



Laboratory of Mouse Molecular Genetics

Mouse genomics, hybrid sterility, Prdm9, meiotic silencing, chromosome substitution strains

Jiří Forejt

jiri.forejt@img.cas.cz

www.img.cas.cz/research-groups/jiri-forejt

We identified the first vertebrate hybrid sterility gene *Prdm9* [Meisetz], encoding a meiotic histone H3 lysine-4 tri-methyltransferase. Positional cloning was confirmed by a rescue experiment using the intact *Prdm9* transgene in bacterial artificial chromosomes with the “fertility” *Hst1f* allele. Identification of the *Prdm9* hybrid sterility gene reveals a role for epigenetics in speciation and opens a window to a systems approach to the hybrid sterility gene network. The second hybrid sterility gene, *Hstx2*, showing Dobzhansky-Muller incompatibility with *Prdm9*, was mapped to a 4.7 Mb interval on Chromosome X. Six protein-coding genes and a cluster of miRNA genes are tested as possible candidates of *Hstx2*. To characterize the incompatibilities underlying hybrid sterility, we phenotyped reproductive and meiotic markers in male mice with altered copy numbers of *Prdm9*. A partial rescue of fertility was observed upon removal of the B6 allele of *Prdm9* from the azoospermic [PWD x B6]F1 hybrids, whereas removing one of the two *Prdm9* copies in PWD or B6 background had no effect on male reproduction.

Chromosome substitution, or consomic strains C57BL/6J-Chr # PWD/Ph/ForeJ, constructed in our laboratory are used for dissecting the genomic architecture of sterility of *Mus m. musculus* x *Mus m. domesticus* hybrids. We study meiotic X-chromosome inactivation by genome-wide expression profiling and by monitoring the transcription profiles and histone modifications in meiotic and postmeiotic testicular cells of carriers of male-sterile autosomal rearrangements and in male-sterile inter-species hybrids.

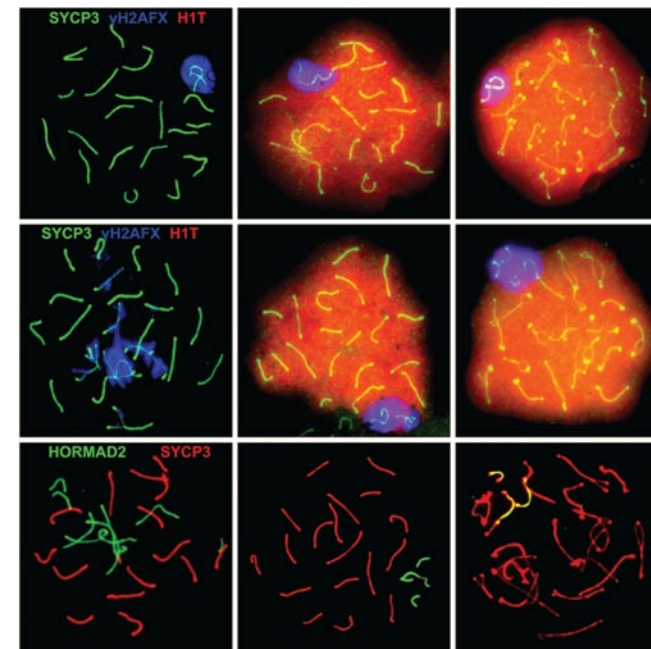


Fig. 1. Synaptic failure of homologous chromosomes in PWD x B6 inter-subspecific hybrids. SYCP3 protein component of synaptonemal complexes, phosphorylated histone H2AFX, testis-specific histone H1T and HORMAD 2 protein decorated unsynapsed chromosome axes are visualized by immunostaining of chromosome spreads of pachytene and diplotene primary spermatocytes. First row - fertile control B6 parent. Second and third row - sterile [PWD x B6] F1 hybrid. Note the disrupted sex body carrying X and Y chromosomes in early-mid pachytene of sterile males (first column).



- GACR, GA13-08078S - Genomic architecture and molecular basis of hybrid sterility of the mouse, 2013-2017, J. Forejt
- GACR, 14-20728S - Subspecies-specific function of meiotic genes in mouse gametogenesis, 2014-2016, O. Mihola



1. [Bhattacharyya T, Reifova R, Gregorova S, Šimeček P, Gergelits V, Mistrik M, Martincova I, Pialek J, Forejt J:](#) X Chromosome control of meiotic chromosome synapsis in mouse inter-subspecific hybrids. **PLoS Genet** 2014.
2. [Flachs P, Bhattacharyya T, Mihola O, Pialek J, Forejt J, Trachtulec Z:](#) Prdm9 incompatibility controls oligospermia and delayed fertility but no selfish transmission in mouse intersubspecific hybrids. **PLoS One** 2014 9(4): e95806.
3. [Jansa P, Homolka D, Blatny R, Mistrik M, Bartek J, Forejt J:](#) Dosage compensation of an aneuploid genome in mouse spermatogenic cells. **Biol Reprod** 2014 90(6): 124.
4. [Bhattacharyya T, Gregorova S, Mihola O, Anger M, Sebestova J, Denny P, Šimeček P, Forejt J:](#) Mechanistic basis of infertility of mouse intersubspecific hybrids. **Proc Natl Acad Sci U S A** 2013 110(6): E468-77.
5. [Forejt J:](#) Hybrid Sterility, Mouse. **Brenner's Encyclopedia of Genetics** 2013 Second Edition: 582-585.



Standing from the left: Ondřej Míhola, PhD / Research Associate, Václav Gergelits / PhD Student (until 2014), Petr Jansa, PhD / Research Fellow, Petr Flachs, MSc / PhD Student, Vladana Fotopulosová, MSc / Research Assistant, Prof. Jiří Forejt, MD, DSc / Head of Laboratory
Sitting from the left: Mária Balcová [Dzúr-Gejdošová] MSc / PhD Student, Barbora Faltusová, M.Sc / PhD Student, Irena Chvátalová, MSc / Research Assistant, Jana Perlová / Technician, Soňa Gregorová, MSc / Research Assistant, Lenka Kašíková / Diploma student (since 2013)

Not in the picture: Tanmoy Bhattacharyya, MSc / PhD Student, Lenka Šebestová / Diploma student (since 2014)