Project Details	
Project Code	NMH27Ca Harwood
Title	Gene-diet interaction and psychiatric risk: A study based of FADS 2 and dietary polyunsaturated fatty acids (PUFAs).
Research Theme	Neuroscience & Mental Health
Project Type	Other
Summary	Mental Health: nature or nurture? For psychiatric disorders the answer is both, but to explain how, we need to know the molecular mechanisms? Psychiatric Nutrigenomics is a new research area at the interface between mental health genomics and dietary metabolism that aims to address this question. As a case study, you will investigate FADS2, a psychiatric risk gene that is required for PUFA metabolism, establishing how genetics and fatty acid metabolism interact to increase psychiatric risk. You will receive interdisciplinary skills training in data science, bioinformatics, AI tools and human stem cell techniques, working with GW4 and international research partners.
Description	Background: We will train a student in inter-disciplinary research skills, gained by a project in Psychiatric Nutrigenomics. This is an emerging research area that was pioneered by a GW4 Development Award "Nutriomics for Brain Health" and crosses between mental health genomics and dietary metabolism, bridging a knowledge gap in our mechanistic understanding of how gene–diet interactions influence mental health. The student will investigate the molecular mechanism that links FADS2 genetic variants and altered polyunsaturated fatty acid (PUFA) metabolism to psychiatric disorders. FADS2 encodes fatty acid desaturase that converts dietary essential lipids into the long-chain polyunsaturated fatty acids (LC-PUFAs), omega-6 arachidonic acid (AA) and omega-3 eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA). These are critical for brain development as they regulate neurogenesis, synapse formation, neuronal activity and neuroinflammation. Genetic variation in FADS2 is associated with bipolar disorder, while Mendelian randomisation studies support a protective role of omega-3 fatty acids for affective disorders. Parallel in silico studies integrating genetic and neuroimaging data (genome imaging) have shown that psychiatric disease risk is associated with altered white matter microstructure and disrupted lipid metabolism in astrocytes is implicated in its development. Astrocytes are the principal regulators of brain lipid metabolism, providing metabolic, inflammatory and trophic support for neuronal maturation and function. Astrocyte biology offers a good starting position to probe the mechanistic interaction of FADS2 mutation and diet. Aim: This project takes an interdisciplinary approach combining wet and dry lab techniques to establish how FADS2 mutation affects astrocyte neurodevelopment and function to elevate psychiatric risk. It has four research objectives that can each support standalone publications and together form the basis of a PhD thesis. Objective 1: FADS2-mediated astrocyte neurodevelopment deficits. Human induced pluripotent stem cells (hiPSC) develop neurons and glial cells from the same neural progenitor cell (NPC) population. Previously we reported that high omega 6:3 PUFA ratios affect gene expression during early stages of neurodevelopment. This includes FOXG1, a risk

	gene associated with neurodevelopmental disorders [1]. Pilot studies further show that there is mis-regulation expression of FOXG1, cyclooxygenase (COX)-dependent lipid signalling and calcium regulation genes in FADS2 mutants. Finally, our single-cell RNA-sequencing (scRNAseq) dataset from NPCs has shown that both FADS2 and FOXG1 genes are co-expressed in an NPC population that is fated to become glial cells. We propose that FADS2 plays a key role in the neurogenesis of astrocyte cell fate specification. The student will undertake further in silico analysis of our scRNAseq data by co-clustering relevant astrocyte-related genes with FADS2 and FOXG1 positive cell clusters; creating a specific FADS2 associated-wikipathway and deploying the AI-tool scGTP [2] to predict how gene transcription is altered by FADS2 mutation. This student-driven analysis will define a gene set, which they will validate by qRT-PCR of NPC-derived RNA. Training and support will be provided by an experienced team within the GW4 Cardiff, Exeter and the international partner, Maastricht. Objective 2: Dysfunction of astrocyte-mediated inflammatory response of FADS2 mutant-derived astrocytes. Using our established protocols in human iPSC culture, differentiation and molecular techniques, the student will generate and characterise astrocytes developed in vitro from control and FADS2 null-mutant iPSC. We predict that loss of FADS gene will disrupt inflammatory responses in mature astrocytes. The student will design and undertake experiments to invest how FADS2 deficiency alters the inflammatory response, via changes of lipid metabolism and COX signalling. Objective supported by Cardiff. Objective 3: Signalling between neurons and FADS2-mutant astrocytes. We have previously demonstrated interaction between human oligodendrocytes and neuronal function, and we will now take a similar approach for astrocytes [3]. We propose that altered lipid metabolism will modify the astrocyte secretome and its influence on neuronal function. The student will devise a “mix and match” approach to treat control or FADS2 mutant neurons with cell conditioned media from control or mutant astrocytes. They will deploy two functional assays in Cardiff, (MultiElectrode Arrays (MEAs) and calcium flux measurements (FLIPR), to probe neuronal-astrocyte signalling. Objective supported by Cardiff. Objective 4. Genome and transcriptome imaging to map in vitro experimental findings onto the human brain. The student’s gene sets will be used to computationally model the effects of FADS2 genetic changes on the excitatory-inhibitory balance of the human brain. We propose that the molecular cell interactions established in vitro will correlate with brain regions know to be disrupted in psychiatric patients. The student will use their scRNAseq and pathway analysis to seek overlap with psychiatric GWAS data. These will then be mapped in silico to brain regions showing altered white matter and used to inform an existing virtual human brain twin (a computational model) and validated against existing functional brain imaging data. This objective will be supported by the GW4-partner Bath, and international partner, Maastricht. With interdisciplinary experience, the student will create a mechanistic framework, linking PUFA metabolism, astrocyte development and function to psychiatric disease.

	1.doi.org/10.3389/fcell.2023.1166808; 2. doi.org/10.1038/s41592-024-02201-0; 3. doi.org/10.1016/j.stemcr.2018.11.019
Can be completed part time?	No
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