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Leona M and Harry B Helmsley Charitable Trust grant for $2,269,871 awarded to PI

Summary of research
IBD, autoimmunity, genetic modifiers, control-only

Application Lay Summary:

1a: This proposal seeks access to UK Biobank data to support efforts to identify genetic modifiers of polygenic disease risk with a specific focus on inflammatory bowel disease (IBD) and autoimmune diseases. We have developed a statistical approach that only uses population controls. This is attractive because the power of genetic studies is usually limited by availability of case samples, as control cohorts can be drawn from multiple studies, or obtained from massive national resources such as the UK Biobank. An association test obtaining power from within controls only would dramatically improve power. Furthermore, human genetics strategies are generally optimized to find “bad” variants that
cause diseases by focusing on the most severely affected cases and families. The generation of therapeutic hypotheses for preventing disease is far better served by just the opposite – the discovery of protective DNA variants in high-risk (genetic or environmental) individuals that prevent disease provide the required model for therapeutic development. By applying our study design approach specialized to identify “good” variants that confer protective effects, we establish a more direct link between human genetics and therapeutic development.

1b: The research we plan is in agreement with the stated aim of UK Biobank “research intended to improve the prevention, diagnosis and treatment of illness and the promotion of health throughout society”.

This proposal seeks to identify protective genetic modifiers of disease risk which may provide insights into gene targets for downstream translational efforts.

1c: Based on the genetic findings in inflammatory bowel disease case-control studies we will use these genetic variants to compute a polygenic risk score for each individual in the UK population. We will then compare the extremes of the scores (high v low) to identify variants that may be modifying risk of individuals with high risk, i.e. identifying why some individuals remain healthy even though genetic risk profile suggests they should have one of the conditions that we are studying.

1d: We wish to study the full cohort.