**Fine mapping multiple sclerosis**

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**Background**

Genomewide Association Studies (GWAS) have been spectacularly successful at identifying susceptibility loci for Multiple Sclerosis but little knowledge regarding the aberrant biology underlying the development of this devastating disease has yet emerged from these efforts. The associated variants overwhelmingly map to regulatory regions of the genome that are active in immune cells, but extensive linkage disequilibrium and a lack of relevant epigenetic annotation has confounded efforts to translate these discoveries into meaningful insights. This project will overcome these barriers by leveraging the enormous power of the 500,000 genotyped individuals in the UK Biobank, coupled with genotypes from over 10,000 cases and disease specific epigenetic data. These data will enable fine mapping of associated loci to unprecedented resolution and thereby identify mechanisms of disease which will in turn transform the prospects for the development of rational therapy. We believe that the emergence of these powerful resources offer a unique opportunity to radically advance our understanding of the aetiology of multiple sclerosis.

**Experimental approach**

The project will involve developing novel methods to integrate these extensive data sets, which we estimate will provide power to identify manageably sized credible sets of potentially causal variants for more than half of the 200 GWAS loci identified to date. It will extend the Postgap pipeline developed at EMBL-EBI, which fully automates the finemapping and functional interpretation of GWAS results from available genotypic and functional datasets, so as to produce an analysis tool that can be readily re-used by the biomedical community on other diseases and conditions.

One particular methodological advance that can now be tested on the wealth of data available is to boost power in the analysis of multiple sclerosis by utilizing the extensive overlap in genetic architecture that is known to exist between autoimmune diseases. Using colocalization and Mendelian Randomisation methods the project will establish for each associated locus which autoimmune diseases are also influenced by the multiple sclerosis risk variants so that data from these diseases can be included in the mapping efforts. The UK Biobank includes over 50,000 individuals that have some form of immune mediated inflammatory disease including almost 2,000 with multiple sclerosis. By comparing, contrasting and combining the data from these different diseases the project will establish a disease mechanism-based taxonomy for these diseases which will transform the opportunities for stratified medicine and personalized therapy.

**Relevance to health and disease**

Multiple sclerosis is a common cause of chronic neurological disability that affects more than 2 million people worldwide and is a major drain on the health economy. It is a chronic and debilitating disease that in the majority of cases impairs both physical and mental abilities, and greatly reduces quality of life. Although no cure has yet been identified a range of disease modifying treatments are now available that are capable of reducing the number of initial inflammatory episodes. Despite these the majority of patients still ultimately accumulate irreversible disability, and no effective treatments exist for the progressive phase of the disease.

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**Supervisors**

Stephen Sawcer is the Professor of Neurological Genetics at the University of Cambridge and an Honorary Consultant Neurologist at Addenbrookes Hospital. He has worked on the genetics of multiple sclerosis and other neurological conditions for over twenty years. He has coordinated the national recruitment effort in MS which has collected DNA from over 17,000 cases. Prof Sawcer is a leading member of the International Multiple Sclerosis Genetics Consortium (IMSGC).

Daniel Zerbino is a service team and research group leader at EMBL-EBI since 2015. He is specialized in developing high performance bioinformatics analysis tools across an array of applications in genomics and epigenomics. He is now involved in maintaining several databases at EMBL-EBI, in particular Ensembl.