Komparativní genomika a nemoci

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Brno

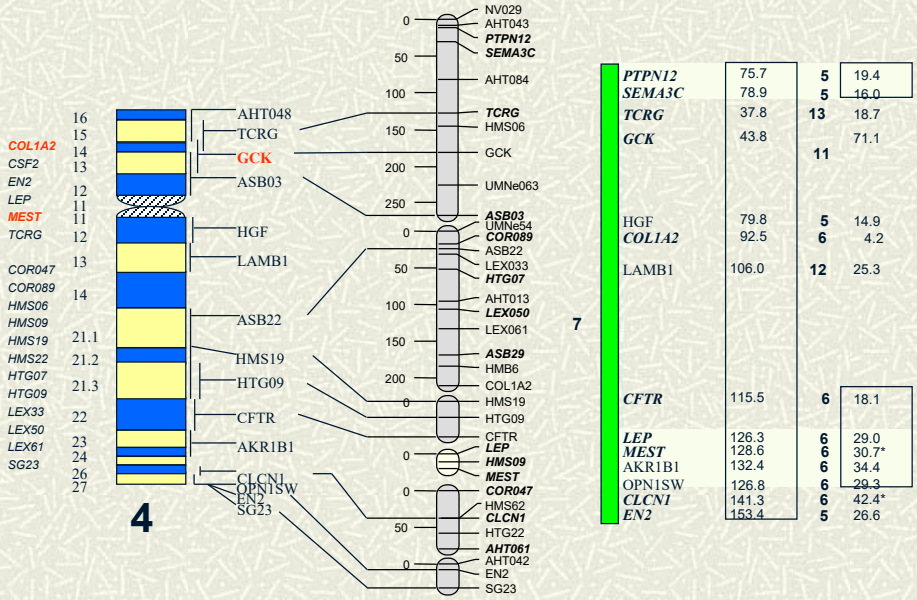
LF MU 2019

Biomodely: podobnost fenotypová

Van Eenennaam BMM 2/15/2012

Animal Biotechnology and Genomics Education

Animální modely a evoluce



Podobnost genomů

- ✓ *Celý genom: primáti: ~98-99%*
- ✓ *Celý genom: člověk myš: ~80%*
- ✓ *Ortologní geny: ~20-99%*

1atgtgcccgc cgcgcggcct cctccttgtg gccatcctgg tcctcctaaa ccacctggac 61
cacctcagtt tggccaggaa cctccccaca gccacaccag gcccaggaat gttccagtgc 121
ctcaaccact cccaaaacct gctgaggacc gtcagcaaca cgcttcagaa ggccaggcaa 181
accctagaat tctactcctg cacttctgaa gagatcgatc atgaggatat cacaaaagac 241
aagagcagca ccgtggcggc ctgcctcccc ctggaactcg ccccgaacga gagttgcctg 301
gcttccagag agatctcttt cataactaat gggagttgcc tgacccccgg aaaggcctct 361
tctatgatga cgctgtgcct tagcagcatc tatgaggact tgaagatgta ccaggtggag 421
ttcaaggcca tgaatgccaa gctgttgata gatcctcaga ggcagatctt tctggatgag 481
aacatgctga cagccattga caagctgatg caggccctga acttcaacag tgagactgtg 541
ccacaaaagc cctcccttga aggactggat ttttataaaa ctaaagtcaa gctctgcatc 601
cttcttcatg ccttcagaat ccgcgcagtg accatcaaca ggatgatggg ctatctgaat 661
gcttcctaa

Genomika a holistický přístup: Genom je víc než souhrn genů

Slide courtesy of Prof. Jamie McLeod, UK Lexington

Komparativní genomika

Srovnávací = *mezidruhová srovnání*

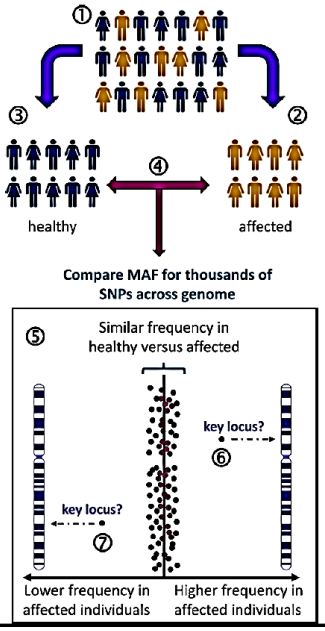
Genomika = *srovnání genomů*

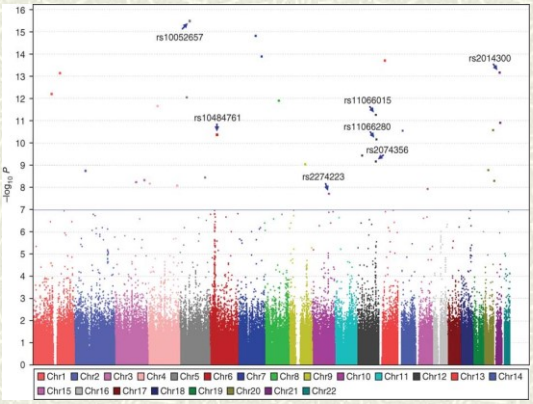
Význam

- ✓ ***Teoretický:*** *evoluce, adaptace, selekce*
- ✓ ***Praktický:*** *biomodely*

Aplikace:
GWAS a modelové komplexní znaky

Essays in Biochemistry (2018) **62** 643–723
https://doi.org/10.1042/EBC20170053

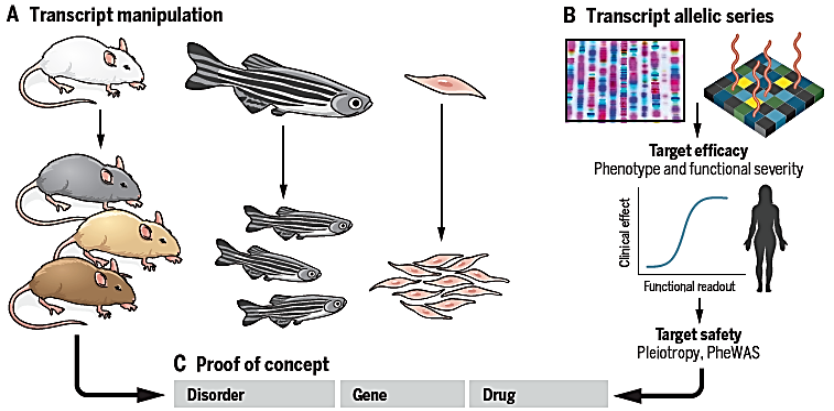





Published Genome-Wide Associations through 12/2012
Published GWA at p<5X10-8 for 17 trait categories
Digestive system disease
Cardiovascular disease
Metabolic disease
Immune system disease
Nervous system disease
Liver enzyme measurement
Lipid or lipoprotein measurement
Inflammatory marker measurement
Hematological measurement
Body measurement
Cardiovascular measurement
Other measurement
Response to drug
Biological process
Cancer
Other disease
Other trait
National Human Genome Research Institute
NHGRI GWA Catalog
www.genome.gov/GWAStudies
www.ebi.ac.uk/fgpt/gwas/ EMBL-EBI

GWAS a nové cíle terapie

Fig. 2. Identifying therapeutic targets. (**A**) Effector transcripts identified at genetic signals are genetically manipulated to recapitulate in vivo effects on gene expression (e.g., CRIPSR knockdown or overexpression) in human cell lines (e.g., iPS cell–derived models) and in animal models, which can be phenotyped. (**B**) Additional alleles are identified using sequence data and assessed for their relationship to disease risk or related traits. To provide insight into the therapeutic window, in vitro functional severity and clinical severity are explored to establish the relationship between target perturbation and outcome. Potential adverse on-target effects are investigated using genome-wide datasets for other disorders [phenome-wide association studies (PheWAS)]. (**C**) Examples of therapeutic targets confirmed or identified by human GWAS.



C Proof of concept

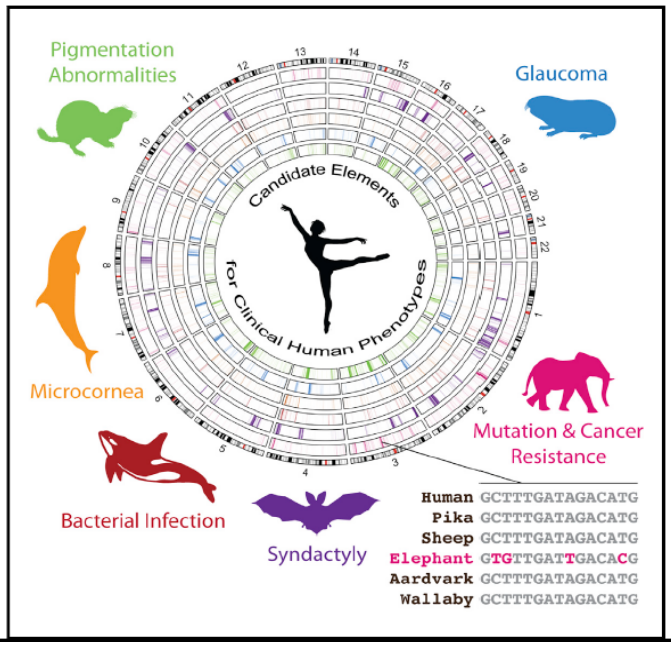
Disorder	Gene	Drug
Type 2 Diabetes	*KCNJ11/ABCC8*	Sulphonylureas
Type 2 Diabetes	*PPARG*	Thiazolidinediones
Type 2 Diabetes	*SLC30A8*	ZnT8 antagonists
Osteoarthritis	*TGFB1*	INVOSSA
Hypocholesterolemia	*PCSK9*	PCSK9 inhibitors
Psoriasis	*IL23, IL23A*	Risankizumab

Zeggini *et al.*, *Science* 365, 1409–1413 (2019) 27 September 2019

Cell Reports

Accelerated Evolution in Distinctive Species Reveals Candidate Elements for Clinically Relevant Traits, Including Mutation and Cancer Resistance

Graphical Abstract



Authors

Elliott Ferris, Lisa M. Abegglen, Joshua D. Schiffman, Christopher Gregg

Correspondence

chris.gregg@neuro.utah.edu

In Brief

Ferris et al. report an analysis of accelerated evolution in the elephant, little brown bat, big brown bat, orca, dolphin, naked mole rate, and thirteen-lined ground squirrel that reveals candidate functional genomic elements for shaping somatic mutation rate, cancer risk, digit development, immunity, glaucoma, pigmentation, and other clinical phenotypes.

Cell Reports 22, 2742–2755, March 6, 2018

Komparativní genomika a biomodely

- ✓ ***Evoluce:*** *mechanismy fylogeneze, speciace*
- ✓ ***Struktura:*** *sekvenční podobnost, homologie, ortologie, identifikace genů a genových drah*
- ✓ ***Společné mutace:*** *biomodely nemocí i normální variability*

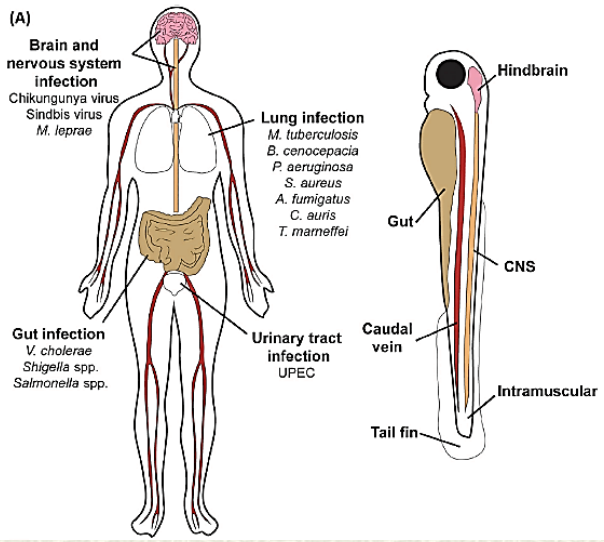
Animální modely

- Laboratorní modely: *hlodavci, Nematoda, Dánio, Drosophila*
- Domácí zvířata: *pes, prase, kůň, kočka atd.*

Netradiční laboratorní modely

Key Figure

Human Infections Studied in Zebrafish



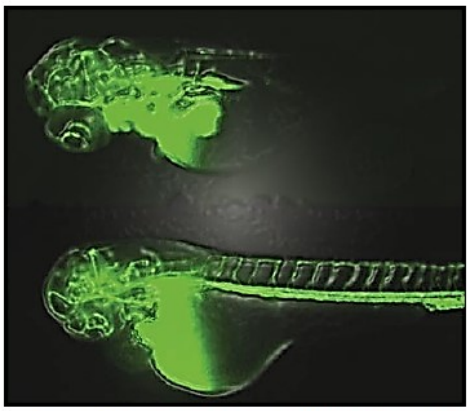


Image courtesy of Randall Peterson, Harvard Medical School and Massachusetts General Hospital, Boston, MA.

Fluorescent microangiograms of zebrafish homozygous for the gridlock mutation, which models human coarctation of the aorta. The vascular defect apparent in the upper embryo has been corrected in the lower embryo by treatment with the small molecule GS4012.

Netradiční laboratorní modely

SCIENTIFIC REPORTS

OPEN

Highly conserved molecular pathways, including Wnt signaling, promote functional recovery from spinal cord injury in lampreys

Received: 6 February 2017
Accepted: 18 December 2017
Published online: 15 January 2018

Paige E. Herman[1], Angelos Papatheodorou[1], Stephanie A. Bryant[1], Courtney K. M. Waterbury[1], Joseph R. Herdy[1], Anthony A. Arcese[1], Joseph D. Buxbaum[1], Jeramiah J. Smith[2], Jennifer R. Morgan[1] & Ona Bloom[1]

Laboratory Mouse

Education

Caltech, Oxford, Stanford, Harvard, MIT, Princeton, Cambridge, Imperial, Berkeley, Chicago, Yale, ETH Zurich, Columbia, UPenn, John Hopkins, UCL, Cornell, Northwestern, UMichigan, Toronto, Carniege Mellon, Duke, UWashington, UTexas at Austin, GA Tech, Tokyo, Melbourne, Singapore, UBC, Wisconsin-Madison, Edinburgh, McGill, Hong Kong, Santa Barbara, Karolinska Institute, UMinnesota, Manchester ... and just about every other major university, medical school & research institution in the world.

Nobel Prizes

1905 - Transmission and treatment of TB
1906 - Structure of Nervous System
1907 - Role of protozoa in disease
1908 - Immunity to infectious diseases
1928 - Investigations on typhus
1929 - Importance of dietary vitamins
1939 - Discovery of antibacterial agent, Prontosil
1945 - Discovery of penicillin
1951 - Yellow fever vaccine
1952 - Discovery of streptomycin
1954 - Culture of the polio virus
1960 - Understanding of immunity
1970 - Understanding of neurotransmitters
1974 - Structural & functional organisation of cells
1975 - Tumour-viruses and genetics of cells
1977 - Hypothalamic hormones
1984 - Techniques of monoclonal antibody formation
1986 - Nerve growth factor and epidermal growth factor
1990 - Organ transplantation techniques
1992 - Regulatory mechanisms in cells
1996 - Immune-system detection of virus-infected cells
1997 - Discovery and characterisations of prions
1999 - Discovery of signal peptides
2000 - Signal transduction in the nervous system
2004 – Odour receptors and organisation of olfactory systems
2008 - Role of HPV and HIV in causing disease
2010 - Development of in vitro fertilization
2011 - Discoveries around innate and adaptive immunity

Overview

- Involved in around 75% of research
- Short life-span and fast reproductive rate means mice are suitable for studying disease across whole life cycle
- 98% of genes have comparable genes in humans
- Similar reproductive and nervous systems and suffer many of the same diseases as humans including cancer diabetes and anxiety
- Can be genetically modified to include human genes in enhance biological relevance
- Can act as an avatar for a human cancer to allow drug therapies to be trialled safely

Research Areas

Alzheimer's disease, anaesthetics, AIDS & HIV, anticoagulants, antidepressants, asthma, blindness, bone and joint disease, brain injury, breast cancer, cardiac arrest, cystic fibrosis, deafness/hearing loss, Down's sndrome, drugs for high blood pressure, transplant rejection, Hepatitis B, C & E, Huntington's disease, influenza, leukaemia, malaria, motor neurone disease, multiple sclerosis, muscular dystrophy, Parkinson's disease, prostate cancer, schistomiasis, spinal cord injury, stroke, testicular cancer, tuberculosis,

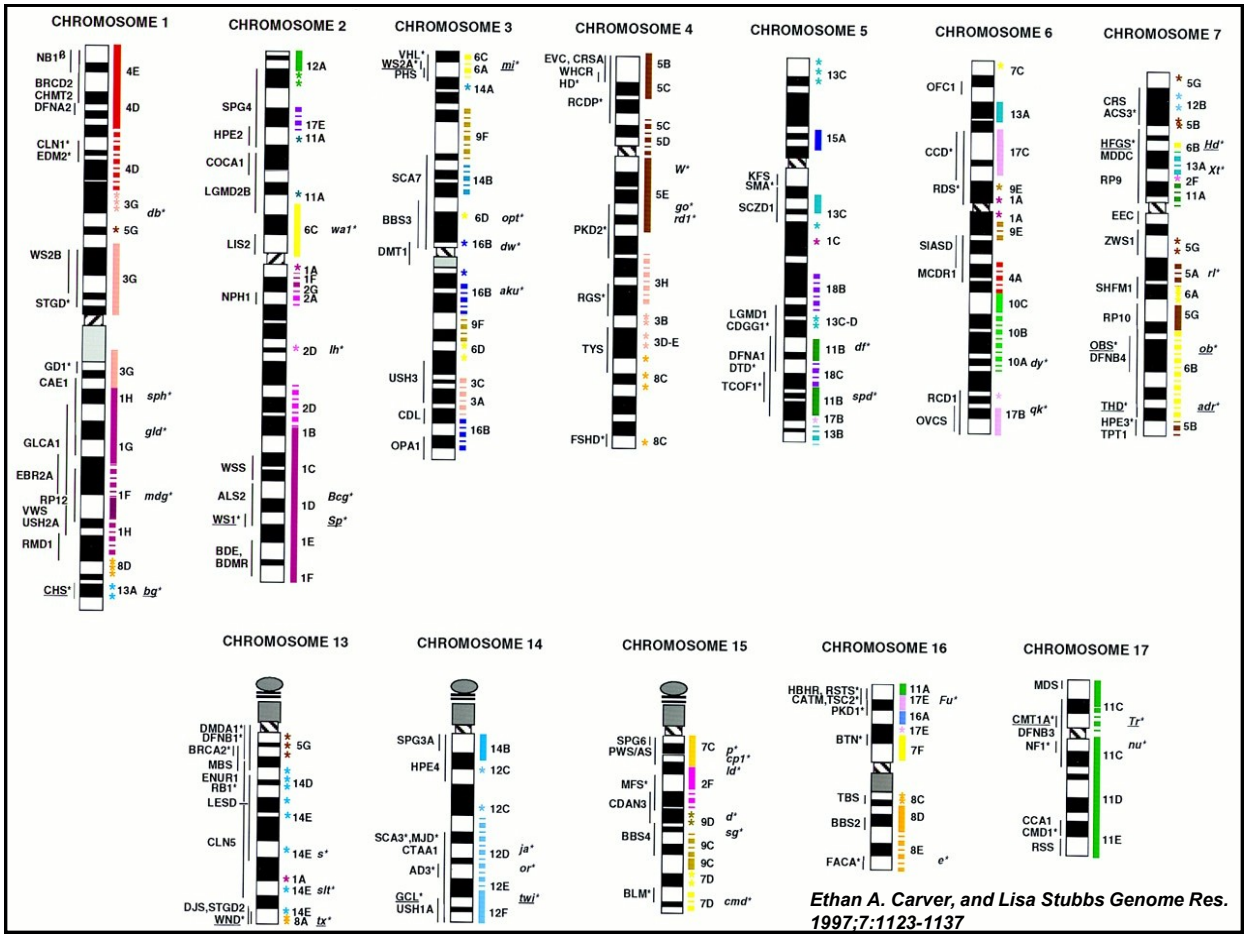
CV of a Lifesaver

Contact

www.understandinganimalresearch.org.uk
www.animalresearch.info
www.amprogress.org
www.speakingofresearch.com

Myš jako model lidských onemocnění

- *http://www.cmhd.ca/databases/index.html*
- *http://www.informatics.jax.org/*
- *http://www.mouseclinic.de/*


CHROMOSOME 1
CHROMOSOME 2
CHROMOSOME 3
CHROMOSOME 4
CHROMOSOME 5
CHROMOSOME 6
CHROMOSOME 7
CHROMOSOME 13
CHROMOSOME 14
CHROMOSOME 15
CHROMOSOME 16
CHROMOSOME 17
Ethan A. Carver, and Lisa Stubbs Genome Res. 1997;7:1123-1137

Inbrední modely: princip

Isogenní (syngenní) kmeny

AA bb x aa BB

AaBb

AABB AAbb aaBB aabb

Genomická definice kmenů laboratorních zvířat

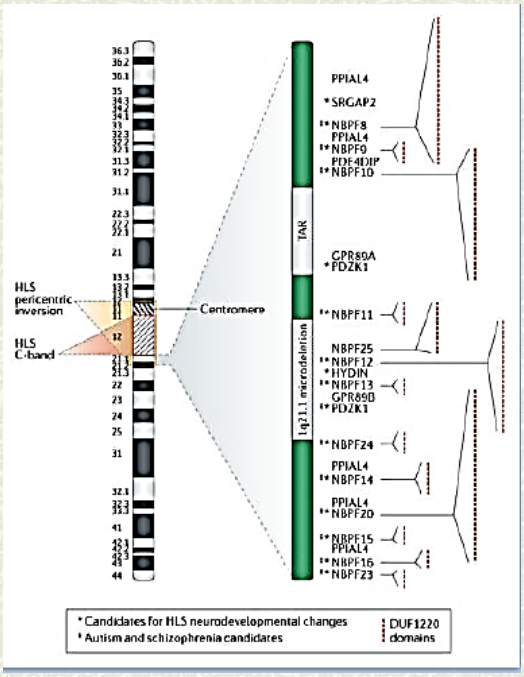
Kmeny/linie LZ (myší/LZ)

International Mouse Strain Resource Center (IMSR)

http://www.findmice.org/

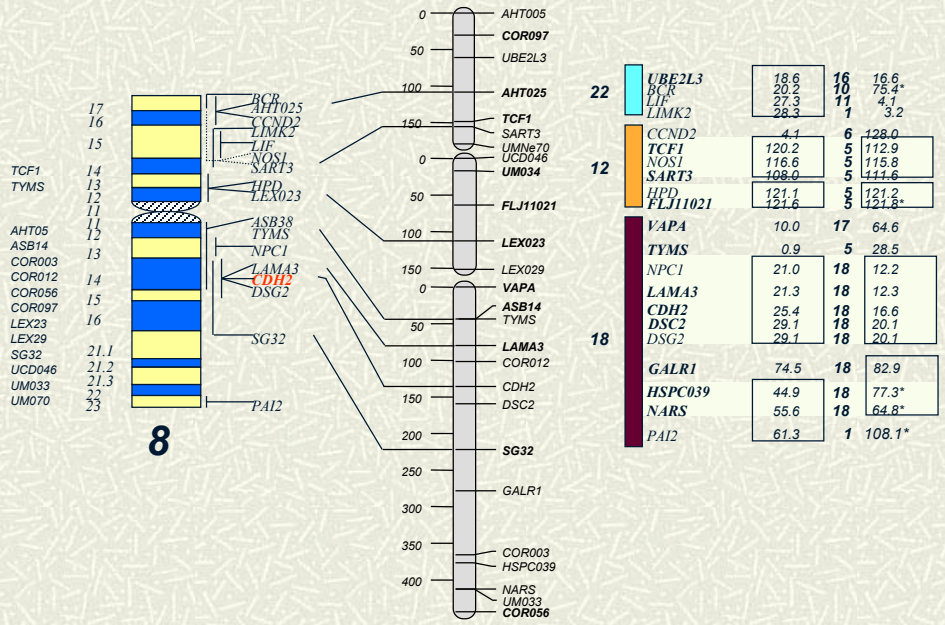
- ***Existující: >24.000***
- ***Potenciál: 200.000***

Animální modely a evoluce

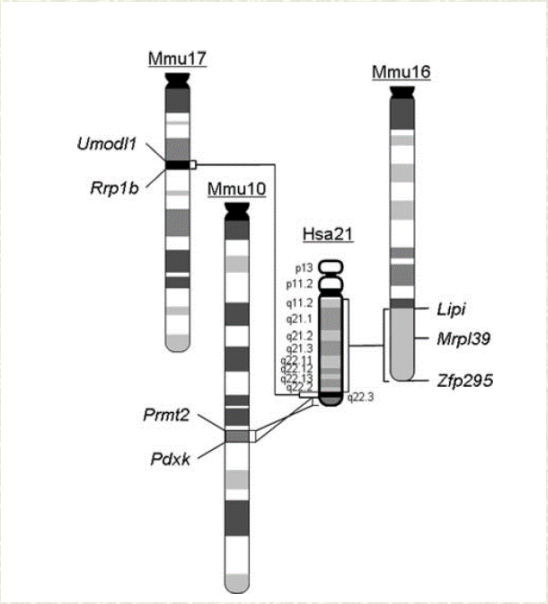


O´Bleness et al. 2012

Komparativní genomika: kůň a člověk



Animální modely a evoluce: Myší model *Downova syndromu*



➢ *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2893810/*

Domácí zvíře jako model

1. **Domestikace jako „evoluce v akci“**
2. **Model lidských znaků (nemocí)**
   (psi a nádory, kočky a 250 analogů lidských nemocí)
1. **Model rychlé aplikace základní vědy do praxe**

Domestikace: neolitická revoluce

The most important technological development ever to occur in human history was the domestication of plants (agriculture) and animals (pastoralism). Together these developments are called the Neolithic Revolution and they allowed the development of urban centers (towns and, later, cities), trade and most of the other things we consider to be components of "civilization."

http://www.rivervalleycivilizations.com/neolithic.php

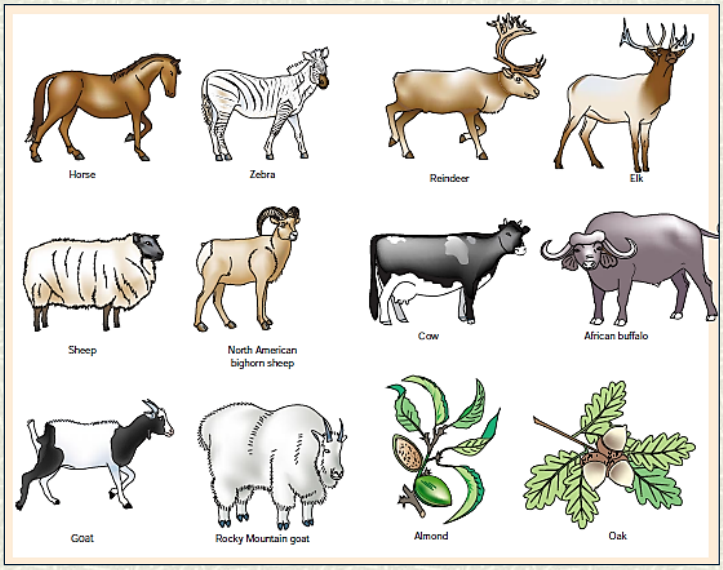
Příklad: domácí pes

Domestikace psa

1. **Ochočení**
2. **Adaptace na novou dietu**
3. **Selekce na další (extrémní) znaky**

Figure 1
Geographic origins and age of the oldest validated fossil dog specimens in Eurasia. Points are dog fossil sites, with colors indicating their age. Modified from Frantz et al. (32) with permission from AAAS.

Comparisons of domesticated wild species (left of each pair) and their never-domesticated close relatives (right)



Daimond Nature 2002

Geny a ochočení

SCIENCE ADVANCES | RESEARCH ARTICLE

GENETICS

Structural variants in genes associated with human Williams-Beuren syndrome underlie stereotypical hypersociability in domestic dogs

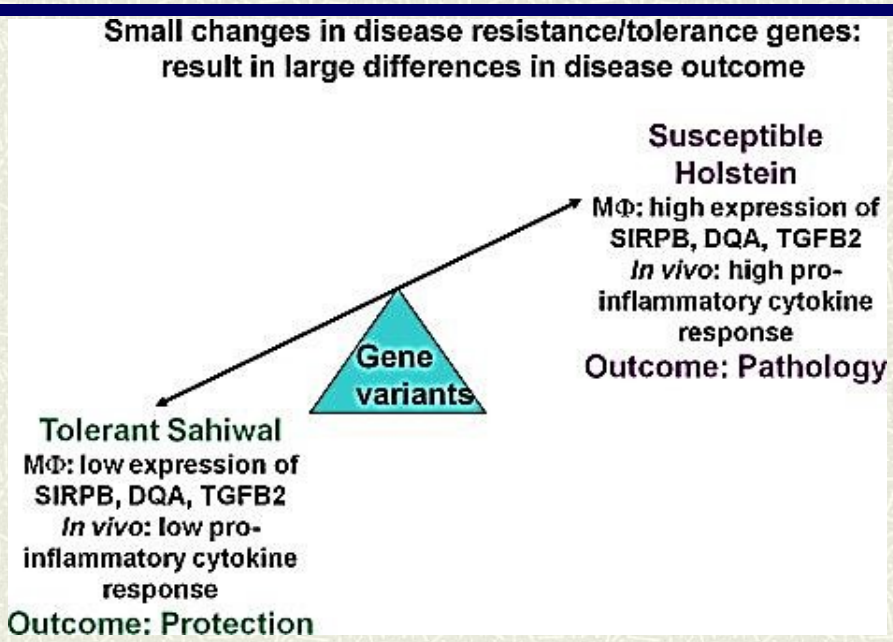
Bridgett M. vonHoldt,[1]*† Emily Shuldiner,[1,2]* Ilana Janowitz Koch,[1] Rebecca Y. Kartzinel,[1] Andrew Hogan,[3] Lauren Brubaker,[4] Shelby Wanser,[4] Daniel Stahler,[5] Clive D. L. Wynne,[6] Elaine A. Ostrander,[3] Janet S. Sinsheimer,[7] Monique A. R. Udell[4]

Although considerable progress has been made in understanding the genetic basis of morphologic traits (for example, body size and coat color) in dogs and wolves, the genetic basis of their behavioral divergence is poorly understood. An integrative approach using both behavioral and genetic data is required to understand the molecular underpinnings of the various behavioral characteristics associated with domestication. We analyze a 5-Mb genomic region on chromosome 6 previously found to be under positive selection in domestic dog breeds. Deletion of this region in humans is linked to Williams-Beuren syndrome (WBS), a multisystem congenital disorder characterized by hypersocial behavior. We associate quantitative data on behavioral phenotypes symptomatic of WBS in humans with structural changes in the WBS locus in dogs. We find that hypersociability, a central feature of WBS, is also a core element of domestication that distinguishes dogs from wolves. We provide evidence that structural variants in *GTF2I* and *GTF2IRD1*, genes previously implicated in the behavioral phenotype of patients with WBS and contained within the WBS locus, contribute to extreme sociability in dogs. This finding suggests that there are commonalities in the genetic architecture of WBS and canine tameness and that directional selection may have targeted a unique set of linked behavioral genes of large phenotypic effect, allowing for rapid behavioral divergence of dogs and wolves, facilitating coexistence with humans.

Domácí zvířata jako biomodel

- ✓ *Vysoká fenotypová diversita a menší genetická heterogenita než u lidí*
- ✓ *Plemena vs. inbrední kmeny*
- ✓ *Mnoho homologických i analogických nemocí*

Plemena domácích zvířat vs. laboratorní modely



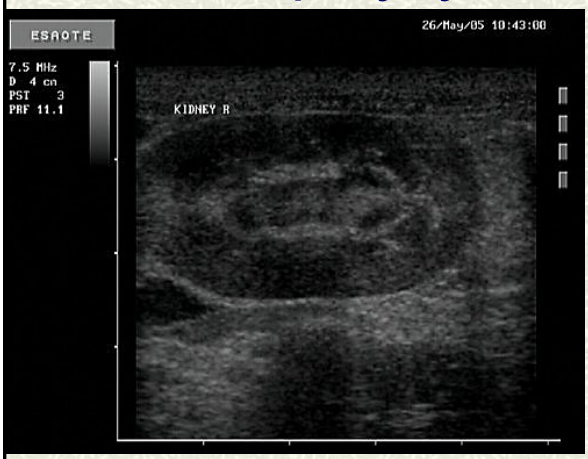
Glass et al. Vet Immunol Immunopathol 2012

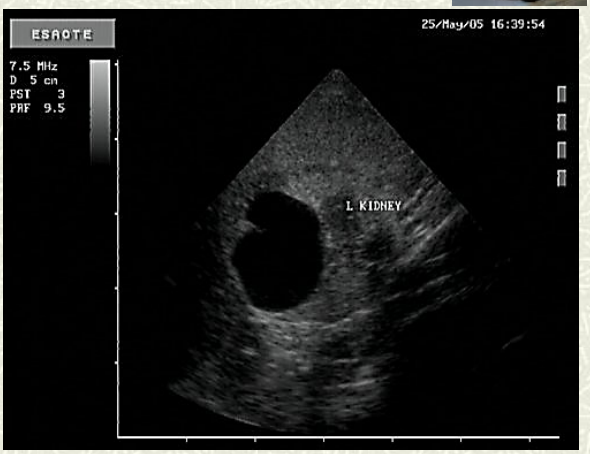
Příklady zvířecích modelů a možnosti extrapolace na lidský organismus

1. Monogenní dědičné nemoci
2. Komplexní nemoci
3. Genetická vnímavost k nemocem

Zvířecí modely monogenních dědičných nemocí

PKD – polycystic kidney disease

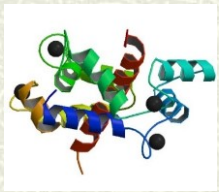




Stejná biologická podstata, stejné projevy, stejná dědičnost

Zvířecí modely monogenních dědičných nemocí

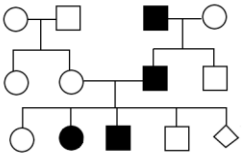
Syndrom maligní hypertermie



Stejná biologická podstata, jiný kontext, jiné projevy

Monogenní mutace

Stejná biologická podstata, jiné projevy - populace



Dominantní vs. recesivní choroby

Zvířecí modely komplexních nemocí

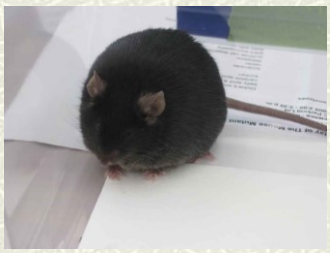


Table 2. Swine Biomedical Models

Model	*Current Ref.*
• **Heart physiology**	
○ Stent design, tissue engineering of blood vessels	[25, 26]
○ Atherosclerosis	[9, 10]
○ Myocardial infarction	[27, 28]
○ Ex vivo heart model	[29]
○ Emergency procedures	[30, 31]
• **Reproductive function**	
○ Maternal-fetal interactions	[14]
○ Embryo development	[15-17]
○ Sperm	[20, 21]
• **Transplantation**	
○ Cell and organ transplants	[32, 33]
○ Xenotransplantation	[5, 34, 35]
○ Drug therapies and biotherapeutics	
• **Skin physiology**	
○ Percutaneous permeation	[36, 37]
○ Contact dermatitis	[38]
○ Skin equivalent culture model	[39]
○ Melanoma	[40,41]
• **Brain**	
○ Stroke - focal cerebral ischemia	[42]
○ AIDS dementia - Multinucleated giant cell formation	[43]
○ Drug binding sites and interactions	[44]
• **Gut physiology and Nutrition**	
○ Gut structure and intestinal metabolism	[45, 46]
○ Obesity	[47]
○ Probiotics and gut physiology	[48, 49]
○ Biologic and immunological basis of food allergies	[50, 51]
• **Biomechanical models**	
○ Response to injury	[52]
○ Imaging techniques	[53, 54]
○ Bone density analyses - Osteoporosis	[55]
• **Tissue engineering**	
○ Cartilage repair - chondrocytes	[56]
○ Spinal fusion	[57]
○ Organ specific gene delivery	[58]
○ Lens capsule epithelial cells for cataract repairs	[59, 60]
○ Polymer scaffolds	[61, 62]
○ Tooth development - dental enamel	[63]
• **Respiratory function**	
○ Neonatal respiratory distress	[64]
○ Thoracic artificial lung	[65]
○ Disease models and therapies: Asthma	[66,67]
• **Infectious disease models**	
○ Therapeutics: Vaccines, Biotherapeutics, Drug therapies	[68, 69]
○ Developmental Interactions	[70, 71]
○ Mucosal tissue responses	[72-75]
○ Genomics of host responses	[76]

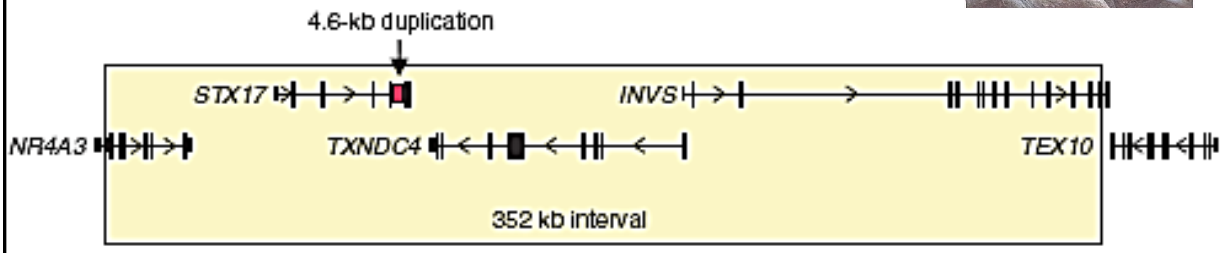
Zvířecí modely komplexních nemocí

Melanom

nature genetics

A *cis*-acting regulatory mutation causes premature hair graying and susceptibility to melanoma in the horse

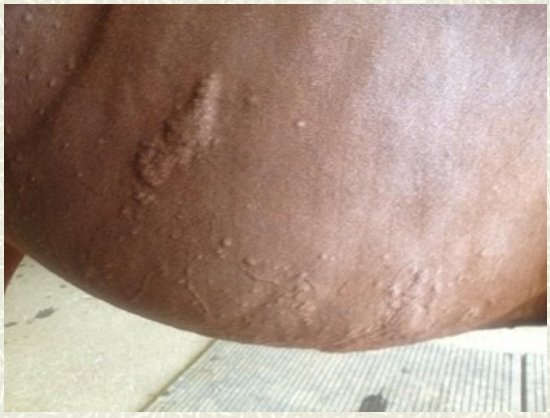
Gerli Rosengren Pielberg[1], Anna Golovko[1,12], Elisabeth Sundström[2,12], Ino Curik[3], Johan Lennartsson[4], Monika H Seltenhammer[5], Thomas Druml[6], Matthew Binns[7], Carolyn Fitzsimmons[1], Gabriella Lindgren[2], Kaj Sandberg[2], Roswitha Baumung[6], Monika Vetterlein[8], Sara Strömberg[9], Manfred Grabherr[10], Claire Wade[10,11], Kerstin Lindblad-Toh[1,10], Fredrik Pontén[9], Carl-Henrik Heldin[4], Johann Sölkner[6] & Leif Andersson[1,2]

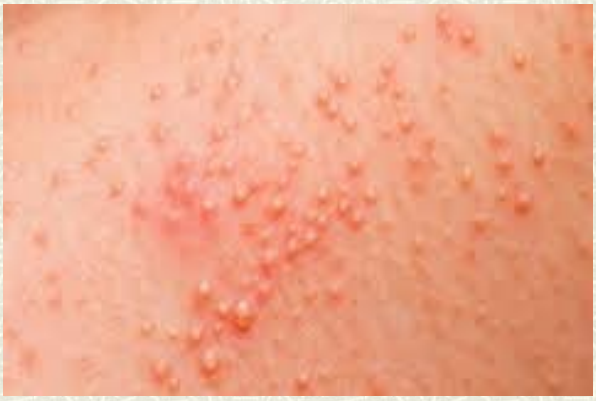


Příklad neinformativní podobnosti

Zvířecí modely komplexních nemocí

Atopická dermatitida

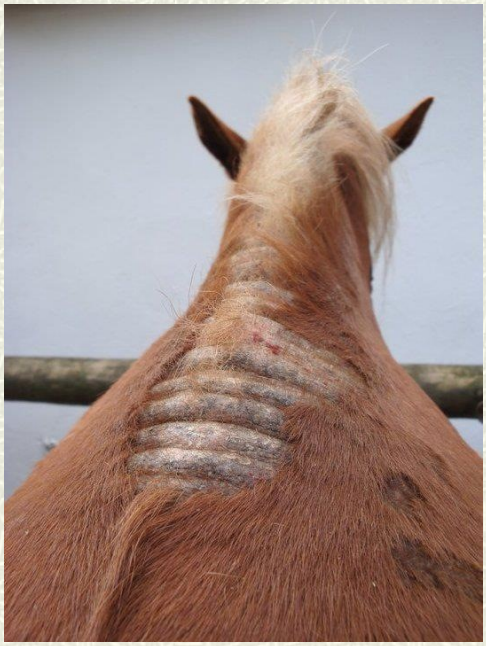




Stejné projevy, stejný mechanismus, stejné geny


Letní dermatitida islandských koní

Letní dermatitida islandských koní



Zvířecí modely komplexních nemocí

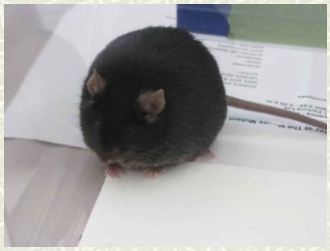
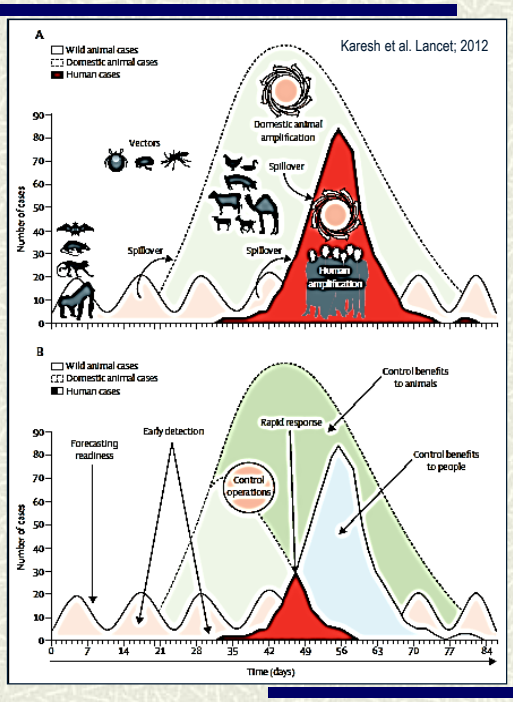


Table 2. Swine Biomedical Models

Model	*Current Ref.*
• **Heart physiology**	
○ Stent design, tissue engineering of blood vessels	[25, 26]
○ Atherosclerosis	[9, 10]
○ Myocardial infarction	[27, 28]
○ Ex vivo heart model	[29]
○ Emergency procedures	[30, 31]
• **Reproductive function**	
○ Maternal-fetal interactions	[14]
○ Embryo development	[15-17]
○ Sperm	[20, 21]
• **Transplantation**	
○ Cell and organ transplants	[32, 33]
○ Xenotransplantation	[5, 34, 35]
○ Drug therapies and biotherapeutics	
• **Skin physiology**	
○ Percutaneous permeation	[36, 37]
○ Contact dermatitis	[38]
○ Skin equivalent culture model	[39]
○ Melanoma	[40,41]
• **Brain**	
○ Stroke - focal cerebral ischemia	[42]
○ AIDS dementia - Multinucleated giant cell formation	[43]
○ Drug binding sites and interactions	[44]
• **Gut physiology and Nutrition**	
○ Gut structure and intestinal metabolism	[45, 46]
○ Obesity	[47]
○ Probiotics and gut physiology	[48, 49]
○ Biologic and immunological basis of food allergies	[50, 51]
• **Biomechanical models**	
○ Response to injury	[52]
○ Imaging techniques	[53, 54]
○ Bone density analyses - Osteoporosis	[55]
• **Tissue engineering**	
○ Cartilage repair - chondrocytes	[56]
○ Spinal fusion	[57]
○ Organ specific gene delivery	[58]
○ Lens capsule epithelial cells for cataract repairs	[59, 60]
○ Polymer scaffolds	[61, 62]
○ Tooth development - dental enamel	[63]
• **Respiratory function**	
○ Neonatal respiratory distress	[64]
○ Thoracic artificial lung	[65]
○ Disease models and therapies: Asthma	[66,67]
• **Infectious disease models**	
Therapeutics, Vaccines, Biotherapeutics, Drug-Receptors	[68, 69]
○ Developmental Interactions	[70, 71]
○ Mucosal tissue responses	[72-75]
○ Genomics of host responses	[76]

Infekce, zvířata a lidé: genetika vnímavosti

- ✓ *Více než 60% lidských infekčních onemocnění je způsobeno patogeny společnými pro divoce žijící nebo domestikované druhy zvířat* *(Karesh et al. 2012)*
- ✓ *Předpoklad podobných mechanismů odolnosti a vnímavosti*



Příklad: bakteriální zoonózy

Anaplasma phagocytophilum
Bacillus anthracis
Bartonella sp.
Borrelia sp.
Brucella sp.
Burkholderia sp.
Campylobacter sp.
Capnocytophaga sp.
Chlamydophyla
Clostridium sp.
Corynebacterium ulcerans
Coxiella
Ehrlichia sp.
Escherichia coli

Francisella tularensis
Helicobacter sp
Leptospira sp.
Listeria sp.
Mycobacterium sp.
Orientia tsutsugamushi
Pasteurella sp.
Rickettsia sp.
Salmonella sp.
Shigella sp.
Staphylococcus aureus
Streptococcus sp.
Vibrio sp.
Yersinia sp.

Christou, Clin Microbiol Infect 2011

Table 1 | **Farm animal models for human pathogens or diseases**

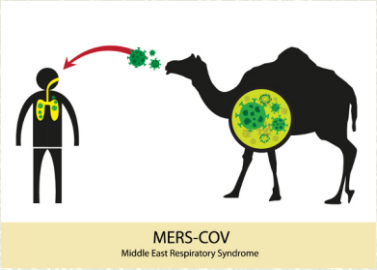
Animal pathogen	Farm animal hosts	Human disease or pathogen	Examples of studied disease processes
Bovine papilloma viruses	Cattle	Human papilloma viruses	Latency mechanisms of papilloma viruses and vaccine development
Bovine respiratory syncytial virus	Cattle (calves)	Human respiratory syncytial virus	Vaccine development
Caprine arthritis encephalitis virus and Visna/maedi virus	Goats and sheep	HIV	Genetic susceptibility and lentivirus–host adaptation
Cryptosporidium parvum	Cattle (calves) and swine (piglets)	*Cryptosporidium parvum*	Therapeutic treatment testing and clinical responses to diverse strains
Hepatitis E virus	Swine and chickens	Hepatitis E	Mechanisms of pathogenesis and vaccine development
Marek's disease virus	Chickens	Virus-induced lymphoma	The role of immune control and evasion in neoplasma formation and mechanisms of virus-induced lymphoma
Mycobacterium bovis	Cattle, goats and swine	Human tuberculosis	Mechanisms of pathogenesis, host defences and vaccine development
Salmonella enterica	Cattle (calves)	Human enteritis	The role of virulence factors on infection and *S. enterica* pathogenesis

Lanzas et al. Nature Reviews 2010

Koronaviry

SARS

MERS

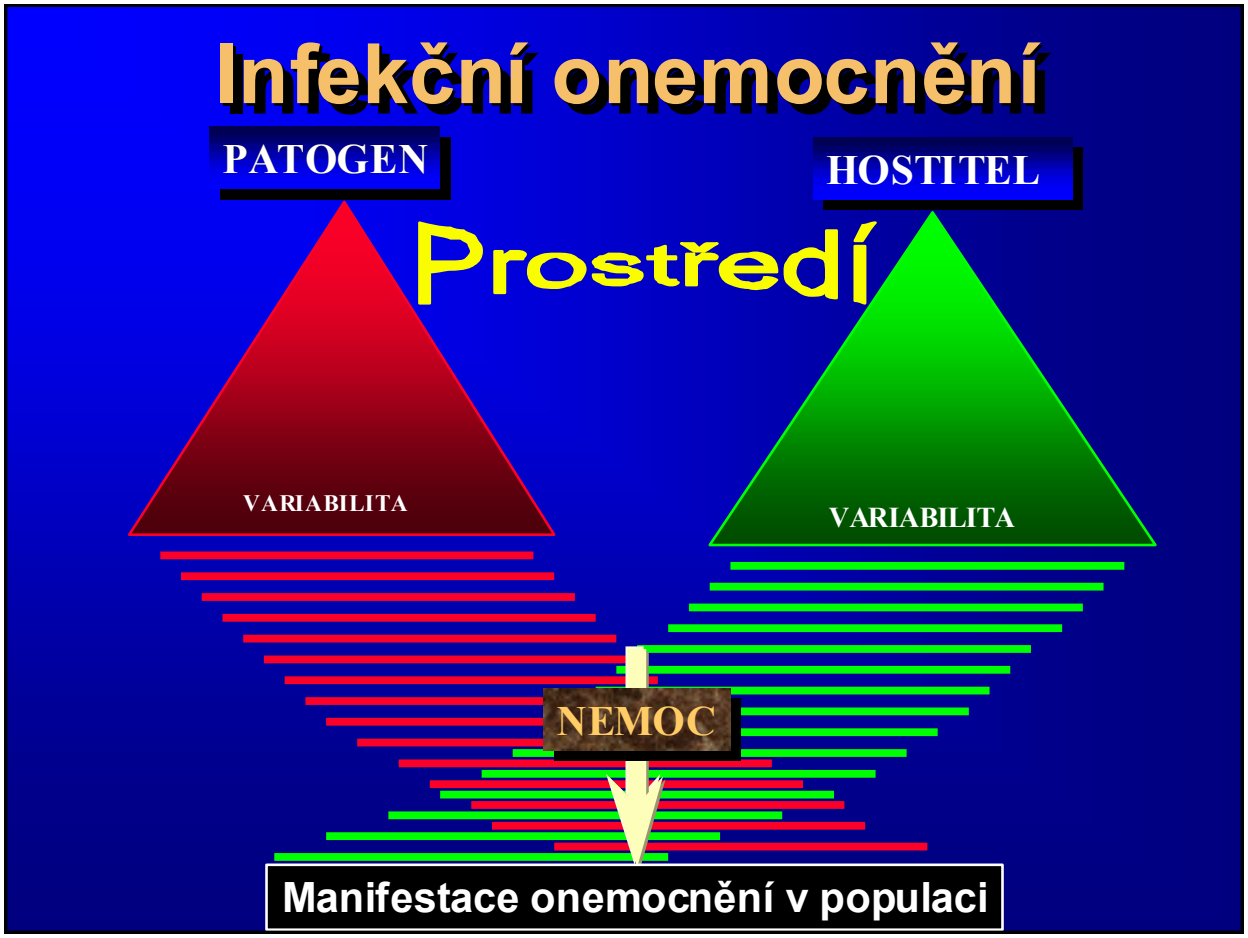


SARS-CoV-2

Nemoc

Reakce organismu na patogenní noxu

Ovlivněná charakterem noxy, prostředím a aktuálním stavem organismu a jeho genetickým založením


Infekční onemocnění
PATOGEN
HOSTITEL
Prostředí
VARIABILITA
VARIABILITA
NEMOC
Manifestace onemocnění v populaci

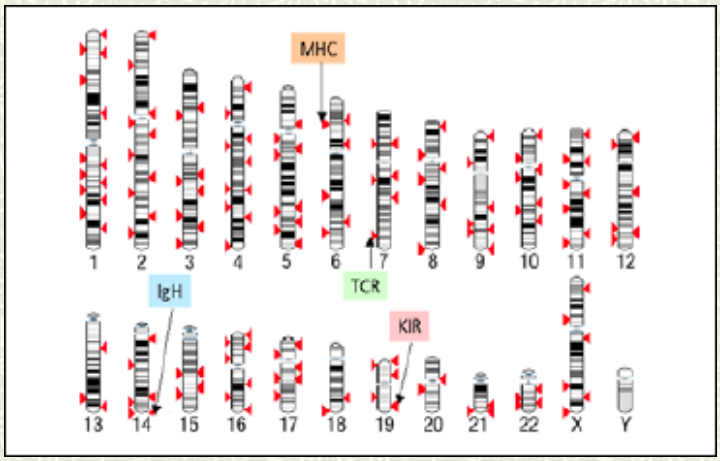
Biologický princip

Nemoc, selekce, adaptace, evoluce:

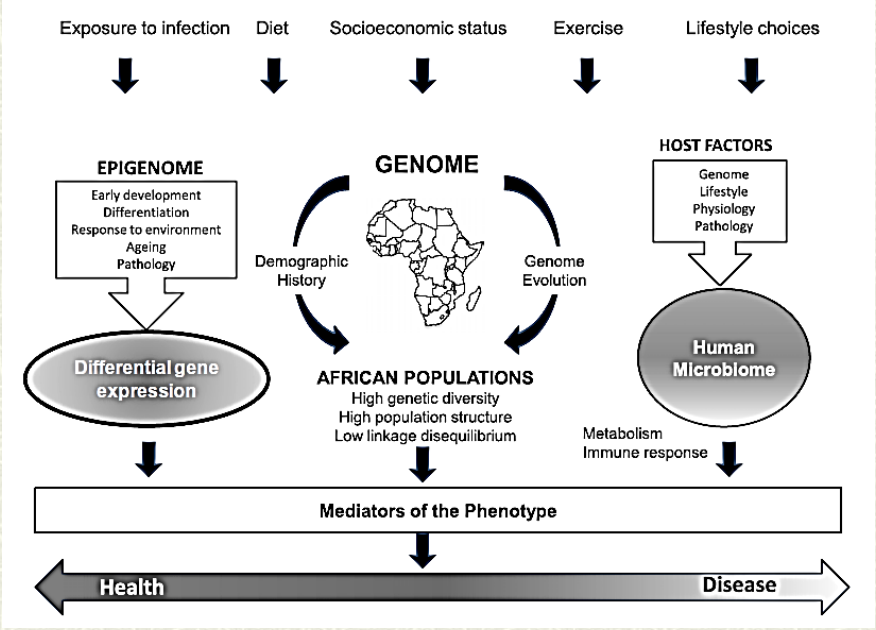
Genetická variabilita reakce na patogeny je výsledkem evolučních interakcí mezi hostitelem a patogenem

Hostitel

Imunogenom: 5% genomu



Genetika vnímavosti k infekcím

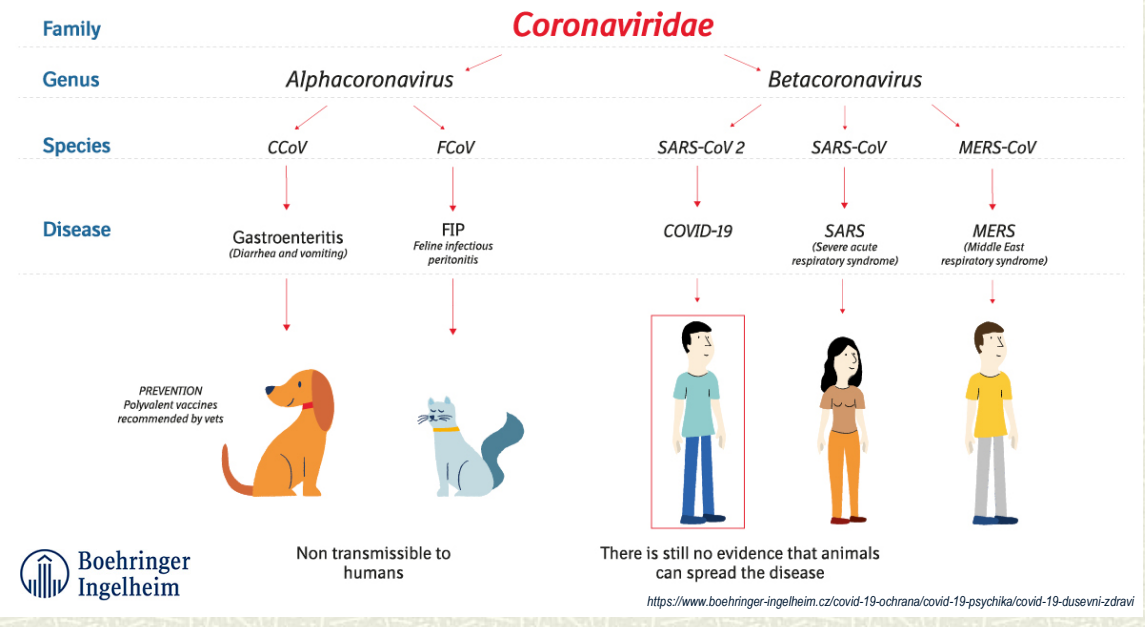


Ramsay FEBS Lett 2012

Příklady

- ✓Noroviry, rotaviry (*FUT2)*
- ✓AIDS (CCR5)
- ✓Malárie (Duffy)
- ✓*COVID 19 (AB0, IFN typ 1)*

Koronaviry


Family
Coronaviridae
Genus
Alphacoronavirus
Betacoronavirus
Species
CCoV
FCoV
SARS-CoV 2
SARS-CoV
MERS-CoV
Disease
Gastroenteritis
(Diarrhea and vomiting)
FIP
Feline infectious peritonitis
COVID-19
SARS
(Severe acute respiratory syndrome)
MERS
(Middle East respiratory syndrome)
PREVENTION
Polyvalent vaccines recommended by vets
Boehringer Ingelheim
Non transmissible to humans
There is still no evidence that animals can spread the disease
https://www.boehringer-ingelheim.cz/covid-19-ochrana/covid-19-psychika/covid-19-dusevni-zdravi

Koronaviry

INVITED REVIEW
Immunological Reviews WILEY

The role of host genetics in the immune response to SARS-CoV-2 and COVID-19 susceptibility and severity

Inna G. Ovsyannikova | Inna H. Haralambieva | Stephen N. Crooke | Gregory A. Poland | Richard B. Kennedy

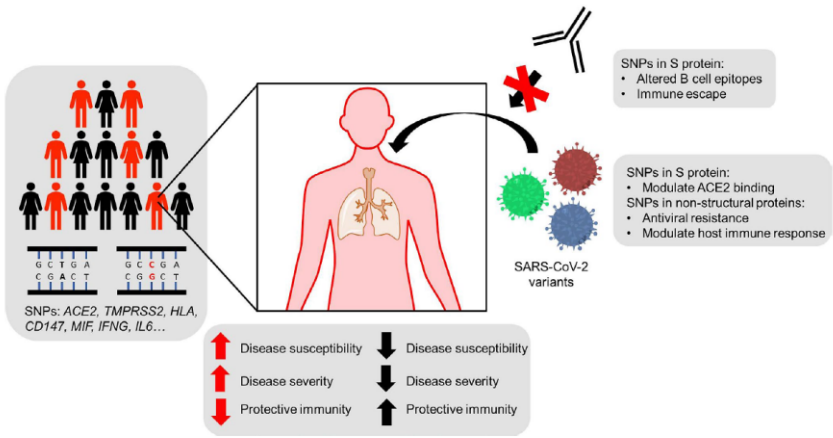
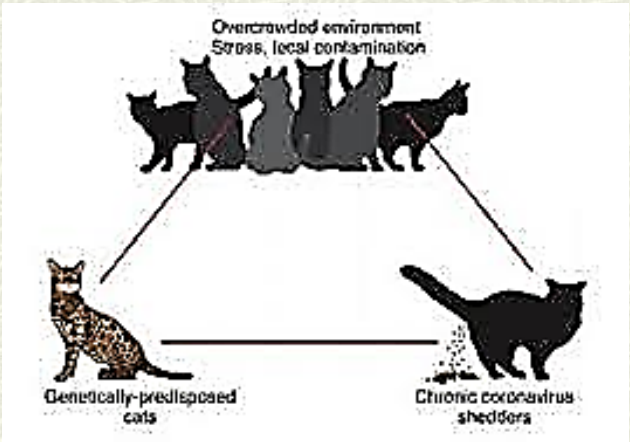
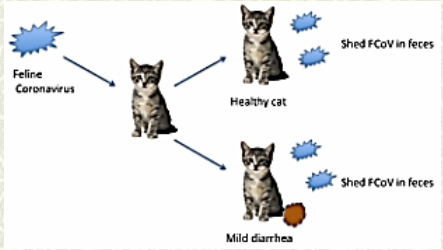
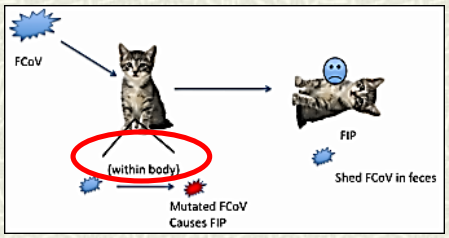


FIGURE 1 The impact of host genetics and viral variation on SARS-CoV-2 infection and COVID-19 severity. Individuals in the population harbor single nucleotide polymorphisms (SNPs) across a variety of genes (eg, *ACE2*, *TMPRSS2*, *HLA*, *CD147*, *MIF*, *IFNG*, *IL6*) that have been implicated in the pathology and immunology of SARS-CoV-2 and other pathogenic coronaviruses. These and other genetic variants may modulate disease susceptibility, increase or decrease disease severity, alter the variety of symptoms developed, and affect the magnitude and/or quality of the immune responses against SARS-CoV-2. In addition to host genetic variation, genetic variants of SARS-CoV-2 (and other pathogenic coronaviruses) can exhibit differences in biological activity. Single amino acid mutations in the spike glycoprotein can modulate ACE2 binding or alter B cell epitopes to promote immune escape or render monoclonal antibodies ineffective, while mutations in non-structural/accessory proteins can promote the development of resistance to antivirals, alter T cell epitopes, disrupt cell mediated immunity, and modulate host cellular interactions with viral particles

Feline Infectious Peritonitis







Podobné patogeny, Ortologní geny

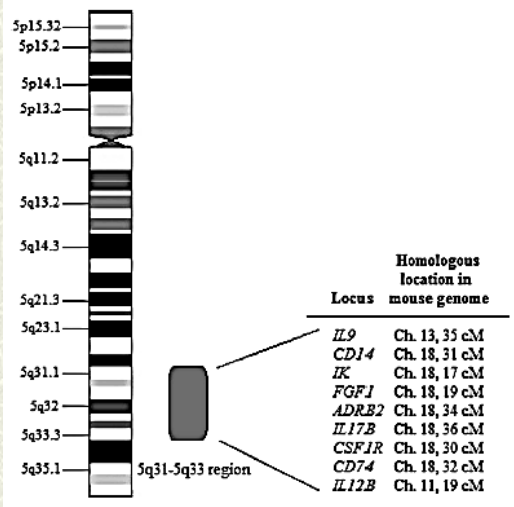


Fig. 3. Location of the 5q31-q33 region on chromosome 5 linked to the control parasitic levels in human malaria. Candidate genes and their homologous locations in the mouse genome are shown at *right*. The figure was drawn with the chromosome design and information based on National Center for Biotechnology Information (177) and Ensembl (22) data.

Malárie, chřipka

DOI:10.1111/irv.12079
www.influenzajournal.com
Stream 2: Review Update

An updated systematic review of the role of host genetics in susceptibility to influenza

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The World Health Organization has identified studies of the role of host genetics on susceptibility to severe influenza as a priority. A systematic review was conducted in June 2011 to summarise the evidence on the role of host genetics in susceptibility to influenza, and this report updates that previously published review. Animal studies suggest that genetic control of susceptibility to severe influenza in mice is complex and not controlled by a single locus, but there is encouraging evidence that some of the host genetic determinants of susceptibility to severe disease may be common across influenza subtypes. Although a number of studies on genetic susceptibility to influenza in humans have been published recently, all are underpowered and unreplicated, so do not provide robust statistical evidence of an association between the identified genetic loci and susceptibility. One study does however present convincing functional evidence for an important role for IFITM3 in susceptibility to severe influenza in mice, and some evidence that this may also be important in human A/H1N1/pdm2009 infection.

Keywords Animal model, host genetics, human influenza, susceptibility, systematic review.

Please cite this paper as: Horby *et al.* (2013). An updated systematic review of the role of host genetics in susceptibility to influenza. Influenza and Other Respiratory Viruses 7(Suppl. 2), 37–41.

MxA gen u prasat, slepic, koní

Vývoj člověka, imunogenom, selekce

http://ancients-bg.com/wp-content/uploads/2016/04/0021.jpg

- ✓ *Migrace a sympatrie hominoidních populací, odlišné infekce*
- ✓ *Nižší diversita genomu i většiny IR genů u Neandrtálců*
- ✓ *Vyšší diversita MHC*
- ✓ *Archaické neandrtálské haplotypy TLR6-TLR1-TLR10*
- ✓ *Balancovaná selekce v lokusech OAS*
- ✓ *IFNG*