

# **Identification and analysis of MHC-linked olfactory receptor genes**

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**A thesis submitted in partial fulfilment of the requirements of Cambridge University for the degree of Doctor of Philosophy.**

**Newnham College, Cambridge University.**

**August 2002**

**This dissertation does not exceed the length limit set by the Biology Degree Committee.**

## **Abstract/Summary of thesis**

Olfactory receptor genes (ORs) are members of the largest known human multigene family of 7-transmembrane receptors; over the past few years, 900-1000 have been identified, existing largely within clusters located on the majority of chromosomes. As their name implies, they are involved in odour perception within the major olfactory epithelium (MOE), although their expression in other tissues, notably the testis, lungs and kidney seems to suggest some non-olfaction related role. The cluster of olfactory receptors located next to the Major Histocompatibility Complex (MHC) were considered to be especially interesting, given that the association between this cluster and the MHC has also been conserved in mouse and rat, and it has been suggested that these genes are involved in detecting odours that control MHC-disparate mate selection.

The aim of this thesis was to identify all olfactory receptor genes located distal to the class I region of the Major Histocompatibility Complex in both the human genome and in the mouse genome, and to study phylogeny, regulation, expression and polymorphism to develop a better understanding of the structure, function and evolution of these genes. In total, 34 MHC-linked ORs were identified in human; within the mouse genome, a larger number of MHC-linked ORs (56) were also identified. Comparing the 2 species, orthologous groups can be identified: groups appear to have undergone both deletions and duplications since mouse-human divergence. An investigation of regulatory elements within the human MHC-linked OR cluster revealed no specific regulatory elements, although a putative locus control region has been identified. Compared to the HLA genes, these OR genes show a limited amount of polymorphism, although existing polymorphisms act to alter the functional repertoire of these genes between individuals and one specific OR gene appears to have an unexpectedly high level of polymorphism.

## Acknowledgements

I am indebted to my supervisor at the Sanger Centre, Stephan Beck, whose knowledge, enthusiasm, patience and resourcefulness have seen me through whenever mine have failed. Many thanks also go to my supervisor at Cambridge University, John Trowsdale. I am also very grateful to a number of people with whom I have worked over the course of this project: Armin Volz and Anke Ehlers at Institut für Immunogenetik, Universitätsklinikum Charité, Humboldt-Universität, Berlin, Simon Forbes at Cambridge University, and Claire Amadou at CNRS, Toulouse – it has been both a highly informative and a highly enjoyable experience. Special thanks must also go to Andreas Ziegler (Institut für Immunogenetik, Universitätsklinikum Charité, Humboldt-Universität, Berlin) – your frequent phone calls were a source of inspiration, motivation and (I admit it, occasionally) fear ! Many thanks also to Kirsten Fischer-Lindahl (HHMI, Dallas, TX) – I have appreciated all your input throughout the course of this thesis.

Moving on to the Sanger Centre, I would like to thank all past and present members of Team 50: Katie Evans, Roger Horton, Melanie Stammers, Vikki Rand, Karen Novik, and Karen Halls – thanks for all the input and advice and the cups of tea and moaning (mine, generally)... I am also very grateful to members of the now (non-existent) Team 33 who did much of the sequencing of this region, as well as members of the Chromosome 6 and mouse project groups at the Sanger Centre. Others at the Sanger Centre who have helped me over the course of this project are too many to name in full - I am privileged to have worked in an environment where help has been offered so freely – but special mention should go to Alex Bateman, Kevin Howe, Matt Craig, Graeme Bethel, Carol Edwards and Andy Mungall. Thanks also to Jill Williamson and Denise Sheer of the Human Cytogenetics Laboratory (ICRF) for their help with the FISH analysis.

On a personal note, thanks must go to the various football teams I have played for and supported whilst doing this thesis – you have provided me with a philosophical approach that being associated with more successful clubs just would not be able to give me and distracted me when I most and least needed it. Thanks to my friends who have allowed me to become even less responsible and cut me huge amounts of slack over the last few months – your understanding and patience is always a lot more than I deserve. I am also grateful to my own source of sunshine, even though it got cloudy, the cloud breaks were great !! Many thanks also go to my parents, Michael and Glynis, for their pillar-like support, unswerving belief and love and the many sandwiches they have made me, especially in the last few weeks. Finally, thanks to the force that has moved in a most mysterious way to shape the big and small events in the universe – I am never grateful enough for everything I have.

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## List of abbreviations

AOB	accessory olfactory bulb
(c)AMP	(cyclic) adenosine 5'-monophosphate
ATP (dATP, ddATP)	adenosine 5'-triphosphate (deoxy-, dideoxy-)
BAC	bacterial artificial chromosome
BLAST	basic local alignment search tool
bp	base pair
BTN	butyrophilin
°C	degrees Celsius
cDNA	complementary deoxyribonucleic acid
chr	chromosome
cm	centimeter
CNS	central nervous system
CpG	cytidyl phosphoguanosine dinucleotide
CTP (dCTP, ddCTP)	cytidine 5'-triphosphate (deoxy-, dideoxy-)
dbEST	database of expressed sequence tags
DNA	deoxyribonucleic acid
dNTP	2'-deoxyribonucleoside 5'-triphosphate
DTT	dithiothreitol
EDTA	ethylenediamine tetra-acetic acid
EMBL	European Molecular Biology Laboratory
EST	expressed sequence tag
FAT10	HLA-F associated transcript 10
FISH	fluorescence 'in situ' hybridisation
FPC	fingerprinting contig
GABA	gamma-aminobutyric acid
GDP	guanine diphosphate
GPCR	G-protein coupled receptor
G-protein	GTP-binding protein
GPX	glutathione peroxidase
GTP (dGTP, ddGTP)	guanine 5'-triphosphate (deoxy-, dideoxy-)
HEK	human embryonic kidney
HFE	Hereditary haemochromatosis locus
HGMP	Human Genome Mapping Resource Centre
HGP	Human Genome Project
HLA	human leukocyte antigen
HMM	Hidden Markov Model
HUGO	Human Genome Organisation
Ig	Immunoglobulin
IHGSC	International Human Genome Sequencing Consortium
Kb	kilobase pairs
l	litre
LB	Luria-Bertani
LD	linkage disequilibrium
LINE	long interspersed nuclear element
M	molar
Mb	megabase pairs
µg	microgram
µl	microlitre



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$\mu$ M	micromolar
min(s)	minute(s)
mg	milligram
MHC	major histocompatibility complex
ml	millilitre
mm	millimetre
mM	millimolar
MOE	major olfactory epithelium
NCBI	National Centre for Biotechnology Information
ng	nanogram
OB	olfactory bulb
OMIM	On-line Mendelian Inheritance in Man
OR	Olfactory receptor
OSN	Olfactory sensory neuron
PAC	P1-derived artificial chromosome
PCR	polymerase chain reaction
PFAM	protein family database
RFP	ret finger protein
RNA (mRNA, rRNA, tRNA)	ribonucleic acid (messenger-, ribosomal-, transfer-)
RNase A	ribonuclease A
rpm	revolutions per minute
RP	ribosomal protein
RT-PCR	reverse transcription polymerase chain reaction
SDS	sodium dodecyl sulphate
sec(s)	second(s)
SINE	short interspersed nuclear element
snoRNA	small nucleolar RNA
SNP	single nucleotide polymorphism
STS	sequence tagged site
TEMED	N, N, N', N'-tetramethylethylenediamine
TM	Transmembrane domain
TrEMBL	Translated EMBL database
Tris	tris(hydroxymethyl)aminomethane
U	unit
UTR	untranslated region
uv	ultraviolet
V	volt
v/v	volume/volume
VNO	vomeronasal organ
VR	pheromone receptor
W	watt
w/v	weight/volume
WGS	whole genome shotgun
YAC	yeast artificial chromosome
ZNF	zinc finger protein

## Publications

Publications describing parts of this thesis:

Ehlers, A., Beck, S., Forbes, S., Trowsdale, J., Uchanska-Ziegler, B., Volz, A., **Younger, R.**, and Ziegler, A. (2000) MHC-linked olfactory receptor loci exhibit polymorphism and define extended HLA/OR haplotypes *Genome Res* 10(12):1968-78.

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