LABORATORY OF

MOUSE MOLECULAR GENETICS

Mouse subspecies, speciation, *Prdm9*, meiotic recombination and chromosome pairing, synaptonemal complex, X-chromosome inactivation

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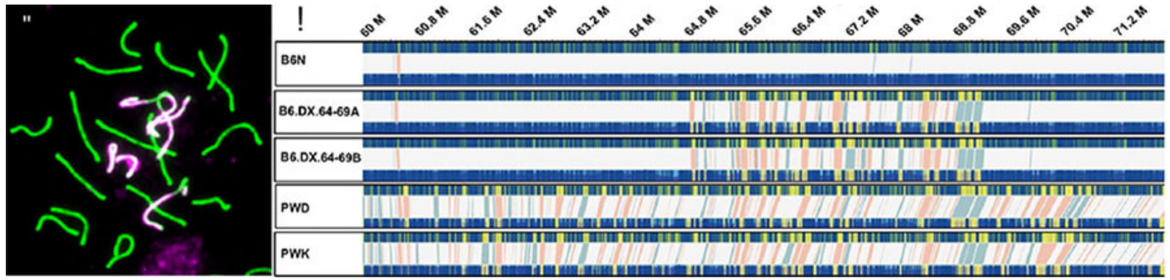
Hybrid sterility is defined as a situation when two species, each of which is fertile, produce a hybrid progeny, which is sterile. Hybrid sterility thus disrupts free exchange of genes between populations, an essential prerequisite for origin of new species. We identified the first and up to now the sole "speciation" gene in mammals, which controls hybrid sterility between two mouse subspecies. This gene, PR domain-containing 9 *(Prdm9)*, determines the sites of genetic recombination in the genome of mice and most other mammals. In sterile hybrids, PRDM9 allelic incompatibility causes disorders in DNA repair and in meiotic chromosome pairing, resulting in male infertility. Another, still undiscovered major hybrid sterility gene in mice is located within the Hstx2 locus on Chromosome X and modulates the effect of *Prdm9*.

We are currently trying to identify the X-linked hybrid sterility gene and to understand the molecular mechanism of its interaction with *Prdm9* and other minor hybrid sterility genes. We use the combination of high-resolution whole-genome genetic mapping and RNA-seq for molecular profiling of isolated populations of spermatogenic cells. By combining immunofluorescence microscopy techniques and fluorescence in-situ hybridization, we study meiotic chromosome pairing and synapsis and male-specific X-chromosome transcriptional inactivation, which are the processes affected in sterile male hybrids. Finally, we re-visit and re-define the chromosomal hybrid sterility by using the panel of inter-subspecific chromosome substitution strains in the *Prdm9*-controlled model of "synthetic hybrid sterility."



Left: Immunofluorescence microscopy of nuclear spread of chromosomes from primary spermatocyte at pachytene stage from a sterile hybrid male. Synaptonemal complexes of individual chromosome pairs are visualized by immunostaining of SYCP3 protein (green). Asynapsed chromosomes are decorated by anti-HORMAD2 antibody (orange). From: Forejt J. Can a non-coding genomic sequence provoke infertility of interspecific hybrids? Hommage to Theodosius Dobzhansky (Nature Portfolio Ecology & Evolution Community. May 31, 2018 (with permission). Right: Subspecies-specific structural variants (SVs) in the Hstx2 locus and in flanking regions revealed by genome optical mapping (Bionano Genomics). Each box contains a comparative analysis of a de-novo optical map (bottom), and the mm10 genome assembly in-silico reference B6 map (top) representing domesticus and musculus mouse subspecies (B6N, PWK, PWD) and a consomic strain (B6.DX.64-69A, B6.DX.64-69B). From: Lustyk D. et al. Genomic structucture of Hstx2 modifier of *Prdm9*-dependent hybrid male sterility (Genetics, Vol. 213, 1047–1063 November 2019).

Selected publications:

1. Valiskova B, Gregorova S, Lustyk D, Šimeček P, Jansa P, Forejt J*. Genic and chromosomal components of *Prdm9*-driven hybrid male sterility in mice (Mus musculus). Genetics. 2022 Aug 30;222(1):iyac116. doi: 10.1093/genetics/iyac116.
2. Forejt J*, Jansa P, Parvanov E. Hybrid sterility genes in mice (Mus musculus): a peculiar case of PRDM9 incompatibility. Trends Genet. 2021 Dec;37(12):1095-1108. doi: 10.1016
3. Gergelits V, Parvanov E, Simecek P, Forejt J*. Chromosome-wide characterization of meiotic noncrossovers (gene conversions) in mouse hybrids. Genetics. 2021 Mar 3;217(1):1-14. doi: 10.1093/genetics/iyaa013.
4. Mukaj A, Piálek J, Fotopulosova V, Morgan AP, Odenthal-Hesse L, Parvanov ED*, Forejt J*. *Prdm9* Intersubspecific Interactions in Hybrid Male Sterility of House Mouse. Mol Biol Evol. 2020 Dec 16;37(12):3423-3438. doi: 10.1093/molbev/msaa167. PMID: 32642764; PMCID: PMC7743643