Project Details	
Project Code	CMD27Ba Méric
Title	Understanding the impact of olfactory genetics, diet and gut microbiota on cardiometabolic health
Research Theme	Cardiometabolic Disease
Project Type	Dry lab
Summary	Olfactory receptor (OR) genes are one of the largest gene families in the human genome, responsible for detecting food-related chemicals. While mostly expressed in the nasal cavity, ORs expressed in the gut may sense host- and microbiota-derived metabolites, raising questions about their role in metabolism and health. Whilst genetics, diet and the gut microbiome are associated with cardiometabolic health, causality remains underexplored. Using computational approaches and existing large human cohort data, this project will test whether inherited OR variation is associated with diet-related behaviour, and metabolic health, and whether the gut microbiome may partly account for any observed associations.
Description	Background and key questions: Cardiometabolic health is shaped by lifestyle, diet, host genetics and the gut microbiota. The interplay and causal links between these components are difficult to study, and mechanisms remain unclear. Olfactory receptor (OR) genes form one of the largest and most variable gene families in the human genome. They are best known for detecting volatile odorant compounds in the nasal olfactory epithelium, but selected ORs are also expressed in non-olfactory tissues, where they may sense host- or microbiota-derived metabolites. This is particularly relevant to short-chain fatty acid (SCFA) biology. For example, some OR protein products have been shown to bind to SCFA structurally, and a recent microbiome genome-wide association study (GWAS; involving the host lab) has linked some of these loci to gut microbial richness. Large-scale whole-genome sequencing and linked cohort phenotyping now make it possible to test whether structured variation across OR loci is associated with diet-related behaviour, gut microbial ecology and cardiometabolic outcomes. This project, based at the University of Bath in collaboration with the Bristol Medical School, will leverage existing large-scale multi-omics human cohort data to test whether patterns of OR genetic variation are consistently associated with diet-related traits, gut microbial features and cardiometabolic outcomes in statistically robust and biologically plausible ways. Two non-exclusive hypotheses will be examined: (1) inherited variation in food-relevant ORs can contribute to differences in diet-related behaviour; and (2) selected extra-nasal ORs are linked to differences in responses to host- or microbiota-related metabolites. Both will be examined with a focus on cardiometabolic health, but the project does not assume direct effects on disease risk. A further aim is to prioritise host-microbiota pathways for future mechanistic work. Objectives: 1) Profile human OR diversity in large cohorts. The student will first construct a curated map of human OR loci and examine their variation in large cohort datasets, using available genotype, exome and whole-genome sequencing data. This will include single-nucleotide variation,

	predicted functional variants and, where data quality allows, copy-number or structural variation across OR gene clusters. The framework will include receptors with well-characterised functions and ligands, as well as less well-characterised ORs that may still show informative patterns of variation. Specific attention will be given to OR loci implicated in food-related perception and those with evidence for extra-nasal metabolic or microbiota-relevant ligand sensing, informed by published GWASs and functional literature. 2) Test associations between OR genetic variation and dietary phenotypes. The student will use population-based cohorts to test whether OR genetic features are associated with dietary patterns and selected dietary variables derived from questionnaire data. Analyses will account for major confounding and design variables. This objective will establish whether OR variation is detectably related to dietary patterns in large human datasets, and whether associations concentrate in biologically plausible OR loci or receptor groups. 3) Test associations with cardiometabolic health. The student will examine whether OR genetic features are associated with cardiometabolic traits, using measured phenotypes in population-based cohorts and, where possible, linked electronic health records. Outcomes will include a focused panel of adiposity, blood pressure, lipid traits, glycaemic traits, type 2 diabetes (T2D) and coronary heart disease (CHD). The student will use existing resources and cohorts already available to the team. 4) Link OR gene variation to the gut microbiome. Where cohorts provide both host genetic and gut microbiome data, including FINRISK 2002, the student will test whether OR genetic variants or feature sets are associated with microbial diversity, composition and functional pathways. Analyses will focus on microbial features linked to fermentation and SCFA metabolism, and on the strongest signals from analyses of diet and cardiometabolic outcomes. 5) Integrate findings across genetics, diet, microbiome and health. For findings that are robust across earlier objectives, the student will use appropriate integration strategies, such as replication, interaction tests, mediation analyses and, where justified, causal-inference methods. This stage is contingent on what emerges from objectives 2-4. If cross-domain overlap is limited, the student will focus on the strongest single-domain findings and their replication or characterisation. Student ownership: The project combines statistical genetics, epidemiology, microbiome science and linked health-record analysis, bringing together expertise in microbiome analysis, bacterial genomics, genetics and cohort analysis. It is structured so that the student can take ownership from the start. In the initial stages, they will help refine the OR feature framework, prioritise candidate receptors, define the dietary and cardiometabolic phenotype hierarchy, and develop a reproducible analysis plan. As results emerge, the student will decide which signals merit replication, microbiome follow-up or causal analysis. They will also have scope to steer the project towards the domain that proves most informative, whether that is OR population genomics, diet-related behaviour, microbiome ecology or cardiometabolic epidemiology. This structure

	gives the project a clear central question while allowing the PhD to remain scientifically productive if some hypothesised links, particularly microbiome-mediated effects, are weaker than expected.
Can be completed part time?	Yes
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