PROGRESS REPORT

Start project	**:** 01-Jul-2025
Period progress report	**:** 01-Jul-2025 – 30-Jun-2026
Date progress report	**:** 31-Jul-2026

---

1. GENERAL DATA

Applicants; co-applicants	**:** Dr. H.G. Huizinga, Prof. Dr. B.C. Jacobs; Dr. R Thomma, Dr. Z. Islam
Institute / research institute	**:** Erasmus MC
Department	**:** Immunology
Address	**:** Dr. Molewaterplein 50, Room Nb-1142a
PO Box and City	**:** 3015 CE Rotterdam
Telephone number	**:** +31 10 7043190
Fax number	**:** +31 10 7044731
E-mail address	**:** h.huizinga@erasmusmc.nl

Project title	: Validation of the genome-wide association study for Guillain-Barré syndrome.

2. OVERVIEW OF SCIENTIFIC PROGRESS IN THE PROJECT

In this project we planned to validate and identify novel genetic variants that associate with Guillain-Barré syndrome (GBS). The first aim of the study was to increase the cohort to at least 2000 patients and to validate our recent GWAS findings in an independent cohort. For this we contacted Prof. Pamela McCombe and dr. Stefan Blum and received the Australian GWAS dataset. In addition, we extended our collaboration with the National Institute of Health (Prof. Bryan Traynor and dr. Ruth Chia) to involve Dr. Joshua Denny, who has access to the All of Us dataset from the NIH and the BioVU dataset from Vanderbildt University. Finally we used publicly available datasets from the UK Biobank and the

FinnGen cohort. When possible, in- and exclusion criteria of the additional cohorts were applied similar to the initial study. ICD10 codes were used to identify patients with GBS. Controls with autoimmune conditions or polyneuropathies were excluded. All genetic data was lifted to human genome build 19 to ensure proper alignment.

Currently we have analyzed 5 datasets, including the initial IGOS dataset. We are still working on the Australian dataset. This study was published in 2018 and investigators used another type of genotyping array, having little overlap with the array we used. We are now rerunning the analysis using raw data of the GBS patients and controls and will re-impute data using HRC v1.1. This is expected to improve overlap of single nucleotide polymorphisms with the other cohorts.

An initial meta-analysis using 4 datasets with 1987 GBS patients and 416340 controls identified a very interesting region on chromosome 7 to be significantly associated with GBS, however when the BioVU data was added (n=158 patients) this significance was lost. It was striking that the direction of association of these SNPs was exactly opposite in the BioVU cohort compared to the other cohorts. Rechecking the analysis procedure did not provide an explanation for this, although it must be noted that the BioVU cohort was relatively small.

We also planned to increase the cohort by testing remaining GBS patients in the IGOS cohort as the initial GWAS was performed when the IGOS study was still ongoing and not all samples were shipped to the central IGOS laboratory. This is still work in progress, but we have made an inventory of the almost 500 remaining EDTA-tubes in the IGOS biobank and have identified at least 89 unique patients with EDTA-blood for DNA isolation (from most patients multiple tubes are present in the biobank). With inclusion of IGOS-related studies like IGOS-ZIKA and IGOS-Kids this number can be further increased.

3. <u>WORK PLAN FOR THE NEXT PERIOD:</u>

For the remaining part of the project, we would like to perform the meta-analysis with addition of the Australian cohort. We will further expand the study cohort with patients from Bangladesh (dr. Z. Islam) and we will genotype the remaining IGOS patients present in the central IGOS biobank. This is needed to perform subgroup analysis stratified for infections, severity and outcome (aim 2 of the project). Finally we will work on a manuscript for publication of the results.

We thank the GBS/CIDP Foundation International for generously supporting our project.