

ABSTRACT

X chromosome inactivation has not been well studied in mammals other than humans and mice. In both species, the inactive X expresses the *XIST/Xist* (X-inactivation specific transcript) non-coding RNA that is crucial for dosage compensation in females. Although both species belong to the same mammalian subclass, *Eutheria*, they show significant differences in imprinting patterns, negative regulation of *XIST/Xist*, and extent of silencing on the inactive X chromosome. Furthermore, the mechanism by which the *Xist* transcript coats and silences the X *in cis* is unknown. This study focuses on X-inactivation in other eutherians, first to unravel domains within *XIST/Xist* of biological significance, and second to investigate whether incomplete silencing in humans is unique within the mammalian subclass. Comparative analysis to predict conserved secondary structures between seven eutherian orthologs revealed common stems in the sequence before the *Xist* A repeat, the A repeat, F repeat, and exon 4. Several complex secondary structures were also similar between rodents but were not conserved in other species. These included the D repeat; structures between the B and D, as well as A and F repeats; and the unique rodent exon 5. The significance of these conserved domains in the context of potential biological functions, and how the structural differences might account for some species-specific differences, is discussed in this thesis.

To investigate the species variability in the extent of silencing, methylation analysis was performed on *Zfx*, *Jarid1C*, *Crsp2*, *Utx*, *Ube1*, *Ar*, and *Fmr1* in the cow and coast mole, in addition to human and mouse. Results from this study suggest that mouse is distinct in its more complete inactivation at several loci – *Zfx*, *Crsp2* – on the evolutionary newer part of the X, and *Ube1* on an evolutionary older part of the chromosome. In addition to evolutionary age, factors such as the position of the centromere, distance from the *X inactivation centre* (*XIC*), and presence of Y homologs failed to consistently explain or predict whether the genes on the X chromosome would escape or be subject to inactivation. Further epigenetic analysis is necessary to understand the distinct mechanisms leading to escape versus inactivation amongst different mammals.

BIOGRAPHICAL NOTES

Born: December, 25, 1981, Surrey
Academic Studies: B.Sc. University of British Columbia, 2003
Current Position: M.Sc. candidate, UBC

GRADUATE STUDIES

Field of Study: Mammalian X Inactivation, Department of Medical Genetics

Courses:

MEDG 510 Advanced Immunogenetics
MEDG 520 Advanced Human Molecular Genetics
MEDG 530 Advanced Human Genetics
MEDG 545 Current Topics Medical Genetics
MEDG 548 Directed Studies

Instructors

Dr. Kelly McNagny
Dr. Rob McMaster
Dr. Jan Friedman
Dr. Wendy Robinson
Dr. Carolyn Brown

AWARDS

NSERC PGS-M, 2004-2005
Medical Genetics Research Day Poster Award, 2004
NSERC USRA, 2003
NSERC USRA, 2002

PUBLICATIONS

Chow, J., Yen, Z., Ziesche, S., and C.J. Brown. Silencing of the Mammalian X Chromosome. *Annu. Rev. Genomics Hum. Genet.* 2005. 6:69–92.

PRESENTATIONS

Poster, American Society of Human Genetics Annual Meeting, 2004
Poster, Medical Genetics Research Day, 2004

SUPERVISORY COMMITTEE

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Dr. Louis Lefebvre (Medical Genetics)
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Dr. Wyeth Wasserman (Medical Genetics)



PROGRAMME

The Final Oral Examination
For the Degree of

Master of Science
Medical Genetics

ZINY YEN

B.Sc., University of British Columbia, 2003

Tuesday, July 26, 2005, 9:00 am
Room 1.410, Life Sciences Centre (LSC)

“Comparative Studies of X Inactivation within *Eutheria*”

EXAMINING COMMITTEE

Chair:

Dr. Anne Rose (Medical Genetics)

Supervisory Committee:

Dr. Carolyn Brown, Research Supervisor (Medical Genetics)

Dr. Louis Lefebvre (Medical Genetics)

University Examiner:

Dr. Sally Otto (Zoology)