Modelling Human Genetic Disorders in Mice

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DECLARATIONS

This thesis is my own work and contains nothing which is the outcome of work done in collaboration except where specifically indicated in the text.

This thesis does not exceed the word limit of 60,000 as set by the Degree Committee for the Faculty of Biology.

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ABSTRACT

Rearrangements of the human genome including deletions, duplications, inversions and translocations play a major role in the pathogenesis of many human diseases. In order to facilitate the discovery of dosage-sensitive genomic regions and genes, and to investigate the contribution of genomic rearrangements to the development of different human disorders, many mouse models carrying genomic rearrangements of syntenic regions of the mouse genome have been generated.

During my PhD I have been involved in the generation and phenotypic analysis of two monosomic mouse models carrying deletions syntenic with 21q11.2–q21.1 and 5q35.2–q35.3 in humans.

The first of these models was generated to investigate the contribution of the genes mapped within the *Lipi–Usp25* interval to the development of both various types of cancer and clinical features diagnosed in patients with Monosomy 21 (a disorder associated with intellectual disability, craniofacial, skeletal and/or cardiac abnormalities, and respiratory complications). Monosomic mice displayed impaired memory retention, which models the intellectual disability observed in patients with Monosomy 21. Moreover, when fed on a high-fat diet, monosomic mice exhibited a significant increase in fat mass/fat percentage estimate, severe fatty changes in their livers, and thickened subcutaneous fat. Thus genes within the *Lipi–Usp25* interval are involved in memory retention and the regulation of fat deposition.

The second of these models has been developed to investigate the contribution of the genes mapped within the *4732471D19Rik–B4galt7* interval to the development of clinical features diagnosed in patients with Sotos syndrome (an overgrowth disorder associated with advanced bone age, intellectual disability, hypotonia, facial, cardiovascular and/or urinary/renal abnormalities). Monosomic mice showed dilation of the pelvicalyceal system in the kidneys, which mimics the renal abnormality observed in patients with Sotos syndrome. Thus haploinsufficiency of a gene (or genes) within the *4732471D19Rik–B4galt7* interval successfully models the renal abnormality observed in patients with Sotos syndrome.

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ABBREVIATIONS

°C	degrees Celsius
μCi	microcurie
μF	microfarad
μg	microgram
μl	microlitre
μM	micromolar
AB2.2	129S7/SvEvBrdHprt^{b-m2}
ABR	auditory brainstem response
aCGH	array comparative genomic hybridization
AS	Angelman syndrome
BAC	bacterial artificial chromosome
BMC	bone mineral content
BMD	bone mineral density
BME	β-mercaptoethanol
BMI	body mass index
bp	basepair
cDNA	complementary DNA
CGH	comparative genomic hybridization
cm	centimeter
dB	decibel
ddH_20	double-distilled H_20
DECIPHER	Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources
DEXA	dual-energy X-ray absorptiometry
DGS	DiGeorge syndrome
DMEM	Dulbecco's Modified Eagle Medium
DMSO	dimethyl sulfoxide
dNTP	deoxyribonucleotide triphosphate
DSB	double-strand break
dsDNA	double-stranded DNA

E14Tg2a	129P2/OlaHsd
EDTA	ethylenediaminetetraacetic acid
EFT	Ewing family tumours
ELISA	enzyme-linked immunosorbent assay
EDMD	Emery-Dreifuss muscular dystrophy
ES	embryonic stem
FBS	foetal bovine serum
FISH	fluorescence in situ hybridization
FPLD	familial partial lipodystrophy of the Dunnigan
g	gram
gDNA	genomic DNA
GPS	glutamine/penicillin/streptomycin
HAT	hypoxanthine-aminopterin-thymidine
HFD	high-fat diet
HGPS	Hutchinson-Gilford progeria syndrome
HMT	histone-methyltransferase
HSA	human chromosome
HSW	high stringency wash
HT	hypoxanthine-thymidine
H&E	haematoxylin and eosin
Ig	immunoglobulin
IMS	industrial methylated spirit
ipGTT	intra-peritoneal glucose tolerance test
kb	kilobase
kHz	kilohertz
LB	lysogeny broth
LCR	low-copy repeat
LDL	low-density lipoprotein
LIF	leukaemia inhibiting factor
LOD	logarithm of odds
LOH	loss of heterozygosity
loxP	locus of crossover P1
LPS	lipopolysaccharide

LRP	lipoprotein receptor-related protein
LSW	low stringency wash
Mb	megabase
mbar	milibar
mg	miligram
MICER	Mutagenic Insertion and Chromosome Engineering Resource
ml	mililitre
mm	millimeter
mM	milimolar
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NAHR	non-allelic homologous recombination
NCBI	National Center for Biotechnology Information
NEFAC	non-esterified free fatty acids
NFD	normal-fat diet
ng	nanogram
NHEJ	non-homologous end joining
NID	nuclear receptor interaction domain
nm	nanometer
NR	nuclear receptor
NSCLC	non-small cell lung carcinoma
OD	optical density
OMIM	Online Mendelian Inheritance in Man
OS	osteosarcoma
OSCC	oral squamous cell carcinomas
PBS	phosphate buffered saline
PCR	polymerase chain reaction
PCR-SSCP	polymerase chain reaction-single strand conformation polymorphism
PEV	position-effect-variegation
pH	potential of hydrogen
PHD	zinc-finger plant homeodomain
PWS	Prader-Willi syndrome
PWWP	proline-tryptophan-tryptophan-proline

qRT-PCR	real-time quantitative PCR
RA	retinoic acid
rpm	revolutions per minute
s	seconds
SAC	SET-associated cysteine-rich
SCC	squamous cell carcinomas
SCLC	small cell lung carcinoma
SDS	sodium dodecyl sulfate
SET	Su(var)3-9, Enhancer-of-Zeste, Trithorax
SMS	Smith-Magenis syndrome
SMCR	SMS critical region
snoRNA	small nucleoar RNA
SNP	single nucleotide polymorphism
SoS	Sotos syndrome
SSC	saline-sodium citrate
SSLP	simple sequence length polymorphism
STS	sequence-tagged site
TAE	Tris-acetate-EDTA
TBST	tris buffered saline with Tween 20
TC	tissue culture
Tris	tris(hydroxymethyl)aminomethane
TRAIL	tumour necrosis factor related apoptosis-inducing ligand
TSG	tumour suppressor gene
U	unit
UV	ultraviolet
V	volt
VCFS	velocardiofacial syndrome
WAT	white adipose tissue
WBS	Williams syndrome

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