ABSTRACT

The profound influence that the gut microbiome exerts on diverse aspects of human physiology presents opportunities for therapeutic interventions. However, to be effective, the design of these interventions must account for variations in the nature of host-microbiome interactions between individuals. Amongst factors known to shape microbiome characteristics, human genetics is arguably the least well understood.

This thesis explores the influence of a common genetic variant that affects the production of mucosal α(1,2)-fucosylated glycans on mucosal secretions and occurs in around 20% of the human population. Specifically, it focuses on the relationship between expression of this trait and the retention and proliferation within the gut of common probiotic strains of Bifidobacterium species that differ in their ability to utilise α(1,2)-fucosylated glycans as an energy source. The investigation utilised a mouse model in which littermates varied in their ability to secrete α(1,2)-fucosylated glycans (*Fut2*$^{+/+}$ or *Fut2*$^{-/-}$) into which probiotic bacterial preparations were introduced by oral gavage. The consequences of gut microbiota disruption, a common trigger for probiotic use, was explored through antibiotic exposure prior to bacterial instillation. Probiotic dynamics and their relationships with host genotype and the characteristics and integrity of the gut microbiota were explored using a range of molecular and culture-based approaches. Amongst notable findings were significant differences in baseline gut microbiology, probiotic persistence, and impact of antibiotic disruption, according to *Fut2* genotype.

The findings described within this thesis establish an important association between a common human genetic polymorphism, the gut microbiome, and the potential to derive benefit from attempts to modulate host-microbiome interactions using probiotics. The insight gained into the influence of genetic polymorphisms and bacterial dynamics have profound and far-reaching consequences for the development and interpretation of probiotic interventions.