Manchester-China Scholarship Council-PUHSC

PhD Programme 2014

Why study at The University of Manchester?

The University of Manchester is one of Britain's most famous and forward-thinking universities, with a rich heritage stretching 180 years and an exciting agenda for the future. Many major advances of the 20th century began here, including the birth of the computer, the splitting of the atom and the creation of the first test tube baby. Today, research remains at the heart of the University and the quality, breadth and volume of research activity is unparalleled in the UK, with strong collaborative links with industry and public services. We have hosted a number of Nobel Prize winners in the past (including Archibald V Hill in Physiology and John Sulston in Physiology/Medicine) and have more Nobel Prize winners as current staff than any other British University.

The University of Manchester is Britain's largest single-site university and, in partnership with Central Manchester University Hospitals NHS Foundation Trust, has formed Europe's largest academic campus, creating an impressive hub for research and healthcare. We have a long history of hosting visiting scholars and students from China. Manchester has a large Chinese community of more than 3000 current students and, to many, it is a 'home away from home'. Only 2 hours from London by train, Manchester is perfectly located for sightseeing opportunities!

Why research genomic medicine?

Genomic Medicine is transforming healthcare using new technologies to personalise medicine, improve diagnosis, predict response to drugs and offer patients new treatment opportunities.

The University of Manchester and Central Manchester University Hospitals NHS Foundation Trust have a rich history of genomic medicine dating back to 1965 with the appointment of Professor Alan Emery, one of the founding fathers of the field.

Today the Genomic Medicine team is one of the largest and most comprehensive departments in Europe, serving a regional population of over 4.5 million with all major sub-specialist areas (dysmorphology, neuromuscular, neuropsychiatric, neurological, ophthalmic, cardiac and cancer genomics) and a number of national specialist services (including the lysosomal storage disorders and neurofibromatosis types 1 and 2). Manchester has an exceptional record in rare disease gene identification, with 29 such genes defined since 1993. Many of these genes were defined by our current PhD supervisors.

'At a time when genomic knowledge is expanding so quickly, the impact of genomic discoveries on diagnosis, management, and treatment is increasing very quickly. Personalised medicine is becoming a reality for oncology, paediatrics and for adult medicine. Consequently, it is certain that an understanding of the scientific basis of these discoveries, of their impact, and of the future use is becoming necessary for those delivering healthcare as well as for the scientists across the medical spectrum.' **Professor Graeme C.M. Black (DPhil, FRCOphth) Director, Institute of Human Development, The University of Manchester.**

Why do your PhD with us?

The University of Manchester and Manchester Academic Health Science Centre (MAHSC) have an alliance with PUHSC and are currently establishing a joint international Centre of Excellence in Genomic Medicine. The collaboration is led by the Centre of Genomic Medicine in the Institute of Human Development, Faculty of Medical and Human Sciences. The vision of the joint centre is to become a world leading translational research centre for rare disease and cancer genetics, to improve patient care and diagnosis.

Our 3 year PhD projects will appeal to students attracted to the medical specialtys of Genomic Medicine, Cardiology or Medical Ophthalmology, and interested in the research areas of genomics, molecular biology, cell and developmental biology, *in vivo*, regenerative medicine or bioinformatics.

Students will have the opportunity to present results from their PhD research at a joint Manchester–PUHSC Symposium in Manchester in 2016 and at relevant national or international conferences. A number of our students have had first author papers published during their PhDs, in journals such as The American Journal of Medical Genetics [1,2,3] and Nature Genetics[4]. During their PhD, students have access to Manchester's Graduate School Training Programme, which provides postgraduates with the skills, attributes and knowledge to thrive as independent researchers and professionals.

'As a PUSHC graduate, I found Manchester a fascinating place to work and study. When I left the University of Cambridge and joined The University of Manchester in 2003, I was instantly motivated by the highly active and dynamic atmosphere across the campus and the forward-thinking culture here. I am especially proud to work in the Manchester Centre for Genomic Medicine, the leading Centre in Europe which demonstrates very high integration of research, training and clinical services in medical genetics. In 2012, we started a major collaboration with PUHSC aiming to establish a multi-million pound joint Centre of excellence in Genomic Medicine, among which the Manchester-PUHSC PhD programme forms an essential part of the collaboration. Therefore, I would highly recommend you apply to this attractive joint PhD programme.' ***Dr Tao Wang (MBBS, PhD) Senior Lecturer in Medical Genetics, The University of Manchester.***

Funding provided

Our PhD programme covers all the costs of doing your PhD; tuition fees and research expenses at The University, one return airfare (China-UK-China) and living expenses for Manchester (the last two provided by the China Scholarship Council [CSC]). We have funding for up to 5 projects, commencing in October 2014.

Application Process

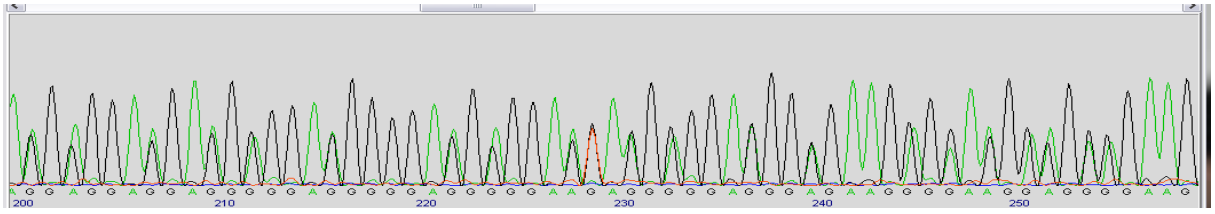
To be considered for the award, applicants must:

(1) Apply by sending your CV and a covering letter to the relevant supervisor(s) at The University of Manchester by email. Application deadline: **31st January 2014** *AND*

(2) Submit a separate application to the CSC by its stated deadline, following the local application procedures in China. Note that the local CSC application process is separate to Manchester's processes and their deadlines will differ to ours.

Questions?

If you have any general questions about this PhD programme or studying in Manchester, please contact Dr Sarah George (sarah.george-2@manchester.ac.uk). We look forward to receiving your application!



1 Mutations in PRDM5 in brittle cornea syndrome identify a pathway regulating extracellular matrix development and maintenance. Burkitt Wright EM, Spencer HL, Daly SB, Manson FD, Zeef LA, Urquhart J, Zoppi N, Bonshek R, Tosounidis I, Mohan M, Madden C, Dodds A, Chandler KE,Banka S, Au L, Clayton-Smith J, Khan N, Biesecker LG, Wilson M, Rohrbach M, Colombi M, Giunta C, Black GC. Am J Hum Genet. 2011 Jun 10;88(6):767-77.

2 LRIG2 mutations cause urofacial syndrome. Stuart HM, Roberts NA, Burgu B, Daly SB, Urquhart JE, Bhaskar S, Dickerson JE, Mermerkaya M, Silay MS, Lewis MA, Olondriz MB, Gener B, Beetz C, Varga RE,Gülpınar O, Süer E, Soygür T, Ozçakar ZB, Yalçınkaya F, Kavaz A, Bulum B, Gücük A, Yue WW, Erdogan F, Berry A, Hanley NA, McKenzie EA, Hilton EN, Woolf AS, Newman WG. Am J Hum Genet. 2013 Feb 7;92(2):259-64.

3 Identification of genomic loci contributing to agenesis of the corpus callosum. O'Driscoll MC, Black GC, Clayton-Smith J, Sherr EH, Dobyns WB. Am J Med Genet A. 2010 Sep;152A(9):2145-59.

4 Briggs TA, Rice GI, Daly S, Urquhart J, Gornall H, Bader-Meunier B, Baskar K, Baskar S, Baudouin V, Beresford MW, Black GC, Dearman RJ, de Zegher F, Foster ES, Francès C, Hayman AR, Hilton E, Job-Deslandre C, Kulkarni ML, Le Merrer M, Linglart A, Lovell SC, Maurer K, Musset L, Navarro V, Picard C, Puel A, Rieux-Laucat F, Roifman CM, Scholl-Bürgi S, Smith N, Szynkiewicz M, Wiedeman A, Wouters C, Zeef LA, Casanova JL, Elkon KB, Janckila A, Lebon P, Crow YJ. (2011). Tartrate-resistant acid phosphatase deficiency causes a bone dysplasia with autoimmunity and a type I interferon expression signature. *Nat Genet*, 43(2), 127-131.

Clockwise from top left: AV Hill Building; University Buildings on Oxford Road; Postgraduate students at graduation; Central Manchester University Hospitals NHS Foundation Trust and Michael Smith Building.

PhD Projects:

Identification of genes that cause schwannomas and meningiomas by next generation sequencing

Supervisors: Dr Miriam Smith and Professor Gareth Evans

http://www.human-development.manchester.ac.uk/staff/miriamsmith
http://www.manchester.ac.uk/research/Gareth.d.evans/

Neurofibromatosis type 2 and schwannomatosis are neurogenetic disorders which predispose patients to the development of both schwannoma and meningioma tumours throughout the nervous system. These tumours, while generally benign, can lead to significant location dependent morbidity.

Our lab is interested in understanding the molecular genetic basis for these tumours. We have a large archive of patient-derived blood and tumour DNA samples which we have recently used to undertake exome sequencing to discover new genes which cause schwannoma and meningioma tumours. We found that germline mutations in the chromatin remodelling gene, *SMARCE1*, cause an inheritable condition of clear cell meningiomas.

We are interested in searching for further genes involved in the development of these tumours and in studying the mechanisms by which schwannomas and meningiomas arise, using appropriate genetic and molecular biology techniques.

Reference: Smith MJ, O' Sullivan J, Bhaskar SS, Hadfield KD, Poke G, Caird J, Sharif S, Eccles D, Fitzpatrick D, Rawluk D, du Plessis D, Newman WG, Evans DG. Loss-of-function mutations in SMARCE1 cause an inherited disorder of multiple spinal meningiomas. Nat Genet 2013;45(3):295-8

MicroRNAs in Notch 3 mediated regulation of arterial function and genetic stroke syndrome CADASIL

Supervisors: Dr Tao Wang and Professor Susan Kimber

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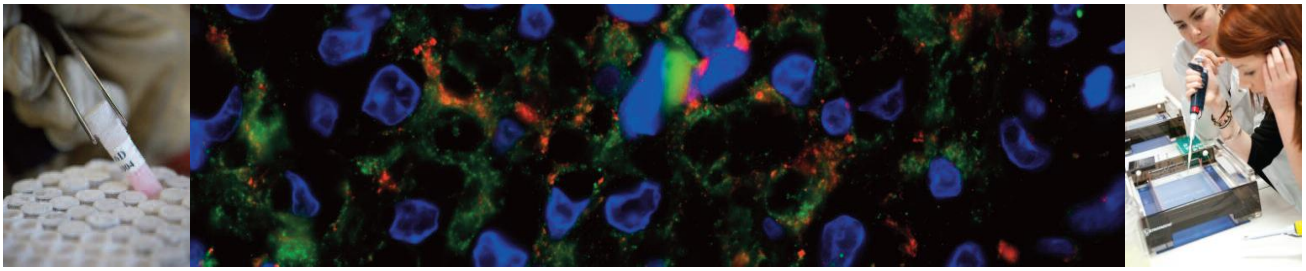
http://www.manchester.ac.uk/research/sue.kimber/personaldetails

Notch proteins are cell surface receptors that transduce signals between neighbouring cells which is critical for cell fate determination during embryonic development and for proper cellular functional maintenance in adulthood. Notch3 is one of the 4 Notch receptors identified in mammals and is predominantly expressed in the smooth muscle cells (SMCs) of human arteries and important in vascular homeostasis. Mutations in the *NOTCH3* gene cause the most common type of genetic stroke syndrome CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephelopathy). The characteristic pathological change in CADASIL is SMCs degeneration in small arteries. Abnormal activation of Notch3 is also found in other conditions such as pulmonary hypertension and common cancers including breast cancer, lung cancer and ovary cancer. However, due to insufficient knowledge on target genes of Notch signalling, the molecular mechanisms by which Notch3 is involved in the disease pathology have been largely unknown, thus specific treatment is not available.

Using adenovirus mediated overexpression of the active form of Notch3 followed by genome-wide gene expression microarray screening, we have identified a number of microRNAs (miRNAs) that were either positively or negatively regulated by Notch3 activation. miRNAs are short (20-24 nt) non-coding RNAs that play an increasingly important role in regulating gene expressions in either physiological or pathological conditions. This PhD project will be using *in vitro* cell model to investigate firstly, the role of these miRNAs in Notch3 mediated regulation of vascular SMCs behaviours including cell growth and survival as well as the interaction with vascular endothelial cells. Secondly, the role of candidate miRNAs-involved Notch3 signalling will be investigated in human pluripotent stem cell differentiation into SMCs. Thirdly, the involvement of the miRNAs in CADASIL molecular pathology will be determined by using induced pluripotent stem cell (iPSC)-derived CADASIL patient-specific SMCs which are under develop in the research group.

Main techniques used in the project: Mammalian cell culture including VSMCs and endothelial cells, human pluripotent stem cell culture and differentiation, cell transfection/virus infection, qRT-PCR, western blotting, immunocytochemistry, florescent microscopy, cell proliferation assay, migration assay, apoptosis assay, siRNA knockdown, luciferase assay, etc.



Functional analysis of a novel protein mutated in Primary Open Angle Glaucoma

Supervisors: Dr Forbes Manson and Professor Graeme Black

http://www.human-development.manchester.ac.uk/staff/90235/
http://www.manchester.ac.uk/research/graeme.black/

Glaucoma is an irreversible chronic degenerative optic neuropathy that is a leading cause of blindness worldwide; the most common form, primary open angle glaucoma (POAG), has a prevalence of 3% in white, and 8% in black, Americans and affects >33 million people worldwide. Approximately 50% of POAG patients have a positive family history and first degree relatives of an affected individual have a 3-9 fold risk of developing the disease. Multiple loci have been reported for POAG (GLC1A-N) but only 4 causal genes have been identified: *MYOC* (GLC1A), *OPTN* (GLC1E), *WDR36* (GLC1G), and *NTF4* (GLC1O). However, mutations in these genes only account for <10% of POAG cases.

We have a 3 generation POAG family with a clear dominant mode of inheritance. This family is a rare and highly valuable resource for the identification of a new glaucoma gene. The pedigree and extensive clinical details we have for this family demonstrates the condition is both highly penetrant and has a late age on onset. We have performed linkage analysis and published a new POAG locus, GLC1Q (Porter *et al.* (2011). IOVS 52:7859-65). Region capture sequencing and whole exome sequencing has identified a missense variant in a novel gene that segregates with the disease in the family and is present in 5/686 POAG patients (MAF 0.007) compared to 53/12,470 controls (MAF 0.004). The mutated residue is conserved in 29/30 vertebrate species and is preferentially expressed in the eye.

We wish to confirm the candidate gene as a new POAG gene by further genetic analysis and functional studies. We will screen the candidate gene in further panels of patients with POAG and control populations. In addition we will screen two other candidate genes identified from whole exome sequencing that lie outside the locus in our POAG family and in POAG cohorts and controls. We will then conduct a functional analysis of the confirmed new wildtype (WT) and mutant POAG proteins. This will include temporal and spatial expression patterns in human and animal models by *in-situ* hybridization and RT-PCR. Cellular localization will be determined by immunofluorescence. Interacting proteins will be identified by immunoprecipitation (an antibody is available) or pull-down. The effect of the mutation on gene expression will be determined by comparative microarray gene expression analysis on cells expressing either the WT or mutant protein. Knockdown studies using morpholino oligonucleotides will be conducted in zebrafish. In addition a mutant line will be generated by genome editing. Collaboration will enable us to test whether the mutant fish develop a raised intraocular pressure and lose vision.

Do Different Human Embryonic Stem Cell And Induced Pluripotent Stem Cells Have Different Propensity To Differentiate To Neurons?

Supervisors: Professor Susan Kimber and Professor William Newman

http://www.manchester.ac.uk/research/sue.kimber/personaldetails
http://www.human-development.manchester.ac.uk/staff/BillNewman

Our laboratory as part of the North West Embryonic Stem Cell Centre (NWESCC) has generated a number of human embryonic stem cells (hESc) lines including those suitable for clinical therapy. We have also generated induced pluripotent stem cells (ipsc) from human somatic cells. The Centre provides a focus for research projects on pluripotency, generation of differentiated derivatives and the stem cell niche. Pluripotent stem cells can form all tissues of the body and have excellent potential as agents for tissue regeneration. In this project the student will compare different pluripotent stem cell lines (chosen from 16 in house hESc lines and 3 iPSC lines available to date) for their ability to differentiate to one of the earliest lineages that of neurons. Different subtypes of neuron will be examined (e.g. dopaminergic cholinergic etc) and micro array and epigenetic analyses used to decipher the molecular mechanisms predisposing stem cells to neural versus endoderm or mesoderm and neural subtypes. Key target genes with strong expression in early neural differentiation will be manipulated as appropriate using and other knock down technologies. New iPSC lines may be made depending on progress. Techniques will include hESc culture, immunofluorescence, immunoprecipitation, Western blotting, microarray analysis, bisulphite sequencing, epifluorescence and confocal microscopy, flow cytometry, both qualitative and quantitative RT-PCR, ShRNAi or lentiviral mediated genetic manipulation and other techniques depending on the results obtained

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Oldershaw RA, Baxter MA, Lowe ET, Bates N, Grady LN, Brison DR, Hardingham TE & **Kimber SJ.** 2010 The directed differentiation of human embryonic stem cells towards chondrocytes *Nature Biotech 28, 1187-1193*

Camarasa MV, Kerr R, Sneddon S, Brison DR & **Kimber SJ** (2010) Derivation of Man-1 and Man-2 research grade human embryonic stem cell lines *J In Vitro Laboratory Science* 46, 386-394.

McKay TR, Camarasa MV, Bates N, Fitzsimmons J, Brison, DR, Aplin, JD & **Kimber SJ** 2011 Generation of continuous immortalised human placental feeders suitable for maintenance of human embryonic stem cells using lentiviral constructs containing BMI and hTert. Stem Cell Research 7,154-162.

Stuart HM, Roberts, NA, Burgu B, Daly SB, Urquhart JE, Bhaskar S, Dickerson JE, Mermerkaya M, Silay MS, Lewis MA, Olondriz BO, Gener B, Beetz C, Varga RE, Gulpınar O, Suer E, Soygur T, Özçakar ZB, Yalçınkaya F, Kavaz A, Bulum B, Gucuk A, Yue WW, Erdogan F, Berry A, Hanley NA, McKenzie EA, Hilton EN, Woolf AS, **Newman WG.** *LRIG2* mutations cause urofacial syndrome. Am J Hum Genet 2013;92(2):259-64

Identification and characterisation of novel genes for urofacial syndrome

Supervisors: Professor Adrian Woolf and Professor William Newman

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http://www.human-development.manchester.ac.uk/staff/BillNewman

Urofacial syndrome (UFS, MIM# 236730) is a rare autosomal recessive condition characterised by bladder dysfunction, dilatation of the renal tract and vesicoureteric reflux (VUR) as well as bowel voiding dysfunction and an abnormal facial expression when attempting to smile.[1] The bladder and renal tract abnormalities seen in UFS have significant overlap with more common bladder dysfunction and VUR, which affects 1 in 100 children.[1]
Previous genetic studies led by our group, discovered that a subset of UFS patients have loss-of-function mutations in either *HPSE2* which encodes heparanase 2 or *LRIG2*, encoding leucine rich immunoglobulin 2.[2,3] UFS is genetically heterogeneous with further implicated gene(s) yet to be found.[2,3] The function(s) of heparanase 2 and LRIG2 and the molecular pathogenesis of UFS is not yet understood.
The PhD student will use autozygosity mapping and next generation sequencing strategies to identify novel genes causing UFS. The novel gene(s) will then be characterized using models already established for the study of *HPSE2* and *LRIG2* function, including Xenopus. The student will work alongside post-docs working on an MRC-funded program to understand the altered neurobiology leading to UFS.
Addressing these research questions is important as it is anticipated that understanding the genetics and pathogenesis of UFS will improve the management of individuals with UFS and translate to improved management as well as identify therapeutic targets relevant to individuals with common bladder dysfunction and VUR which accounts for 4,000 individuals requiring renal replacement therapy in the UK.[4]
This project involves cutting edge technologies of Affymetrix SNP arrays and next generation sequencing (Illumina HiSeq). Both techniques have been successfully applied by the supervisors previously (including Nat Genet 2013;45(3):295-8; Am J Hum Genet 2013;92(4):605-13; Am J Hum Genet 2013;92(2):259-64). The student will receive extensive experience in study design, undertaking the experimental procedures and importantly in the bioinformatic analysis of this complex data. Within the Manchester Centre for Genomic Medicine is a dedicated bioinformatics team who will train and support the student to learn these state of the art skills.
The characterization of the temporo-spatial expression and function of the novel gene identified in the first part of the project is at the heart of understanding developmental biology. The use of *Xenopus* as a model is well established by our group and the student will gain exposure to a number of techniques to determine the effects of the altered novel gene expression. The opportunity to consider the relationship of the novel UFS gene with HPSE2 and LRIG2 provide a clear framework to develop the project.

References

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2.Daly SB, Urquhart JE, Hilton E, …, Shalev S, Smith R, **Woolf AS**, Black GC, **Newman WG**. Mutations in HPSE2 cause urofacial syndrome. Am J Hum Genet 2010;86(6):963-9.
3.Stuart HM, Roberts, NA, Burgu B, McKenzie EA, Hilton EN, **Woolf AS, Newman WG**. *LRIG2* mutations cause urofacial syndrome. Am J Hum Genet 2013;92(2):259-64
4.Ansell D, Feehally J, Fogarty D, Inward C, Tomson CRV, Warwick G, Williams A (2010) UK Renal Registry 12th Annual Report 2009. Nephron Clin Pract;115(Suppl 1)

Functional genetic studies of human congenital heart disease

Supervisor: Professor Bernard Keavney

http://www.cardiovascular.manchester.ac.uk/staff/bernardkeavney/

Where project will be mainly based: Core Technology Facility, University of Manchester

Background:

Our recent work (see references) has identified a number of human genomic regions in which either copy number variation or single nucleotide polymorphisms are associated with the risk of congenital heart disease, the commonest birth defect and a major cause of childhood morbidity and mortality. Within the identified regions, the mechanisms whereby specific genes influence disease risk is unknown. In this project you will use a variety of techniques including human eQTL mapping, cellular studies and animal modelling approaches to investigate the mechanism of association of one of these loci on chromosome 4 which has been shown to be associated with atrial septal defect. We hypothesise that the non-coding RNA species located at the region of maximal association with ASD on chromosome 4 acts in development to modulate the growth of the atrial septum. Presently target genes for the non-coding RNA, its expression profile in human tissues, and the association between natural variation and gene expression in likely target tissues are unknown. These questions will form the focus of this work.

Hypothesis and Aims:

Hypothesis: SNPs within the non-coding RNA gene in the STX18-MSX1 region of chromosome 4p16 predispose to congenital heart disease via an effect during heart development on the expression of genes either in the region or elsewhere in the genome.

Aims
1. To characterise relationships between top SNPs and gene expression in different tissues
2. To identify target genes of the non-coding RNAs in the hit region
3. To manipulate levels of the non-coding RNAs in cellular systems
4. To contribute to model organism studies elucidating the *in vivo* role of these species.

Techniques:

Human eQTL mapping in a variety of primary tissues
Transfection and knockdown techniques in cellular systems
Bioinformatics analyses of identified gene networks
In vivo gene knockdown/deletion

Key References from the group:

Cordell et al. Nature Genetics 2013; PMID:23708191
Cordell et al. Human Molecular Genetics 2013; PMID:23297363
Soemedi et al. American Journal of Human Genetics 2012; PMID:22939634

Characterization of developmental disorders of chromatin modification

Supervisor: Dr Siddharth Banka

http://www.human-development.manchester.ac.uk/staff/153372/

Enzymatic modification of histone tail residues underpins chromatin modification that is fundamental to many biological processes. H3K4 (histone3 lysine4) trimethylation is an important activating mark for gene promoters. Four out the six mammalian H3K4 methyltransferases belong to the MLL family. Germline mutations in the MLL encoding genes have been recently identified in autism and Kabuki, Wiedemann-Steiner and Kleefstra-like syndromes (1-4). Kabuki syndrome 2 is caused by germline mutations of UTX (encoded by *KDM6A*), a H3K27 methyltransferase that forms complexes with human MLL2 and MLL3 (5).

Intellectual disability is a common feature of all the conditions mentioned above suggesting their importance in neurodevelopment. We hypothesize that haploinsufficiency of MLL/UTX unfavourably affects differentiation of embryonic stem cells into neuronal cell lines via dysregulation of specific genes and pathways.

A multi-disciplinary team of geneticists, developmental biologists and neurodevelopmental scientists will supervise this project to uncover the role of MLL and UTX proteins in neural development by using cutting-edge technologies. Student will have an opportunity to work with human embryonic stem cells, learn techniques of genetic engineering (TALENs or CRISPR/Cas9 system) and molecular biology (polymerase chain reaction, sequencing, Q-PCR, western blotting, whole genome Chip-Seq, transcriptomics, small molecule inhibition, cell proliferation and differentiation assays) and gain familiarity with a range of bioinformatics tools. The project will make significant contribution towards understanding the roles of MLL and UTX proteins in development and lead to novel ideas for further basic science and translational research. Better understanding of histone modifying enzymes is important for many areas of biology, human health and disease.

References

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Characterisation of retinal dystrophy by next generation sequencing

Supervisor: Professor Graeme Black

http://www.manchester.ac.uk/research/graeme.black/

Background The MCGM Retinal dystrophy research programme has developed NGS tools for retinal dystrophy. These have been transformational for health services research (demonstrating clinical need for genetic testing) and for transforming testing available to patients. Current molecular diagnostic services for disorders within the retinal dystrophy umbrella include the target enrichment and high-throughput sequencing of 150 genes known to be associated with retinal dystrophy. Clinical scientists analyse target-enrichment data and identify likely-pathogenic variants through variant frequency and predicted pathogenicity. Data analysis and interpretation remains a significant bottleneck due to the high genetic heterogeneity, the number of genes that cause both dominant and recessive disease and the high frequency of pathogenic missense variants in many of the genes tested. *Accurately determining variant(s) underlying a patient's disorder is vital – it is likely to be key in determining future treatment, and currently dictates the management and determination of prognosis.*

Problems

A number of deficiencies exist in the genetic screen pipelines for clinical service and research that are currently offered for retinal dystrophies in the UK. These include:

(i) Failure to detect likely-pathogenic mutations in a third of patients with presumed autosomal recessive conditions
(ii) Inability of online tools to accurately identify likely-pathogenic mutations
(iii) Failure of these tools to identify variants which are likely to have a functional consequence
(iv) Inability to determine which variant is pathogenic in patients with two or multiple likely-pathogenic mutations.

Aims

The aim of this PhD project is to develop and utilize *in-silico* and statistical approaches to:

(i) Identify key genetic and regulatory players missed by current diagnostic screens
(ii) Develop strategies and protocols to analyse whole exome and whole genome data, increase the pick-up rate of mutations underlying retinal dystrophies and validate the use of whole genome sequencing in a diagnostic context
(iii) Improve predictions of variant pathogenicity, functional effect and patient prognosis;
(iv) Develop molecular diagnostic hierarchies stratified based on disorder, ethnicity, age and genetic composition.

Data

The PhD programme will have access to an abundance of retinal dystrophy patient sequencing data, including:

(i) >100 whole genomes produced in collaboration with Complete Genomics
(ii) A catalogue of target-enrichment diagnostic samples (currently we have access to over 300 samples with data available at diagnostic grade on 105 genes
(iii) A cohort of whole-exome samples (Currently over 50) acquired at the Manchester Centre for Genomic Medicine.

Data will be stratified by ethnicity, age, gender, disorder and diagnostic status and then manipulated to explicitly test a number of hypotheses related to the aims stated above.