Genome Wide Association Study (GWAS) in Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Background

CIDP - although a rare disease - is the most common chronic autoimmune neuropathy. It is associated with damage of the peripheral nerve myelin, resulting in mostly symmetric sensorimotor symptoms including weakness, numbness, areflexia and sensory ataxia. Although the primary cause of the underlying inflammatory process of CIDP is unknown, some studies in the past years have revealed genetic factors that may influence disease susceptibility due to disturbed immunological pathways.
Using microarray analysis, 190 differentially regulated genes have been described in CIDP patients with 26 potentially playing a role in disease pathophysiology by involving inflammatory, but also protective pathways (Puttini et al, 2014). Genes like SH2D2A, the M3 allele of alpha-1 antitrypsin or perforin (McCombe et al, 1985; Notturno et al, 2008; Buttini et al, 2015) have been described to play a potential role in disease development. Further, several HLA associations have been found including a higher gene frequency of HLA-DR2 in female patients (McCombe et a, 2006), higher frequency of HLA-DR3 and DR3/DQ2 (Piccinelli et al, 2019) and a strong association of HLA-DRB15 with anti-NF155 CIDP (Martinez-Martinez et al, 2017). However, only a few of these studies were carried out in a large series of patients or have been replicated in different population.
GWAS have contributed significantly to our understanding of the pathophysiology of complex non-Mendelian disorders. This has been shown in a number of neuromuscular disorders as well, such as in inflammatory myopathies, amyotrophic lateral sclerosis and some non-inflammatory neuropathies. The major limitations to GWAS, particularly in rare disease like CIDP, is the need for large numbers of well-defined cases.
Therefore, we are working on the first GWAS in CIDP within the framework of an international genetics collaboration to identify genetic risks and disease associated pathways for CIDP and share data with colleagues around the world to promote and enhance research on this disorder. Our laboratory is well experienced in whole-exome association studies. We are aiming to collect up to 500 CIDP patients from our center; besides, we already have more than 500 controls to investigate rare variants. The next step toward a fully powered CIDP GWAS is to collaborate with colleagues from around the work.

Specific Aims:

1. To obtain over 500 CIDP samples for the CIDP GWAS with DNA extracted from blood or saliva. Genotyping will also include matched numbers of controls. We wish to obtain as many CIDP samples as possible to increase genetic power of the GWAS, therefore, we are keen to collaborate widely and include other groups and clinicians.
2. Once we hopefully identify significant GWAS association, we will investigate these regions in the exome data and we may need to prove the functional mechanism of certain variants, such as those that potentially effect RNA expression.
3. Genotypes of CIDP samples will be stored in a secure cloud and DNA/date will also be stored securely. After the analysis we are happy to share results with any group wishing to download their data.

Clinical details and sample requirements

- We have IRB/ethics to carry out this work. Data and DNA are stored in a pseudoanonymized way, securely.
- On each CIDP sample we would like core data to confirm the diagnosis with clinical and electrophysiological features as well as basic demographics, gender, age at onset, current age, and treatment response with disease course.
- DNA or biosamples such as blood, saliva or muscle from which we can extract DNA. For DNA ideally >21ul of DNA at >50ng/ul.
- We have a pre-paid UCL FEDEX account so there is no cost for shipping.
- All submitters will be authors on any publications using their samples and they can have their sample SNP data back via dropbox download.

Protocol summary can be done by post:

CIDP information sheet >>> saliva sample + core clinical data >>> send to UCL >>> genotyping for GWAS

Data, sample management and protection

- Unique DNA number will be generated for each sample.
- All DNA samples will be stored safely in the -80 freezers.
- Patient information and clinical details will be confidentially stored in a secured database within Institute of Neurology.

To send samples and join the CIDP GWAS please email; s.nagy@ucl.ac.uk