**University of Leicester**

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| **Project Reference** | BRC Studentships |

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**Section 2 – *Project Information***

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| **Project Title** | The role of rare genetic variants in fibrosis​ |
| **Project Highlights:** | 1. | Improve our understanding of the biology behind a major contributor to world-wide deaths  |
| 2. | Use large datasets and novel statistical methods |
| 3. | Aid in the development of new treatments |
| **Project Summary**  |
| **Background**: ​Fibrosis is where excessive scar tissue becomes deposited. This can impair how organs function and can lead to severe disease and is often fatal. DNA is a string of chemical bases that act as a set of instructions in each of the cells in the body. Studies have shown that an individual’s DNA plays a key role in many fibrotic diseases1-4. Identifying differences in the DNA sequence between individuals (genetic variants) affecting the risk of a trait allows us to identify biological mechanisms associated with the disease and can therefore help in the development of treatments that target these processes. It has been shown that novel therapies with support from genetic studies are twice as likely to be successful during drug development5. ​ **Aim**: ​To understand the role of rare genetic variants in fibrosis​ **Research Plan**: ​This project will use whole-genome and whole-exome sequencing data from disease specific cohorts and population biobanks to understand the role of rare genetic variants in fibrotic disease.  The applicant will initially identify rare pathogenic variants present in the fibrotic cohorts and then test for their association individually with fibrosis. The combined effect of multiple pathogenic variants will then be combined together through collapsing methods and burden tests. These gene scores will then also be tested for their association with fibrosis. For identified variants and genes, bioinformatic follow-up incorporating publicly available transcriptomic data to investigate the role of gene expression and Hi-C data to investigate physical interactions will be employed. Identified genes may also inform further wet-lab functional studies by national and international collaborators. Analyses will be performed using the University of Leicester’s high performance computing cluster using statistical and genetics software (such as R and PLINK). ​ **Expected outcomes and impact**: ​It is expected this work will lead to first-author publications and conference presentations at national and international conferences. These results will lead to further functional analyses by collaborators and may possibly form the basis of future grant applications (as evidenced by our previous work with pulmonary fibrosis) to better understand the biological mechanisms involved. Summary statistics from these analyses will be made publicly available and will feed into analysis pipelines of both academic and pharmaceutical organisations.​  |
| **References**1 Hold et al. Role of host genetics in fibrosis (2009) *Fibrogenesis & Tissue Repair*. 2(1):62 Allen et al. Genome-Wide Association Study of Susceptibility to Idiopathic Pulmonary Fibrosis (2020) *American Journal of Respiratory and Critical Care Medicine*. 201(5):564-5743 Lopez-Isac et al. GWAS for systemic sclerosis identifies multiple risk loci and highlights fibrotic and vasculopathy pathways (2019) *Nature Communications*. 10(1):49554 Vujkovic et al. A multiancestry genome-wide association study of unexplained chronic ALT elevation as a proxy for nonalcoholic fatty liver disease with histological and radiological validation (2022) *Nature Genetics*. 54(6):761-7715 Nelson et al. The support of human genetic evidence for approved drug indications (2015) *Nature Genetics*. 47(8):856-860. |