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Summary of research

Key words: Autoimmunity, Inflammation, Genetics, Environmental factors, Infections, Epidemiology.

Application Lay Summary:

1a: Immune-mediated diseases (IMDs), such as multiple sclerosis, comprise a clinically heterogeneous group of disorders affecting ~3-5% of individuals of European ancestry. Our understanding of the exact mechanisms that lead to these conditions remains limited, but scientific progress has shown that both genetic and environmental factors play important roles. We aim to integrate and analyse the extensive genetic, clinical and epidemiological data available through the UK Biobank, in order to identify key shared but also disease-specific mechanisms that may be targeted for therapeutic benefit.

1b: One of the aims of the UK Biobank is to improve prevention, diagnosis and treatment of a wide range of illnesses. For many of these illnesses, and in particular for IMDs, genetic and environmental factors play an important role in disease susceptibility. A first step towards meeting this aim for IMDs is to elucidate how these risk factors interact, thereby altering immunological responses and promoting disease development. The proposed research aims to integrate UK Biobank epidemiological, clinical and genetic data to identify

parameters for disease risk prediction and diagnosis, and disease mechanisms that may be amenable to drug targeting.

1c: Through recent genomic studies an extensive catalogue of genetic variants that influence IMD susceptibility has been constructed. Many of these variants affect risk to multiple conditions, and in some instances have opposing effects on different disorders. For most variants, however, the mechanisms by which they mediate their effects are unknown. The extensive data sets available through the UK Biobank provide a unique opportunity to perform a comprehensive computational assessment of how genetic and environmental factors influence not one but a breadth of different immunological conditions and clinical phenotypes. The results of these analyses will be integrated with laboratory-based studies.

1d: In order to perform the required computational analyses and to integrate them with laboratory-based findings, this project requires data regarding lifestyle and epidemiological factors, clinical and para-clinical information, and genetic data. In particular, we are requesting information on all individuals with available genetic data, and with the possibility of updating access to resources, as more individuals are genotyped. For those individuals with available genetic data, we would request access to known diagnoses of IMDs and relevant environmental exposures from the clinical records, such as smocking and known episodes of viral and bacterial infections. No samples are requested.

Project extension:

“Our aim is to determining the effect of immune/inflammation-mediated disease (IMD) genetic risk variants on health outcomes and their interaction with environmental factors. The health outcomes include other primary and secondary diagnostic terms, para-clinical parameters and molecular biomarkers, for example, as well imaging-related phenotypes.

We have recently developed a novel Bayesian analytical framework that exploits the hierarchical structure of diagnosis classifications to jointly analyse genetic variants against UK Biobank healthcare phenotypes. Our approach has allowed us to uncover the broader burden of genetic variation associated with a subset of immune/inflammation-mediated diseases (IMDs) - chiefly the common, polygenic autoimmune diseases. We have found novel genetic associations with these diseases, we have revealed the extent of genetic sharing between specific conditions, and we have exposed differences in disease perception or diagnosis with potential clinical implications. Building on this initial work we are also constructing genetic risk scores (GRSs) for other IMDs - including conditions with a neuroinflammatory component, such as multiple sclerosis, schizophrenia and dementia - and querying the impact of these GRSs on other diagnostic terms to better understand the genetic specificity and sharing across these diseases. As an extension to these analyses we aim to interrogate the effect of these GRSs on brain imaging-related phenotypes to assess if such phenotypes may be of predictive value in the context of neuroinflammatory disease diagnosis or prognosis.”