

PRE-CONGRESS COURSE 6

SIG Reproductive Genetics

"Sex chromosomes in human reproduction: towards understanding their basic function"

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PRE-CONGRESS COURSE 6 - PROGRAMME

SIG Reproductive Genetics

Sex chromosomes in human reproduction: towards understanding their basic function

Course co-ordinators: P.H. Vogt (D), S. Viville (F) & K. Sermon (B)

Course description: This course aims to provide an overview of our current understanding of the function of X and Y chromosomes, in human reproduction in general and gametogenesis in particular. Why and how have they evolved, thereby accumulating functional key elements for associated genetic control mechanisms? After having presented a basic and molecular insight into the genomic evolution and conservation of both sex chromosomes, their abnormalities leading to interference in meiosis and inadequate germ cell production will be presented. For the male, Klinefelter syndrome is chosen as an example, while for the female the Turner syndrome will be discussed. Finally, X and Y genes with a clear role in human folliculogenesis and spermatogenesis, will be discussed with a focus on their impact in assisted reproductive technologies.

Target audience: Geneticists with an interest in reproduction, particularly those involved in genetic screening in infertile males; clinical embryologists with a daily experience in the consequences of male infertility, necessitating ART e.g. ICSI; andrologists wishing to brush up their basic knowledge on the genetic causes of male infertility; ART specialists confronted with female infertility of genetic causes.

Programme

- 09.00 - 09.30: Genomic structure and genes of the X and Y chromosomes: evolution and future - **S. Repping (NL)**
09.30 - 09.45: *Discussion*
- 09.45 - 10.15: X chromosome activity in gametogenesis and the strange phenomenon of sex chromosome silencing during male meiosis - **P. De Boer (NL)**
10.15 - 10.30: *Discussion*
- 10.30 - 11.00: Coffee break**
- 11.00 - 11.30: Elucidating the functions of mammalian Y chromosome in spermatogenesis - **P. Burgoyne (UK)**
11.30 - 11.45: *Discussion*
- 11.45 - 12.15: Klinefelter syndrome: genetic variability and consequences for spermatogenesis – **F. Vidal (E)**
12.15 - 12.30: *Discussion*
- 12.30 - 13.30: Lunch**
- 13.30 – 14.00: Turner syndrome and deletions in the X chromosome: genetic variability - **P. Scriven (UK)**

14.00 – 14.15: *Discussion*

14.15 – 14.45 X genes with a role in gametogenesis – **A. Rajkovic (US)**

14.45 – 15.00: *Discussion*

15.00 - 15.30: Coffee break

15.30 - 16.00: Y genes interfering with gametogenesis. - **P.H. Vogt (D)**

16.00 - 16.15: *Discussion*

16.15 - 16.30: Closing remarks – **S. Viville (FR)**

Genomic structure and genes of the X and Y chromosomes: *evolution and future*

Sjoerd Repping, PhD



Layout of course

- Sex determination
- Evolution of human X and Y chromosomes
- Current contents
- The future
- Conclusion



Sex determination – XY/XX

- XY male
- XX female



Nature, May 2008



Sex determination – ZW/WW

- ZW female
- WW male



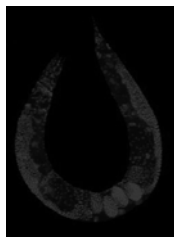
Sex determination – XO/XX

- XO male
- XX female



Sex determination – XO/XX

- XO male
- XX hermaphrodite



Sex determination – haploid/diploid

- Haploid male
- Diploid female



Sex determination – other

- Temperature



Sex determination – other

- Sequential hermaphroditism



Current contents – X chromosome

- Genes

Ross, et al., Nature (2005)



Current contents – Y chromosome



The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes

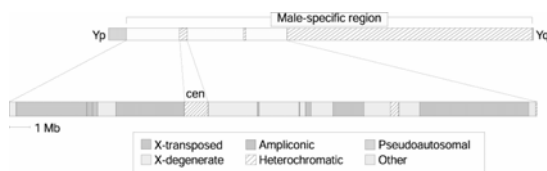
Mark Skalesky, Tomoko Kuroki-Kawaguchi, Patrick J. Min, Roland S. Cordes, Melissa Miller, Laura S. Brown, Edward Ruppert, Takana Yoshida, John All, Timothy Hunt, Karl-Otto Renner, Andrew Robinson, Kim S. Kim, George Fernald, Lorraine Patten, Robert Fulton, Tim Brown, Shou-Fang Hsu, Philip Lathrop, Shawn Leonard, Brian Martin, Rachel Muzler, John McPherson, Nicole Moore, William Reade, Christine Rappaport, Philip Storz, Kimberly Taylor, Susan Beck, Tracy Kneibler, Kelli Scott, Brian Schutte, Cindy Strong, Aye Tin Shikun, Shou-Fang Tang, Robert N. Waterhouse, Richard K. Wilson, Steve Roeder & David C. Page

¹Howard Hughes Medical Institute, Whitehead Institute, and Department of Biology, Massachusetts Institute of Technology, 7 Cambridge Center, Cambridge, Massachusetts 02142, USA
²Genome Sequencing Center, Washington University School of Medicine, 660 South Euclid Boulevard, St. Louis, Missouri 63110, USA
³Center for Reproductive Medicine, Department of Gynecology and Obstetrics, Academic Medical Center, Amsterdam 1007 AZ, the Netherlands

Skalesky, et al., Nature (2003)



Current contents – Y chromosome



Skalesky, et al., Nature (2003)



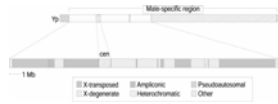
Current contents – Y chromosome

X-Y homologous sequences (PAR)

- Meiotic recombination with the X chromosome

Male Specific Region of the Y (MSY)

- No meiotic recombination
- Four sequence classes:
 - Heterochromatic sequences
 - Euchromatic sequences:
 - X-transposed
 - X-degenerate
 - ampliconic



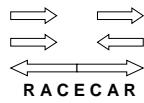
Skaletsky, et al., Nature (2003)



Current contents – Y chromosome

- Ampliconic sequences
 - >99% identical in sequence
- Organisation

- Direct repeats
- Inverted repeats
- Palindromes
- Complex structures



Skaletsky, et al., Nature (2003)



Current contents – Y chromosome

- MSY genes
 - 156 transcription units
 - 78 likely to encode proteins
- Distribution
 - heterochromatic 0 genes
 - X-transposed 2 genes
 - X-degenerate 16 genes
 - widely expressed
 - ampliconic 60 genes
 - testis-specific expression

Skaletsky, et al., Nature (2003)



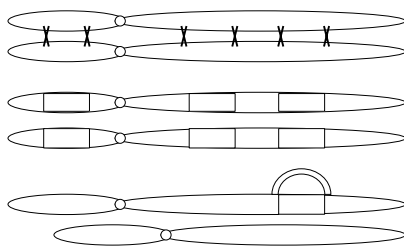
X Y comparison

- Size
 - X: 155 Mb
 - Y: 24 Mb (euchromatic MSY)
- Genes
 - X: 1,098 genes
 - Y: 78 genes
- Authors
 - X: 283 authors
 - 0.55 Mb sequence per author
 - 3.88 genes per author
 - Y: 40 authors
 - 0.60 Mb sequence per author
 - 1.95 genes per author

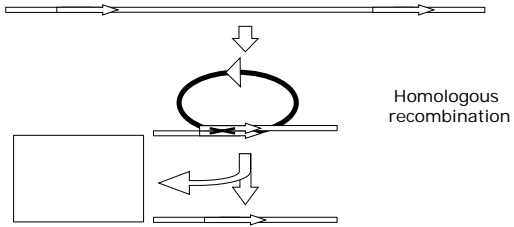
X Y comparison

- Repeats
 - X: ...
 - Y: ...
- Reproduction
 - X: 99 genes testis-specific (9%)
 - Y: 60 genes testis-specific (77%)

Meiotic recombination – genetic sex



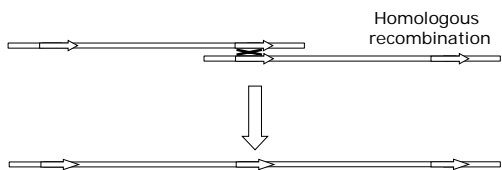
Structural variation - deletions



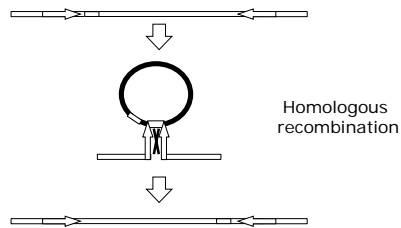
Sun, et al., Hum Mol Genet (2000), Kuroda-Kawaguchi, et al., Nat Genet (2001)
Repping, et al., AJHG (2002), Nat.Genet (2003), Genomics (2004)



Structural variation - duplications



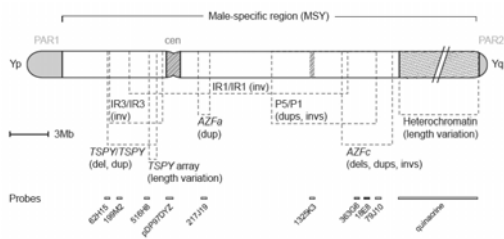
Structural variation - inversions



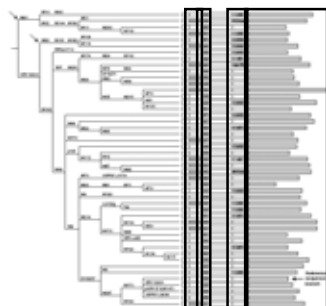
Structural variation - gene conversion



Structural variation – possibilities



Structural variation - results



- Four classes
- TSPY array length (23-64 copies)
 - Heterochromatin (29-54% chromosome)
 - IR3/IR3 inversion
 - AZFc structure

Structural variants
 Deleted Duplicated
 Inverted Large-scale length variation

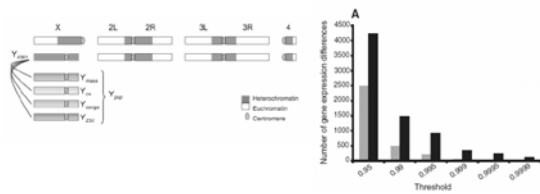
Structural variation - results

- 29 out of 47 chromosomes differ from reference sequence
 - Excluding *TSPY* array and heterochromatin length
 - Degree of variation differs
 - Heterochromatin > *TSPY* > IR3/IR3 > *AZFc*
 - “Only” 10 chromosomes carry a deletion or duplication
 - 79% identical copy number with reference genome
 - Evolutionary selection
 - against deletions
 - against other rearrangements?
- via effects on spermatogenesis.....

Repping, et al., Nat Genet (2006)



Structural variation – other effects

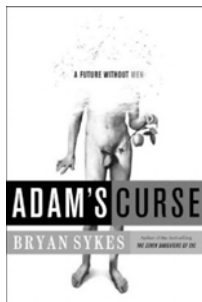


Lemos, et al., Science (2008)



The future

- Disappearing Y?
- Selection against
 - Deletions
 - Other rearrangements?
 - Effect on autosomes?
- Non-sexual reproduction.....



Conclusion

Acknowledgements
