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Meiotic silencing, aneuploidy, genomics, hybrid sterility genes

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Research topics

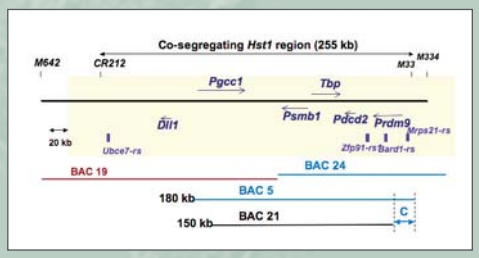
We study **meiotic X-chromosome inactivation** by genome-wide expression profiling and by monitoring X-chromosome histone modifications in meiotic and post-meiotic testicular cells of carriers of male-sterile autosomal rearrangements and in male-sterile inter-species hybrids.

Genetic architecture of hybrid male sterility is analysed on the model of PWD/Ph x C57BL/6 sterile male hybrids. The candidate genes are evaluated by transgenic rescue for the *Hst1* locus and by positional cloning and expression profiling of sorted testicular cells for the *Hstx1* locus.

We have established a **new mouse model of human aneuploidy syndromes**. The Ts43H segmental trisomy of proximal 30 MB of mouse chromosome 17 encompasses over 300 protein-coding genes. Phenome analysis of aneusomic animals is realized by collaboration with Dr. M. Hrabe de Angelis, GSF, Munich.

Chromosome substitution strains C56BL/6.PWD, recently constructed in our laboratory, are used for phenome analysis in collaboration with The Jackson Laboratory, Bar Harbor, Maine, USA (Dr. K.L. Svenson) and for the genetics of gene expression and splicing in a systems genetics project with the Max-Planck-Institute for Molecular Genetics in Berlin (Dr. H. Lehrach).

We have identified the first vertebrate hybrid sterility gene, **the mouse Hybrid sterity 1** *(Hst1)* **with *Prdm9*, encoding a meiotic histone H3 lysine-4 tri-methyltransferase**. Positional cloning was confirmed by hybrid male infertility rescue by using the intact *Prdm9* transgene in bacterial artificial chromosomes with the „fertility" *Hst1*^{f} allele. Identification of the first vertebrate hybrid sterility gene reveals a role for epigenetics in speciation, and opens a window to a hybrid sterility gene network.



Functional mapping of hybrid sterility 1 locus to Prdm9 gene encoding histone H3 lysine-4 methyltransferase. Hybrid male sterility rescue was achieved in transgenic inter-subspecific hybrids (PWD x B6) with BAC5 and BAC24, but not with BAC21. The Prdm9 gene is the only gene shared by BAC5 and BAC24 but absent in BAC21 (see Mihola et al., Science, 2008).

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Selected recent papers

1. Homolka D, Ivanek R, Capkova J, Jansa P, Forejt J. Chromosomal rearrangement interferes with X-chromosome inactivation. **Genome Res.** 2007;17:1431-1437.
2. Gregorová S, Divina P, Storchova R, Trachtulec Z, Fotopulosova V, Svenson KL, Donahue LR, Paigen B, Forejt J. Mouse consomic strains: Exploiting genetic divergence between Mus m. musculus and Mus m. domesticus subspecies. **Genome Res.** 2008;18:509-515.
3. Pialek J, Vyskocilova M, Bimova B, Havelkova D, Pialkova J, Dufkova P, Bencova, V., Dureje L, Albrecht T, Hauffe HC, Macholan M, Munclinger P, Storchova R, Zajicova A, Holan V, Gregorova S, Forejt J. Development of unique house mouse resources suitable for evolutionary studies of speciation. **J Hered.** 2008;99:34-44.
4. Trachtulec Z, Vlcek C, Mihola O, Fotopulosova V, Forejt J. Fine haplotype structure of a chromosome 17 region in the laboratory and wild mouse. **Genetics.** 2008;178:1777-1784.
5. Mihola O, Trachtulec Z, Schimenti JC, Vlcek C, Forejt J. A mouse speciation gene encodes a meiotic histone H3 methyltransferase. **Science.** Published online 11 December 2008 (10.1126/science.1163601).