the same time, clinical research in Parkinson's disease increasingly demands access to well-characterized patient populations, supported by reproducible, scalable genomic workflows that can be embedded directly into trial design and execution.

In this case study, these needs were addressed by combining specialized *GBA1* genotyping with CHDR's clinical research operations, supporting Parkinson's disease research.



GBA1 and *GBAP1* gene homology influence detection of SNVs, indels and recombinant alleles

Challenge

The project addressed several recurring challenges in PD genomic and clinical research:

- **Accurate and unambiguous** *GBA1* sequencing, despite high homology with the *GBAP1* pseudogene
- **Scalable processing** of large patient cohorts across extended timeframes
- **Reliable detection and interpretation** of rare, complex, and population-specific variants
- **Consistent data quality and reproducibility**, suitable for longitudinal clinical research
- **Clinical relevance**, ensuring genomic data directly supports patient stratification and trial enrolment

Solution

To address these challenges, the study approach combined CHDR's clinical infrastructure with GenomeScan's specialized genomic capabilities.

CHDR oversees patient engagement, ethical governance, clinical operations, and integration of genomic data into study design and execution. GenomeScan contributes validated laboratory workflows and bioinformatics expertise for high-resolution *GBA1* analysis at scale.

Key elements include:

- Long-range PCR–based enrichment targeting the entire functional *GBA1* gene
- Dedicated primer design to avoid *GBAP1* pseudogene co-amplification
- High-coverage next-generation sequencing using validated laboratory workflows
- Custom bioinformatics pipelines optimized for sensitive and specific *GBA1* variant detection

Together, these elements enabled robust, clinically meaningful genotyping suitable for use in this clinical research context.

Integrated Workflow

The end-to-end workflow was designed to support continuous, scalable clinical research while maintaining the data quality required for longitudinal studies and regulatory-grade trials.

1. **Sample collection and logistics**
   Patient samples are collected under approved ethical protocols and processed in regular batches, supporting continuous and scalable operations.
2. **DNA isolation and quality control**
   Automated, high-throughput DNA isolation is combined with stringent quality assessment to ensure downstream reliability.
3. **Targeted *GBA1* amplification**
   Long-range PCR selectively amplifies the complete functional *GBA1* gene, including exonic and intronic regions, while excluding the *GBAP1* pseudogene.
4. **Library preparation and sequencing**
   Libraries are prepared using Illumina-compatible workflows and sequenced at ultra-deep coverage on high-throughput platforms.
5. **Bioinformatics analysis**
   Data are analyzed using GenomeScan's *in-house* pipelines, with careful evaluation of allele balance, variant confidence, and clinical significance.

Short-read sequencing workflow applied for GBA1 and Parkinson's disease–related gene analysis in a clinical trial setting.

Data Analysis and Interpretation

Identified variants are classified according to clinical relevance, including:

- Variants associated with Gaucher's disease
- Parkinson's disease–associated risk variants
- Synonymous variants
- Novel or previously unreported variants

Results are reported using both HGVS-compliant nomenclature and conventional allele naming conventions, ensuring accessibility for clinicians, researchers, statisticians, and sponsors. Aggregated analyses support interpretation of disease risk, age of onset, cognitive involvement, and subgroup definition.

From Genotyping to Clinical Trials: Impact at CHDR

Mutations in the GBA1 gene, which encodes the lysosomal enzyme beta-glucocerebrosidase (GCase), lead to reduced GCase activity and represent one of the most significant genetic risk factors for the development of Parkinson's disease (PD). As lysosomal dysfunction is increasingly recognized as a key driver of PD pathology, therapeutic strategies targeting lysosomal pathways, such as GCase modulation, are emerging as promising disease-modifying approaches.

In this case study, CHDR successfully recruited a substantial cohort of genetically confirmed GBA-PD patients within a notably short timeframe, enabling the timely initiation of a phase 1 clinical study evaluating a novel allosteric activator of GCase. This case highlights CHDR's ability to integrate genetic screening, clinical expertise, and operational excellence to accelerate early-phase development of innovative, mechanism-driven therapies.

Impact and Significance

This case study demonstrates how specialized genomic analysis can be combined with clinical research operations to overcome technical limitations and enable population scale genomics with direct clinical applicability.

By embedding accurate *GBA1* genotyping within a monocenter clinical research platform, the case study shows how genomic insight can support targeted clinical trial recruitment and translational research.

More broadly, the work illustrates how genomics, when aligned with clinical operations, can shorten development timelines, improve patient selection, and support the development of therapies in Parkinson's disease.

About GenomeScan

GenomeScan is a genomics solution provider utilizing state-of-the-art Next Generation Sequencing (NGS) technologies. GenomeScan offers customizable solutions to pharmaceutical and biotechnology companies, healthcare providers, and academic institutions. Our service portfolio covers DNA, RNA, and epigenetics sequencing, with applications ranging from early discovery and preclinical drug development to clinical trials and manufacturing.

Our 20+ years of experience in the industry, in-house expertise in oncology, neurology and genetic QC, and robust bioinformatics pipelines let us stand out with the quality of our services. Additionally, competitive turnaround times and workflows that adhere to ISO/IEC 17025 and GCLP guidelines help you advance in your development programs with confidence.

Join the forefront of neurology research with GenomeScan's genomics solutions. For inquiries, collaborations, and a detailed consultation, contact us at **neurology@genomescan.nl.**

About Centre for Human Drug Research

The Centre for Human Drug Research (CHDR) is a full-service CRO and independent research institute specialising in early-phase clinical drug development. Based in Leiden, the Netherlands, CHDR conducts innovative clinical studies and develops unique, mechanism-based methodologies and biomarkers to support the development of new therapies.

By combining scientific excellence, clinical pharmacology expertise, advanced technologies and a dedicated research infrastructure, CHDR helps pharmaceutical and biotechnology companies generate early insights that inform drug development decisions and accelerate clinical programmes. CHDR provides full-service support across the entire study lifecycle, from study design and protocol development through clinical study reporting.

As an independent foundation, CHDR reinvests its earnings into research, innovation and education, contributing to the advancement of clinical drug development and fostering the next generation of drug developers.

For more information, visit: **www.chdr.nl.**

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