Klinická genetika pro mediky

Nové trendy v klinické genetice: genomická medicína

Petr Hořín

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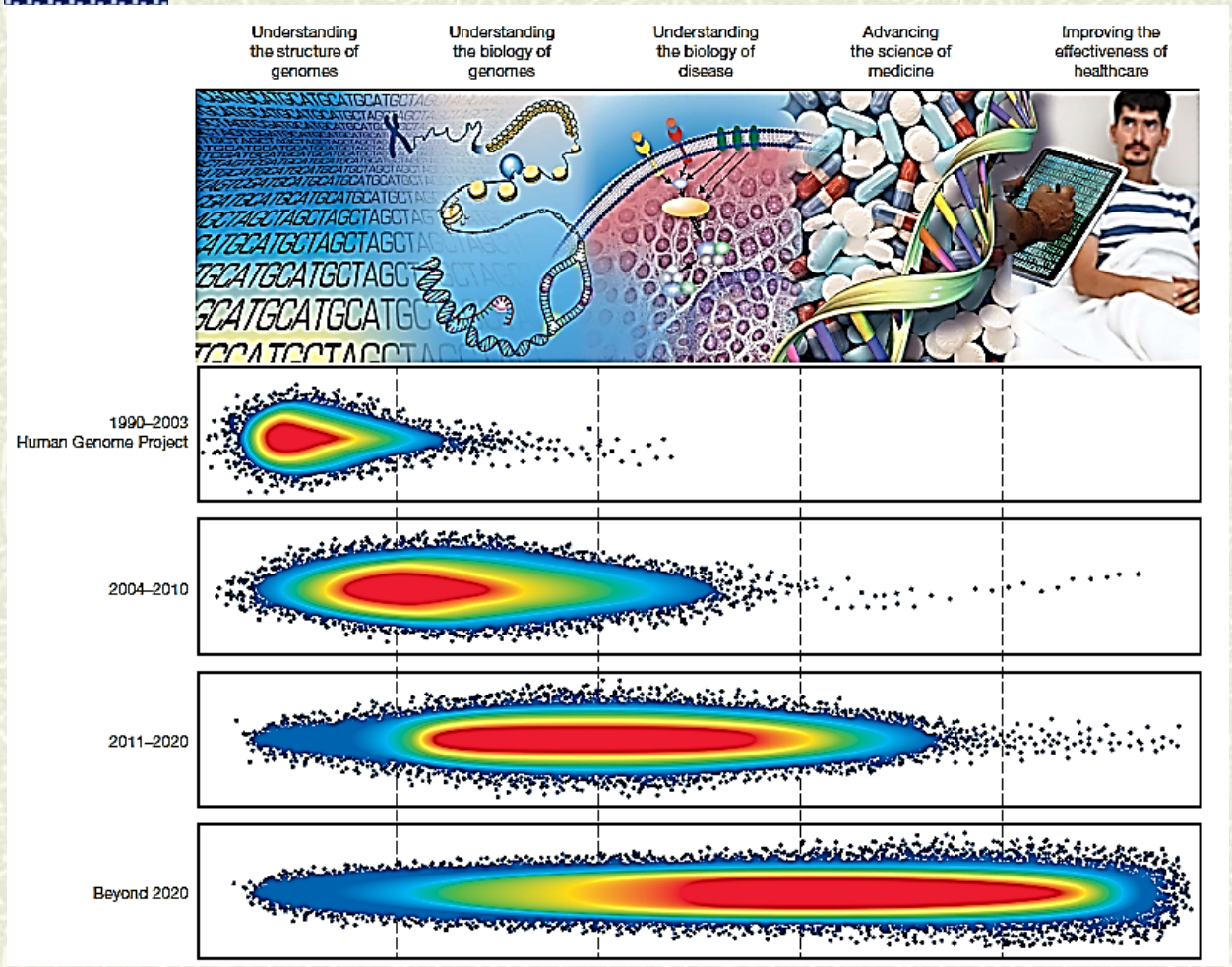
Ústav experimentální biologie PřF MUNI

Genomická medicína:
příspěvek ke konceptu personalizované precizní medicíny



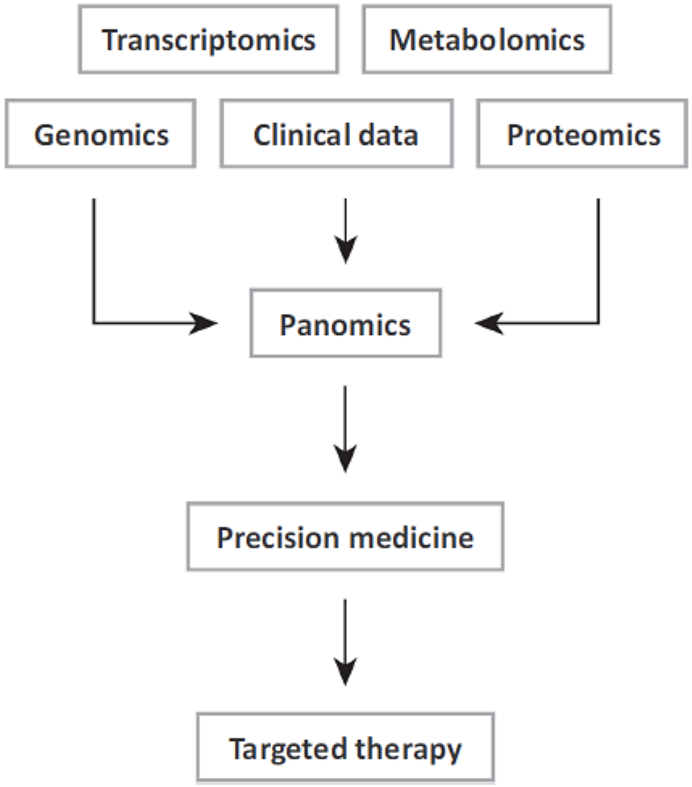
Charting a course for genomic medicine from base pairs to bedside

Green et al. 2011

204 | NATURE | VOL 470 | 10 FEBRUARY 2011

Vrchol vaší profesní kariéry

Současná představa o budoucnosti



Trends in Molecular Medicine

Figure 1. Proposed Model of Precision Medicine Approaches. Data from omic subfields are integrated (panomics) to guide patient care in a manner that accounts for the genetic variation of each patient.

Highlights

Genome sequencing costs are rapidly decreasing; within the coming decade we might anticipate that whole-genome sequencing may be affordable for patients.

Automated high-throughput DNA sequencing and peptide sequencing platforms are currently creating terabytes of information, referred to as 'big data'.

Big data are characterized by the three 'V's: a large volume of data, a high velocity of data production occurring in real time, and the variety of data that can encompass multiple omic subfields.

The analysis of big data has the potential to identify novel biomarkers of disease and targets for therapy. The analysis of large-scale datasets may enable the discovery of diagnostic or prognostic makers that are not readily apparent.

The complexity and vastness of data analysis may ultimately require the development of computational platforms to aid in the discovery of biological pathways underling health and disease.

Panomics for Precision M

Charanjit Sandhu,[1,*] Alia Qureshi,[2] and Andrew Emili[1]

Připomenutí

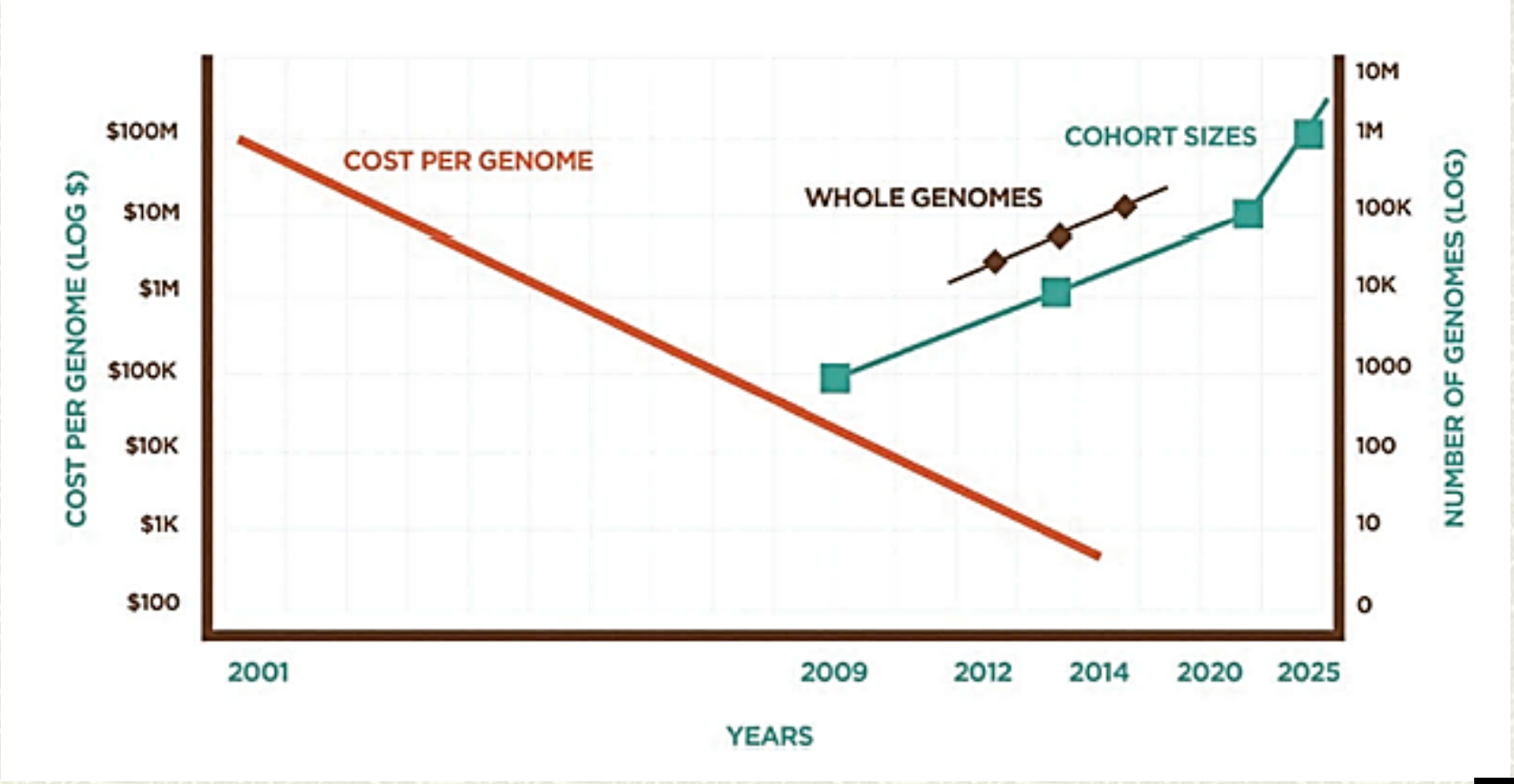
- ✓ *Genetika*
- ✓ *Genomika*

Genomika a holistický přístup: Genom je víc než souhrn genů

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

Strukturní a funkční anotace genomu

Genomická medicína: finanční dostupnost



S. K. DELANEY

Genomická medicína: miniaturizace a automatizace

http://www.humgen.nl/SNP_databases.html

Genomická medicína v praxi

Genetics inMedicine | REVIEW

Open

Implementing genomic medicine in the clinic: the future is here

Teri A. Manolio, MD, PhD[1], Rex L. Chisholm, PhD[2], Brad Ozenberger, PhD[1], Dan M. Roden, MD[3], Marc S. Williams, MD[4,5], Richard Wilson, PhD[6], David Bick, MD[7], Erwin P. Bottinger, MD[8], Murray H. Brilliant, PhD[9], Charis Eng, MD, PhD[10], Kelly A. Frazer, PhD[11], Bruce Korf, MD, PhD[12], David H. Ledbetter, PhD[5], James R. Lupski, MD, PhD[13], Clay Marsh, MD[14], David Mrazek, MD[15], Michael F. Murray, MD[16], Peter H. O'Donnell, MD[17], Daniel J. Rader, MD[18], Mary V. Relling, PharmD[19], Alan R. Shuldiner, MD[20], David Valle, MD[21], Richard Weinshilboum, MD[22], Eric D. Green, MD, PhD[1] and Geoffrey S. Ginsburg, MD, PhD[23]

Genomická medicína v praxi

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PERSPECTIVE

OPEN ACCESS

Toward clinical genomics in everyday medicine: perspectives and recommendations

Susan K. Delaney[a], Michael L. Hultner[b†], Howard J. Jacob[c†], David H. Ledbetter[d†], Jeanette J. McCarthy[e†], Michael Ball[f], Kenneth B. Beckman[g], John W. Belmont[h], Cinnamon S. Bloss[i], Michael F. Christman[a], Andy Cosgrove[j*], Stephen A. Damiani[k,l], Timothy Danis[m], Massimo Delledonne[n], Michael J. Dougherty[o,p], Joel T. Dudley[q], W. Andrew Faucett[d], Jennifer R. Friedman[r], David H. Haase[s], Tom S. Hays[t], Stu Heilsberg[j*], Jeff Huber[u], Leah Kaminsky[v], Nikki Ledbetter[d], Warren H. Lee[w], Elissa Levin[q], Ondrej Libiger[x], Michael Linderman[q], Richard L. Love[m], David C. Magnus[y], AnneMarie Martland[x], Susan L. McClure[z], Scott E. Megill[aa], Helen Messier[ab], Robert L. Nussbaum[ac], Latha Palaniappan[ad], Bradley A. Patay[ae], Bradley W. Popovich[af], John Quackenbush[ag], Mark J. Savant[ah], Michael M. Su[ai], Sharon F. Terry[aj], Steven Tucker[ak], William T. Wong[al] and Robert C. Green[am†]

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Příklad: CGES

Clinical Genome and Exome Sequencing

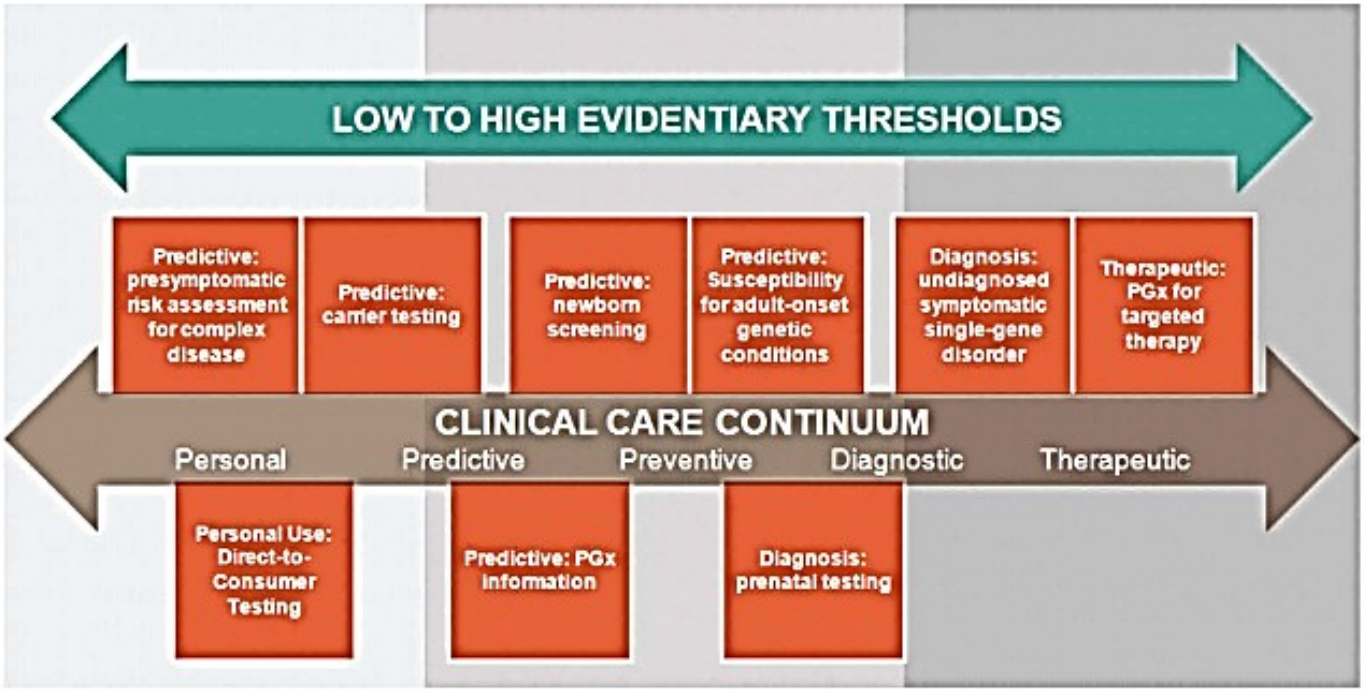


Figure 1. Defining CGES use cases along the clinical care continuum and appropriate evidentiary thresholds for each.

Využití genetického testování

Table 1. Summary of genetic testing.

Test type	Purpose description	Current example(s)
Diagnostic testing	To precisely identify a disease and assist in clinical decision-making	Creatine kinase (CK) level testing for Duchenne muscular dystrophy
Predictive testing	To predict the likelihood of developing a disease	*HTT* gene test for Huntington disease; *BRCA* gene testing for breast cancer
Carrier testing	To understand the likelihood of passing a genetic disease to a child	*CFTR* gene testing for cystic fibrosis
Prenatal testing	To identify disease in a fetus	Expanded alpha-fetoprotein (AFP) for risk of neural tube defects, such as spina bifida and Down syndrome
Newborn screening	To determine if a newborn has a disease known to cause problems in health and development	All states must screen for at least 21 disorders by law, and some states test for 30 or more. Metabolic (e.g. classic galactosemia (GALT)), endocrine (e.g. congenital hypothyroidism) and other disorders tested
Pharmacogenomics (PGx) testing	To determine the optimal drug therapy and dose given a person's metabolic response	The vitamin K epoxide reductase complex subunit 1 (*VKORC1*) test for likely response to the anticoagulant warfarin. *TPMT* gene testing for likely response to thiopurine immunosuppressive therapies
Research testing	To contribute to our understanding of underlying cause of disease	Genome-wide association studies (GWAS) to determine the association of a variant with a trait

Doporučení pro lékaře

Bowdin S et al.: Recommendations for the integration of genomics into clinical practice. Genet Med. 2016 May 12. doi: 10.1038/gim.2016.17. [Epub ahead of print]

Jedním z těchto doporučení je, aby nejen kliničtí genetici, ale i další poskytovatelé lékařské péče porozuměli výhodám a limitacím CGES natolik, aby dokázali korektně interpretovat klinický význam diagnostikovaných genomických variant

Odborná interpretace jako základ aplikací

Dědičná onemocnění

- **Jednoduchá (mendelistická)**

3000 lokusů

- **Komplexní**

900 lokusů

Jednoduchý vs. komplexní

- ✓ *Stejná mutace v různých genomech*
- ✓ *Stejný genom v různých prostředích/obdobích vývoje*
- ✓ *Různé genomy v různých prostředích*
- ✓ *Genom vs. mikrobiom*

Různé genomy v různých prostředích

- ✓ *Rozšifrování komplexního znaku: molekulární disekce*
- ✓ *Interpretace a aplikace získaných dat*

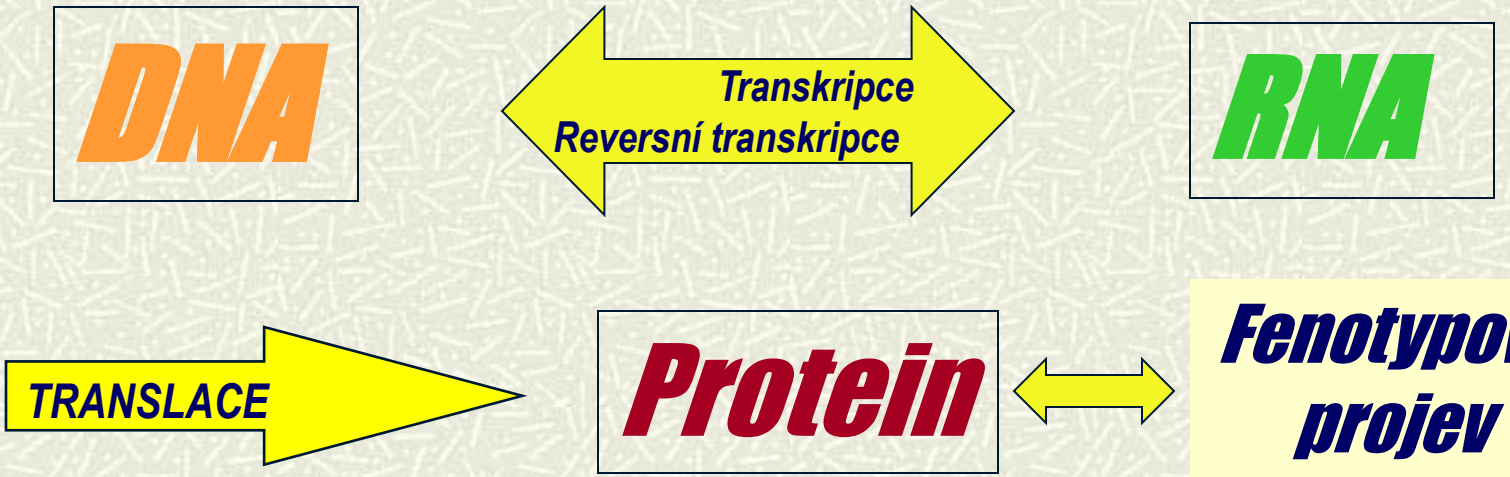
Rozšifrování komplexního znaku:

Holistický přístup

Molekulární disekce komplexních znaků

Molekulární disekce komplexních znaků

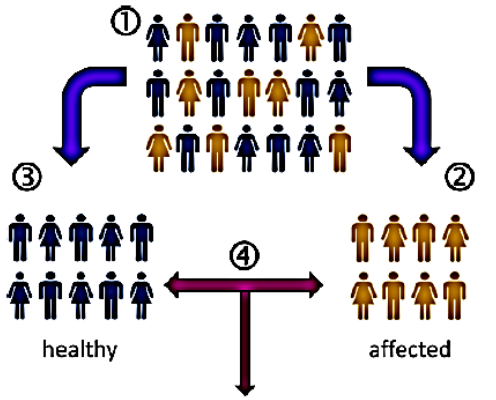
OD FENOTYPU KE GENOTYPU

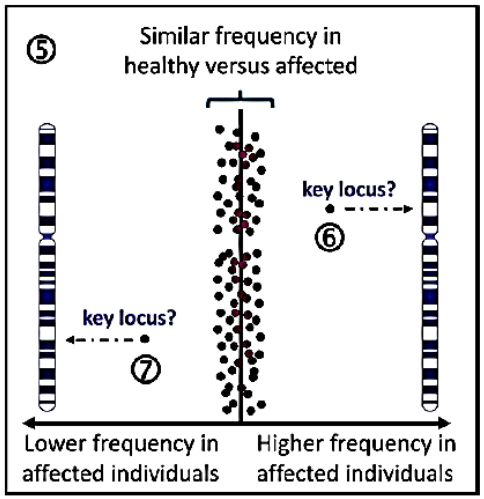


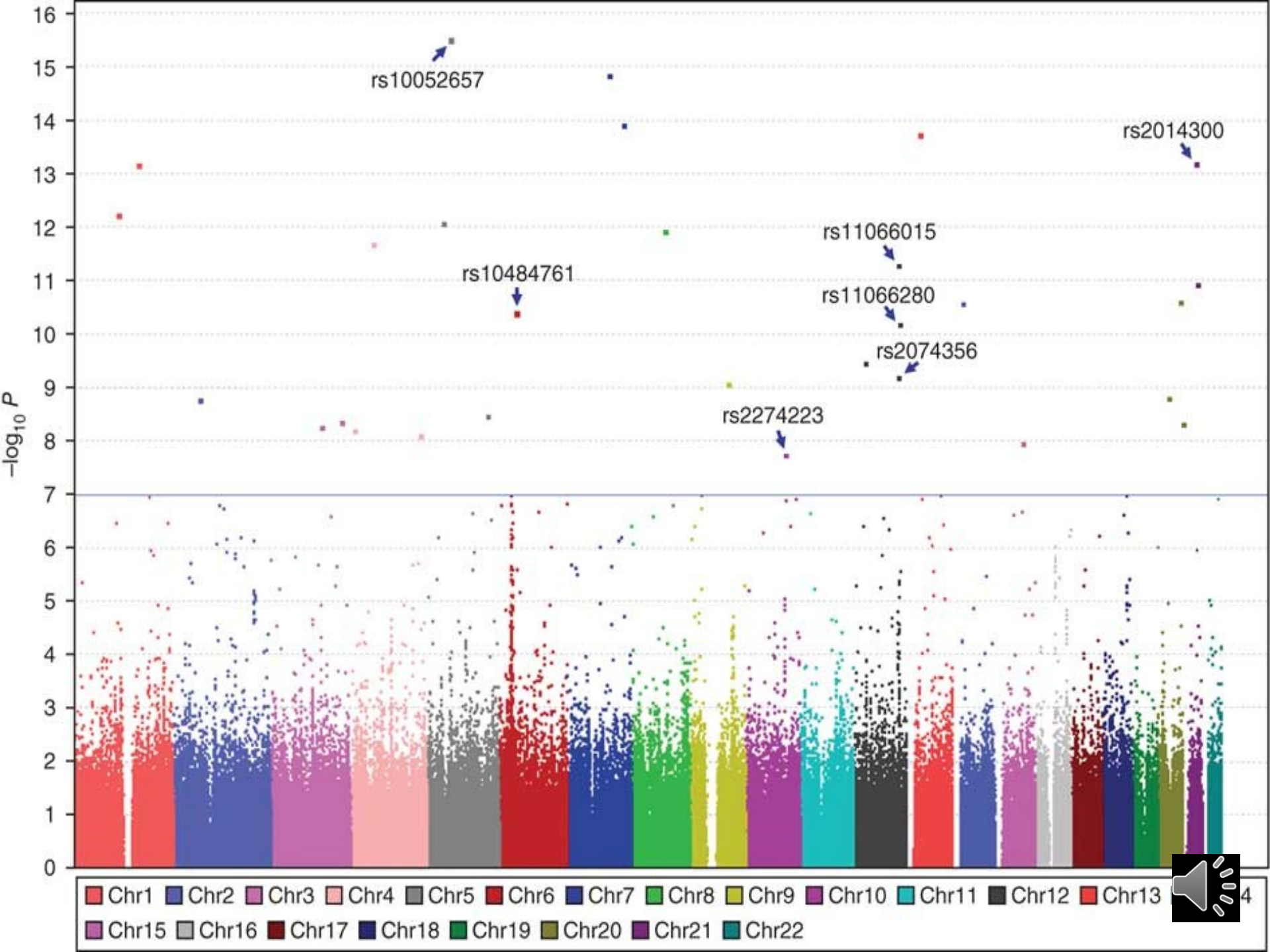
OD GENOTYPU K FENOTYPU

GWAS a komplexní znaky

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



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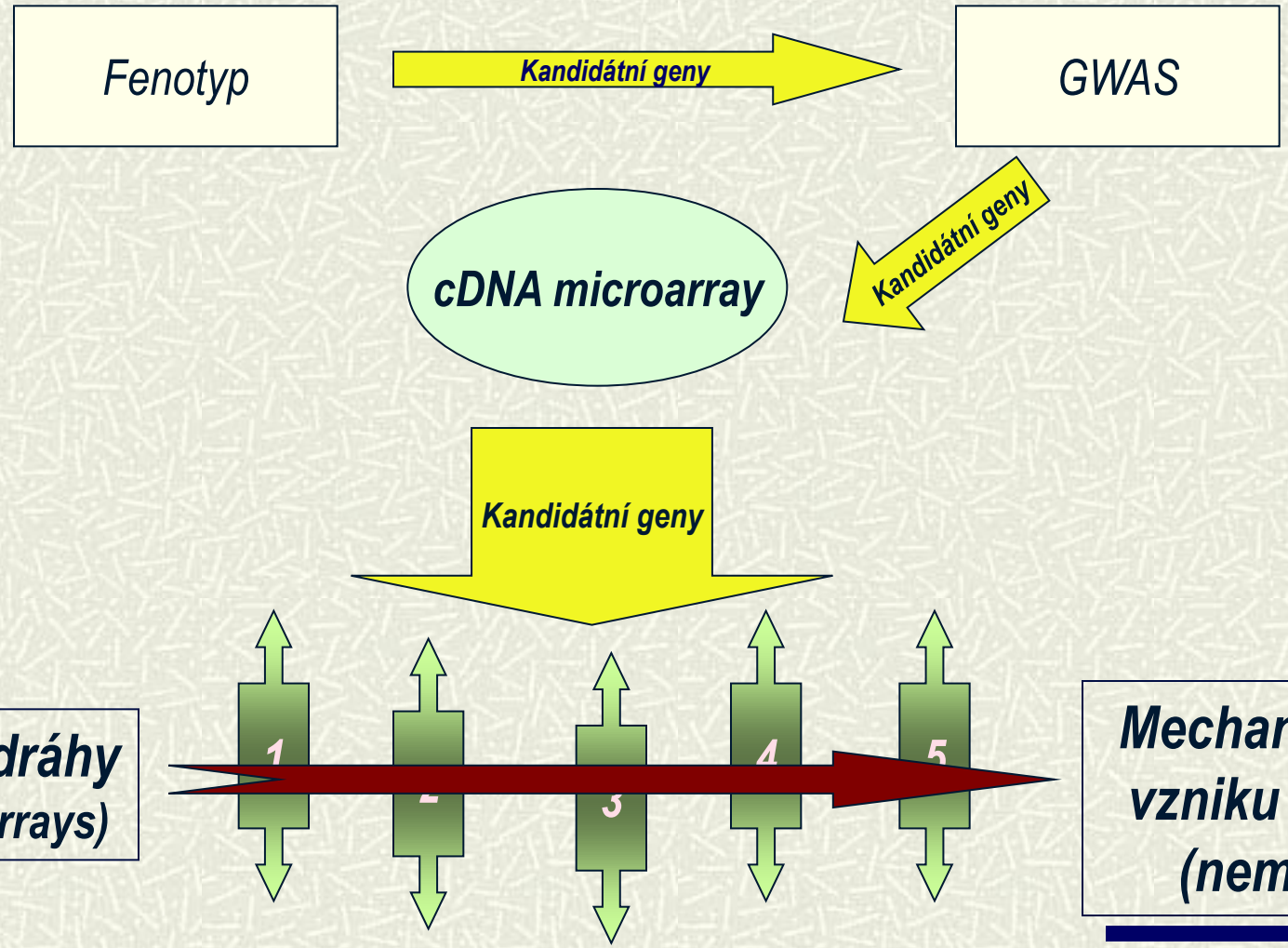
Chr1 Chr2 Chr3 Chr4 Chr5 Chr6 Chr7 Chr8 Chr9 Chr10 Chr11 Chr12 Chr13
Chr15 Chr16 Chr17 Chr18 Chr19 Chr20 Chr21 Chr22

GWAS

- ✓ Princip: ***hledání rozdílů v polymorfních místech genomů (markerech)***
- ✓ Markery: ***SNP***
- ✓ Postup: ***srovnání skupin extrémních fenotypů***
- ✓ Výsledky: ***kandidátní chromosomální oblasti***
- ✓ Další postup: ***mapování oblasti, kandidátní geny***

→ ***Biologická validace: analýza funkce identifikovaných genů***

GWAS a molekulární disekce komplexních znaků



Genové dráhy
a mechanismus nemoci (patogeneze)

http://www.polygenicpathways.co.uk/

Family	Gene
Cholesterol and lipoprotein-related	A2M, ABCA1, APOA1, APOA4, APOC1, APOC2, APOC3, APOE, CD36, CETP, HMGCR, LDLR, LIPA, LRP1, LRP6, LPA, LPL, OLR1, SREBF1
Cytokines	CCL2, CCR2, IL1B, IL1RN, IL6,IL18, TGFB1, TNF
Oxidative stress	ALDH2, GSTM1, GSTT1, HFE, MPO, NOS3, PON1, PON2
Nuclear receptor and related	CYP19A1, ESR1, PPARA
Proteases	ACE, CST3, MMP1, MMP3, SERPINE1
Miscellaneous	BCHE, CBS, CD14, CRP, GNB3, HLA-A2, HTR6, ICAM1, MEF2A, MTHFR, PTGS2, TLR4

Genes associated with both atherosclerosis/hypercholesterolaemia and Alzheimer's

HOLISTICKÝ PŘÍSTUP

Možnost řešení komplexních problémů

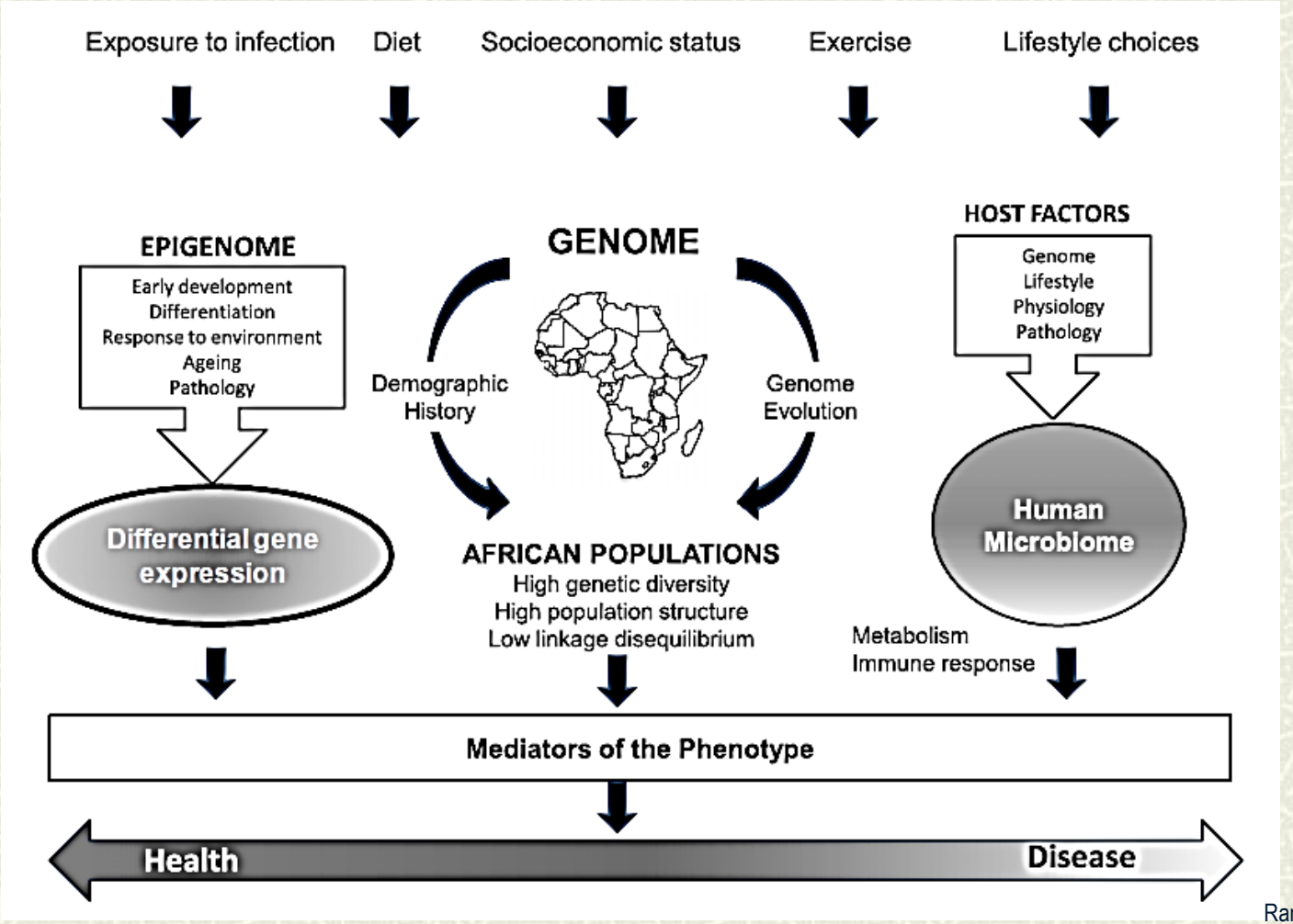
PATOGENEZE NEMOCÍ

Nemoc

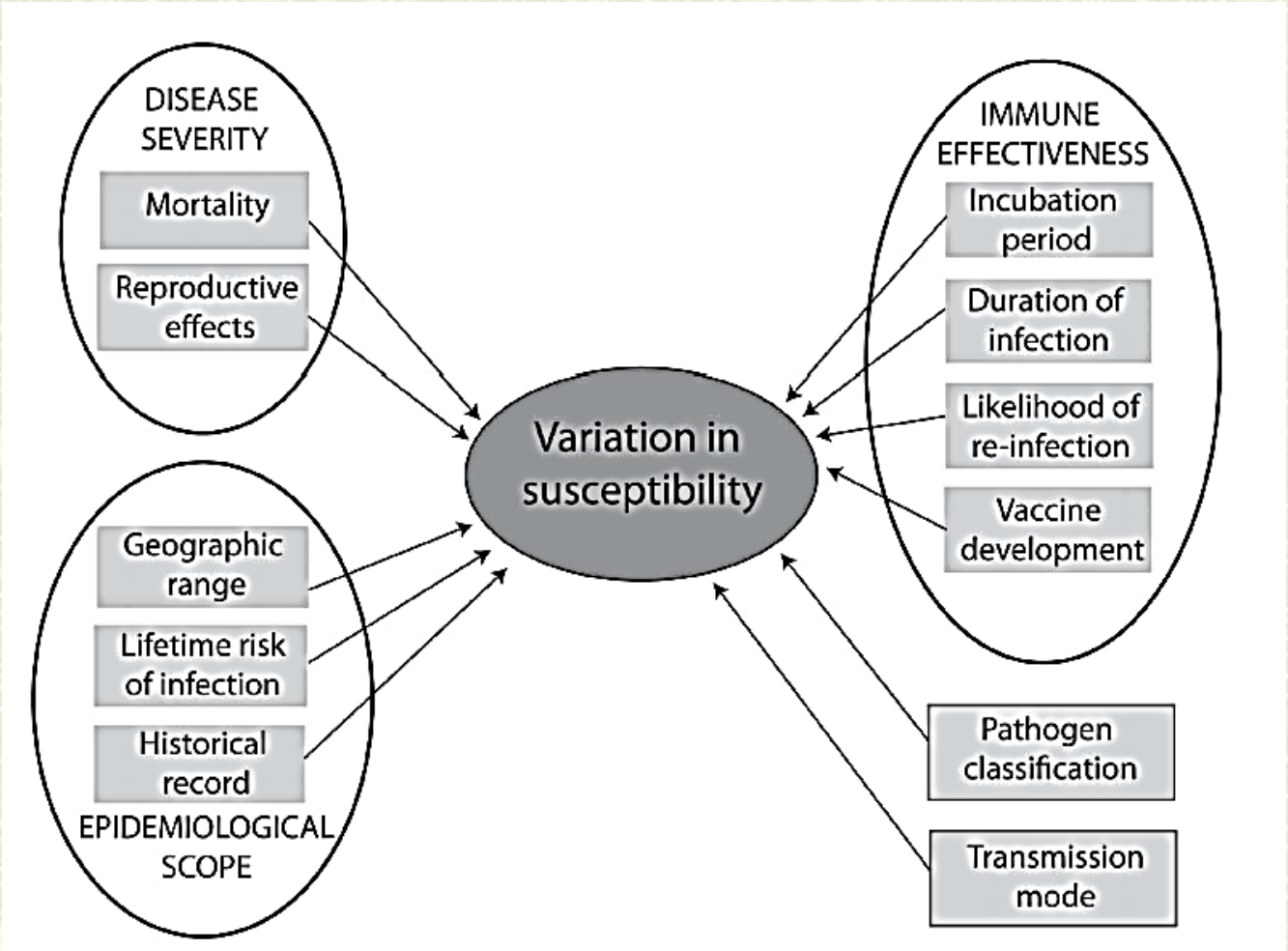
Reakce organismu na patogenní noxu

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

Jeden příklad za všechny: genetika vnímavosti k infekcím



Vnímavost k infekci jako komplexní znak



Baker, Antonovics 2012

Význam definice fenotypu

*Resistence: schopnost omezit replikaci patogena v hostitelském organismu

vs.

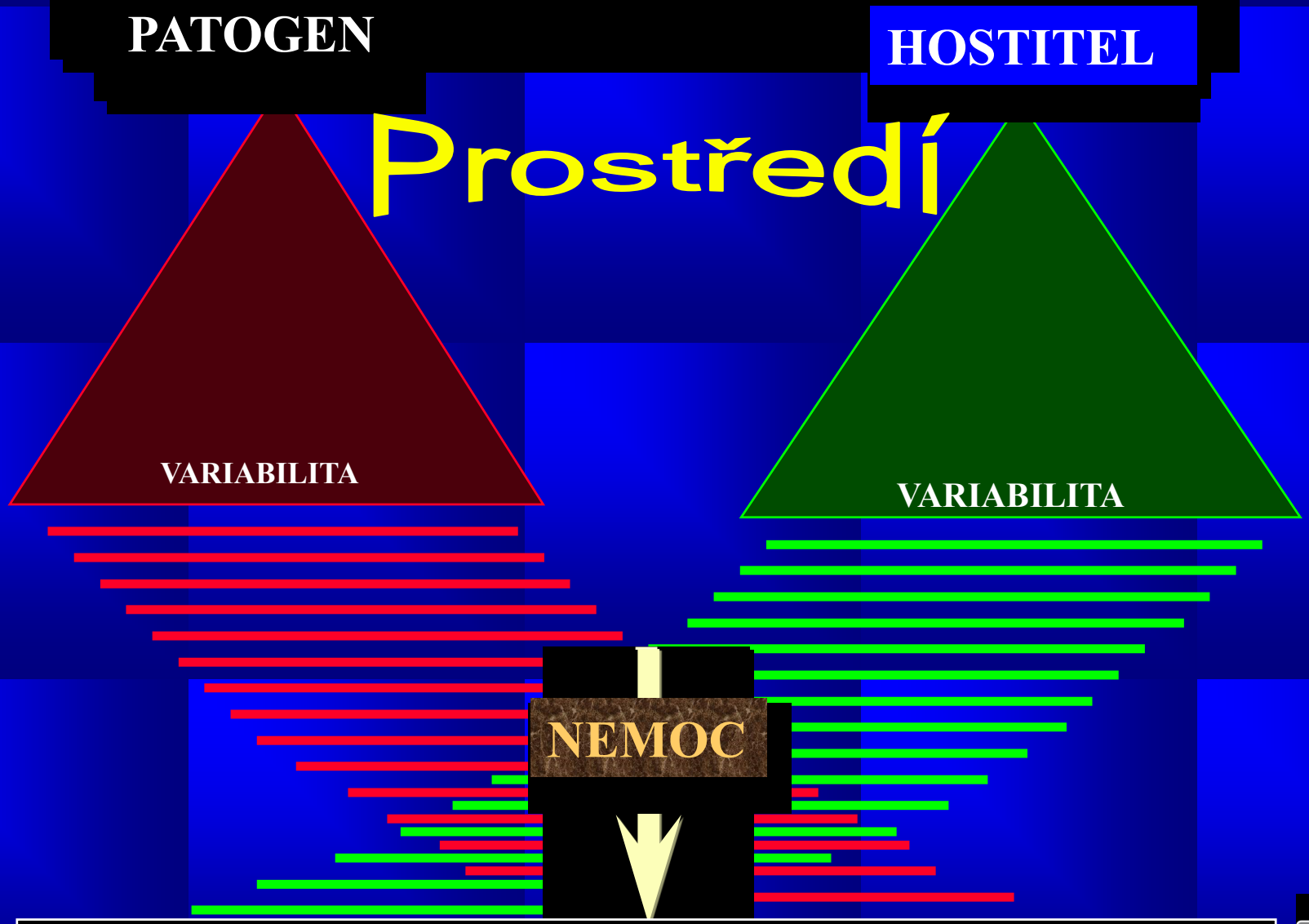
Tolerance: schopnost udržet homeostázu za přítomnosti patogena v organismu

Susceptibilita	Tolerance, nosičství	Resistence

Genetická odolnost/vnímavost (resistence/susceptibilita) k onemocněním

- ✓ Geny ovlivňující zdravotní stav (v interakci s prostředím)
- ✓ Jejich polymorfismy nejsou příčinou onemocnění, ale ovlivňují reakci na (environmentální) patogenní faktory
- ✓ Evoluční kontext a význam
- ✓ V praxi většinou relativní pojem

Infekční onemocnění



Individuální variabilita v manifestaci onemocnění

Infekční nemoc jako výsledek interakce hostitele a patogena

- ✓ *Nemoc jako obranná reakce*
- ✓ *Často jedinečná kombinace hostitele a patogena*
- ✓ *Individuální rozdíly v použití různých imunologických mechanismů v reakci na téhož patogena*
- ✓ *Symptomatologie určena převážně patogenem nebo převážně hostitelem*

Infekční nemoc jako výsledek interakce hostitele a patogena

„The infection must be seen in the context of the countermeasures produced by the parasite, and judged as a dynamic interaction of host and parasite rather than the clearance of an inert antigen by the host immune response“

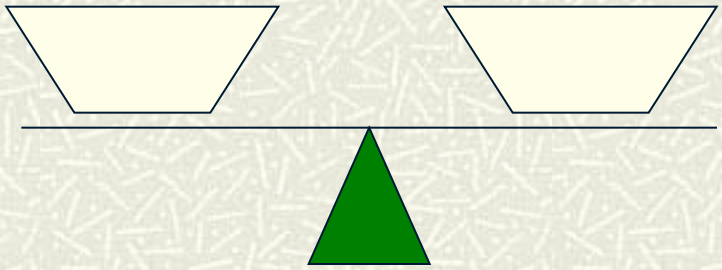
Riffkin et al.,

Nejednoznačný význam variability v imunitní odpovědi: silná nebo slabá?

Skylla and Charybda
odolnosti/vnímavosti k nemocem

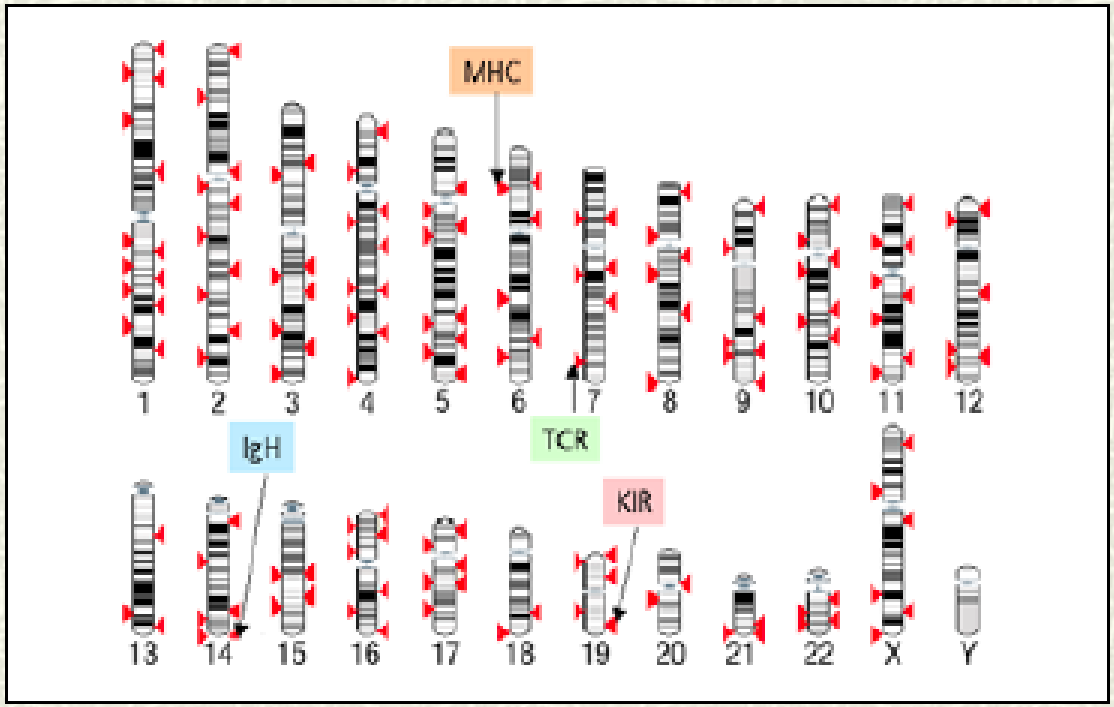
Protektivní imunita
Resistence k infekci

Autoimunita, alergie
Zánět



Geny obranyschopnosti

Imunogenom: 5% genomu



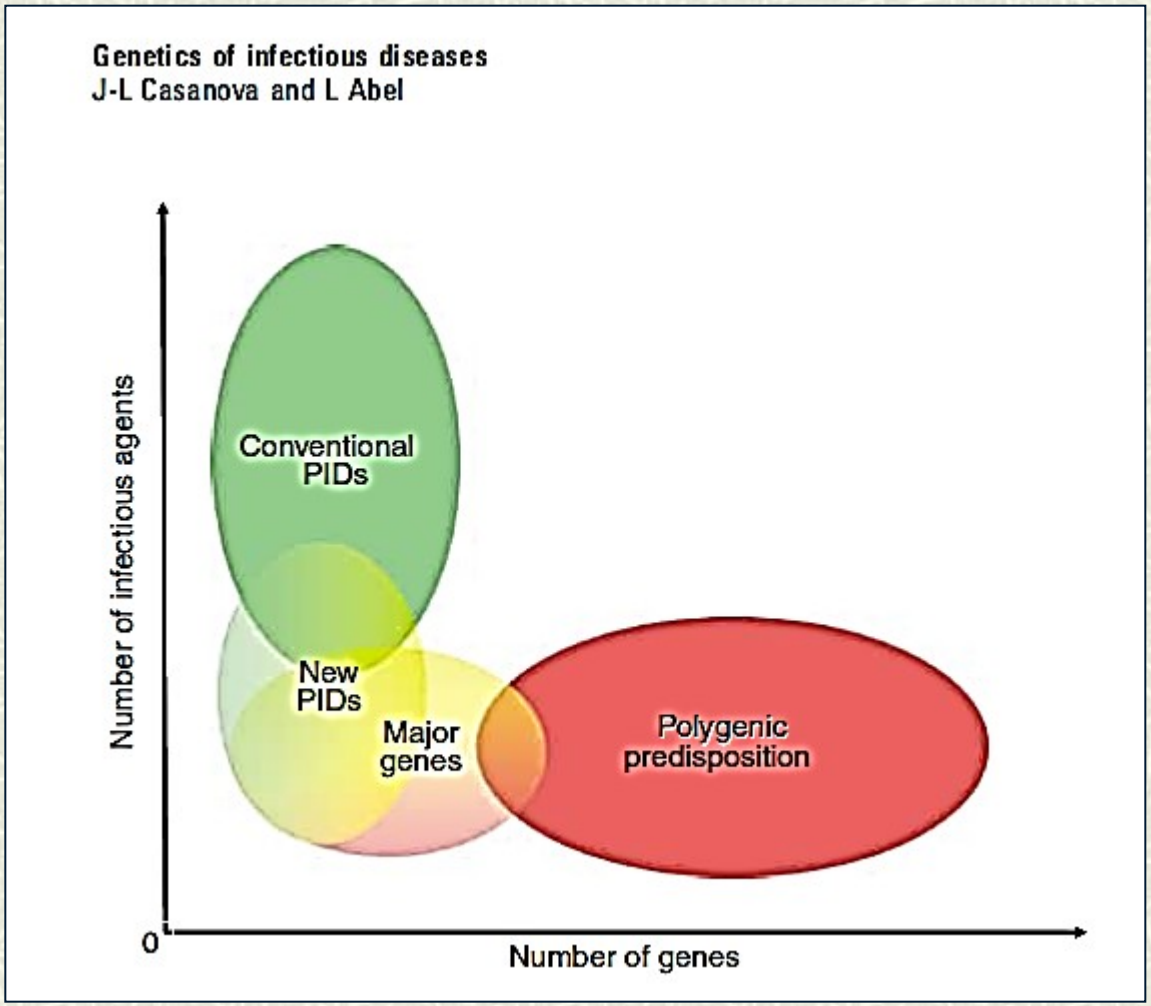
Imunogenom: definice

- ✓ *Geny účastnící se obrany organismu, geny imunitní odpovědi, IR geny*
- ✓ *Imunom: soubor produktů IR genů*
- ✓ *Geny stejného biologického významu, ale mnoha různých funkcí*

Genomická analýza imunogenomu

- ✓ *Imunitní funkce jako jednoduché nebo komplexní znak(y)*
- ✓ *Imunitní funkce jako základ obrany proti infekčním nemocem*

Typy dědičnosti vnímavosti k infekcím



Casanova, Abel EMBO J 2007

Mendelistická dědičnost

Mendelian disorders of immunity to infection associated with predisposition or resistance to specific infections

Infectious agent	Clinical phenotype	Immunological phenotype	Gene
Neisseria	Invasive disease	MAC deficiency	*C5, C6, C7, C8A, C8B, C8G, C9*
	Invasive disease	Properdin deficiency	*PFC*
Mycobacteria	MSMD	IL-12/23–IFN-γ deficiency	*IFNGR1, IFNGR2, STAT1, NEMO, IL12B, IL12RB1*
	Disseminated tuberculosis		
Streptococcus pneumoniae	Invasive disease	IRAK-4 deficiency	*IRAK4*
Epstein-Barr virus	X-linked lymphoproliferative disease	SAP deficiency	*SH2D1A*
Human papillomavirus	Epidermodysplasia verruciformis	EVER1 or EVER2 deficiency	*EVER1, EVER2*
Plasmodium vivax	Natural resistance	Lack of receptor for pathogen	*DARC*
Human immunodeficiency virus-1	Natural resistance	Lack of receptor for pathogen	*CCR5*
Norovirus	Natural resistance	Lack of receptor for pathogen	*FUT2*

Picard et al Curr Opin Immunol 2006

Komplexní dědičnost: GWAS a infekce u lidí

Table 1 Genetic loci identified by genome-wide association studies for host susceptibility to infectious diseases

Disease	Pathogen	Gene or locus	Biological mechanism
AIDS[1]	Human immunodeficiency virus-1	Major histocompatibility complex, class I (*HLA-B–HLA-C*), *CCR5*	Acquired immunity, deletion of viral co-receptor
Hepatitis B[2]	Hepatitis B virus (HBV)	Major histocompatibility complex, class II (*HLA-DP*)	Acquired immunity
Hepatitis C[3,4]	Hepatitis C virus (HCV)	*IL28B*	Innate immunity
Leprosy[5]	*Mycobacterium leprae*	Major histocompatibility complex, class II (*HLA-DR–DQ*), *NOD2*, *TNFSF15*, *RIPK2*, *CCDC122* and *C13orf31*)	Acquired and innate immunity, and unknown mechanisms
Tuberculosis[8]	*Mycobacterium tuberculosis*	18q11.2 (*GATA6*, *CTAGE1*, *RBBP8*, *CABLES1*)	Unknown
Meningococcal disease[7]	*Neisseria meningitidis*	*CFH*, *CFHR3*, *CFHR1*	Innate immunity

De Bakker, Telenti 2010

Netranslatovaný genom a vnímavost k infekcím

- ✓ *Většina hitů GWAS mimo protein kódující oblasti*
- ✓ *Řada SNPs v regulačních oblastech genů*
- ✓ *Vliv na expresi a nemoci, včetně infekcí*

Netranslatovaný genom a vnímavost k infekcím

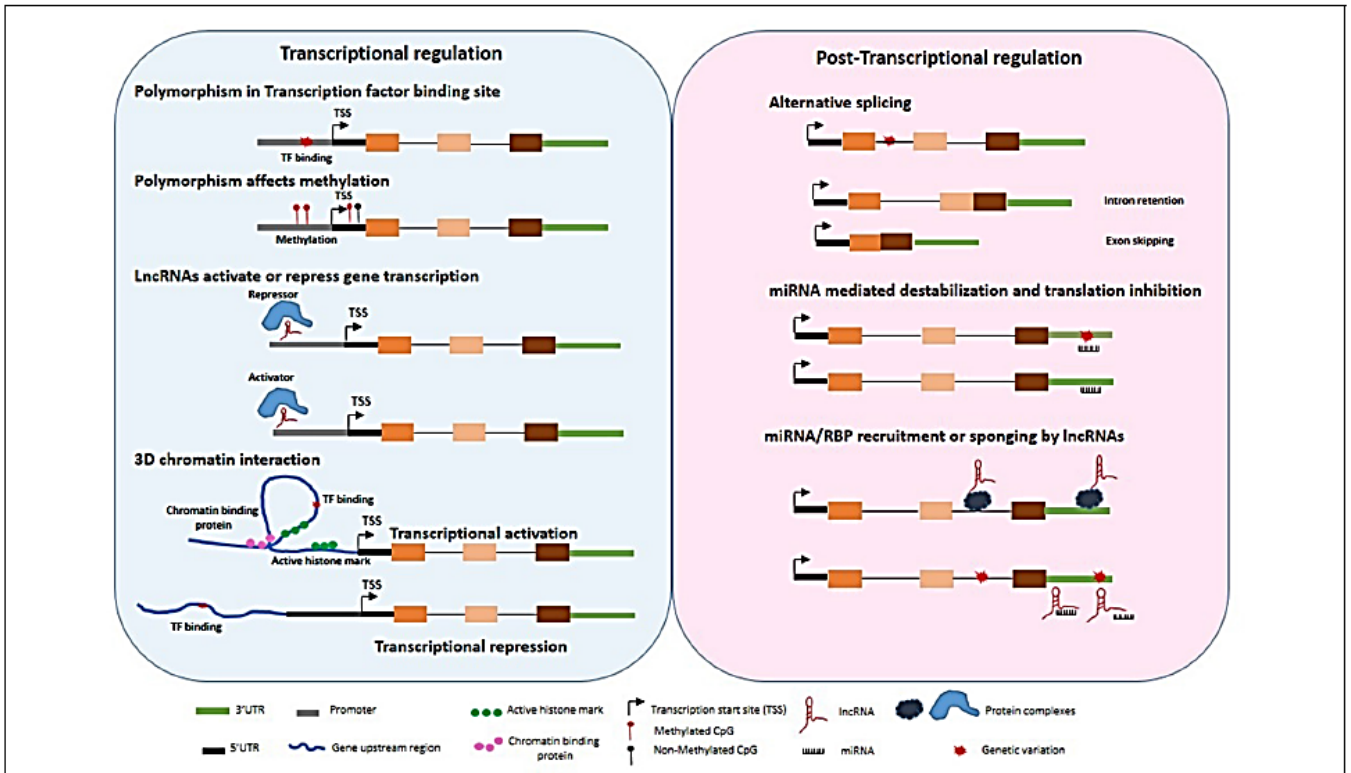


FIGURE 1 | Untranslated gene variations influence regulation of gene expression. Disease associated polymorphisms may alter methylation, transcription factor binding in the gene promoter regions, recruitment of repressor or activators, 3 dimensional chromatin structure, splicing, miRNA binding to 3′UTR, transcriptional and post-transcriptional regulation of target genes through variation in lncRNA expression and function.

Mechanismy nemocí

- ✓ Infekce
- ✓ Alergie
- ✓ Autoimunita
- ✓ Komplexní imunopatologie

Příklady

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

Received: 9 June 2020 | Accepted: 14 June 2020
DOI: 10.1111/imr.12897

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 | Iana H. Haralambieva | Stephen N. Crooke | Gregory A. Poland | Richard B. Kennedy

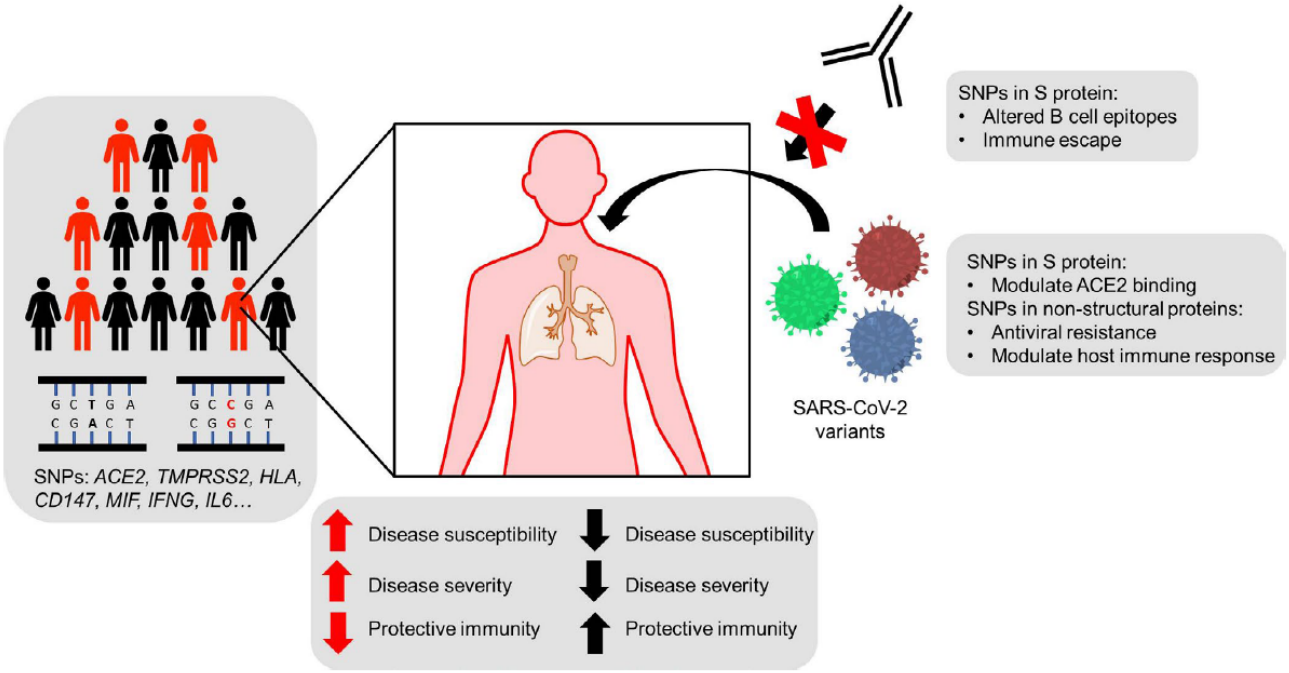
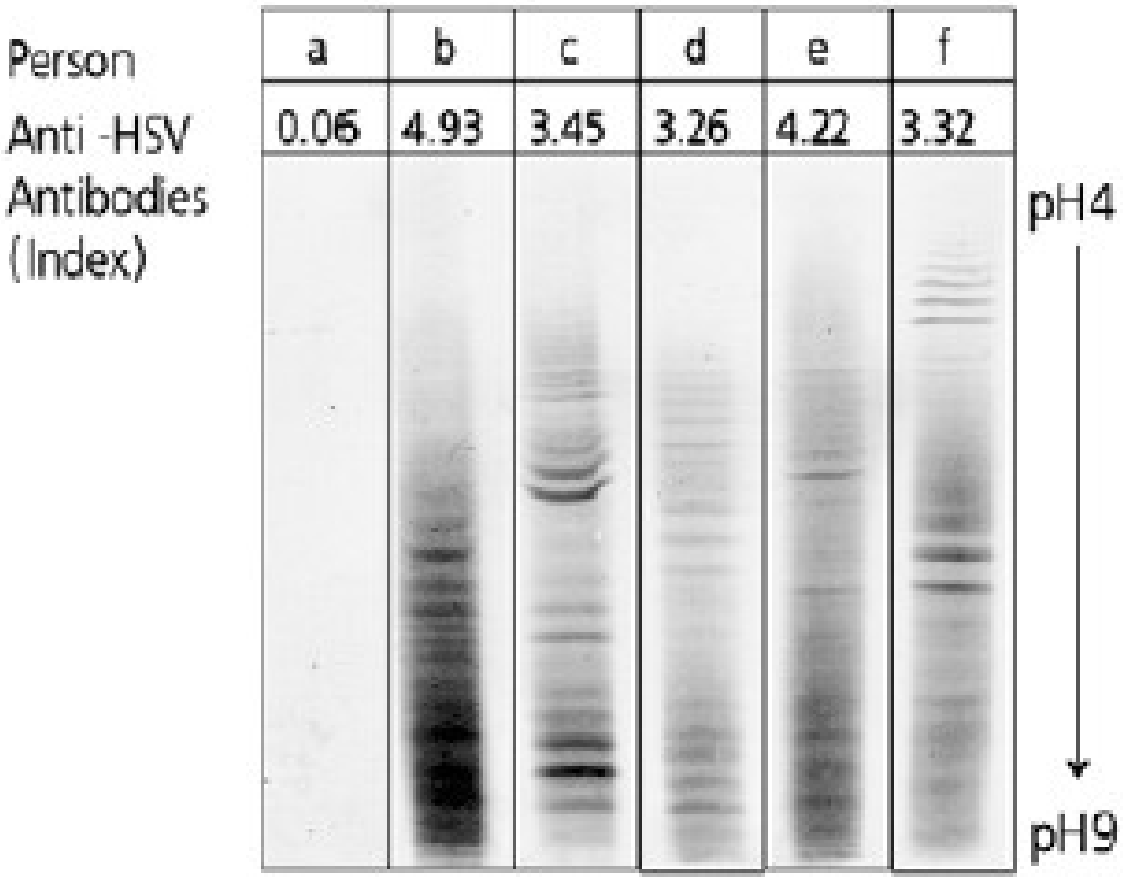


FIGURE 1 The impact of host genetics and viral variation on SARS-CoV-2 infection and COVID-19 severity. Individuals in the population harbor single nucleotide polymorphisms (SNPs) across a variety of genes (eg, *ACE2*, *TMPRSS2*, *HLA*, *CD147*, *MIF*, *IFNG*, *IL6*) that have been implicated in the 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

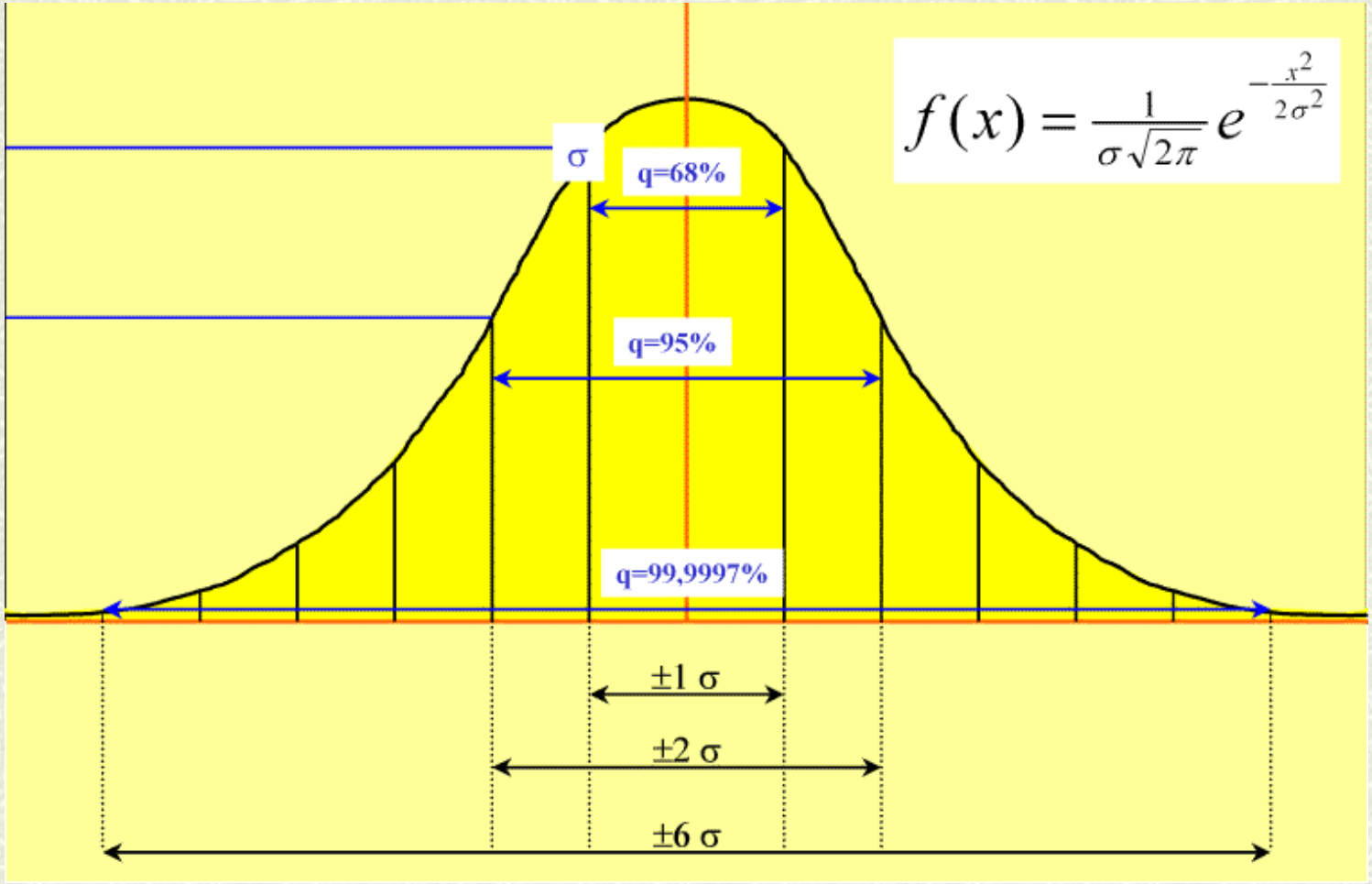
Variabilita antiinfekční imunitní odpovědi u člověka



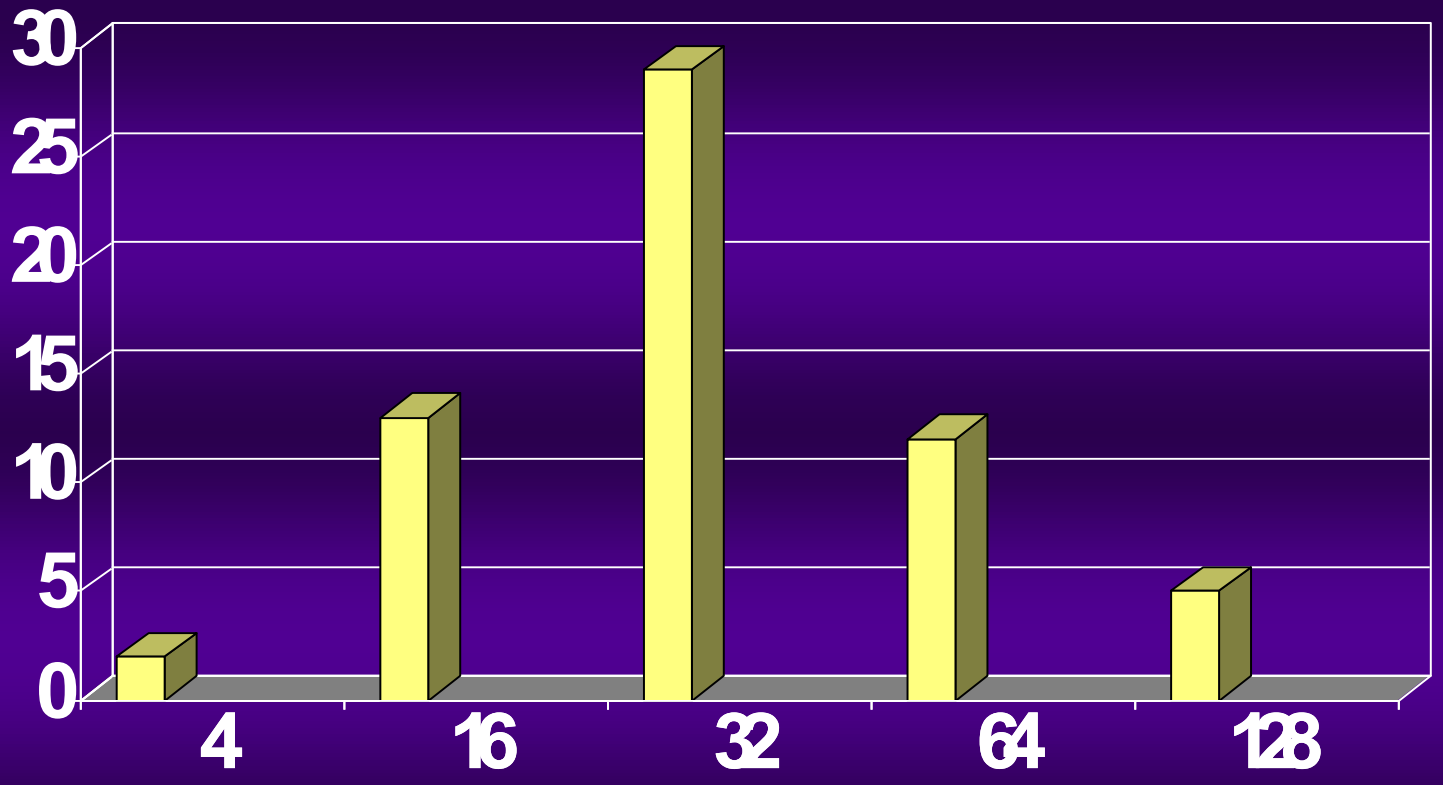
Vakcinace a genetika

- ✓ ***Individuální variabilita imunitní odpovědi po vakcinaci***
- ✓ *Využití genetických principů při produkci nových vakcín, farmakogenomika*

Postvakcinační imunitní odpověď: Gaussovská distribuce



POSTVAKCINAČNÍ TITRY NEUTRALIZAČNÍCH PROTILÁTEK (N=61)



Genetics of vaccination

Table 3. Heritability estimates of vaccination responses in twin studies

Vaccine	Parameter	DZ[a]	MZ[a]	Population	Age	Study	Herita-bility, %	95% CI %	Refer-ences
Measles	antibody	55	45	USA[b]	2–18 years	cross-sectional	89	≥ 52[c]	18
Mumps	antibody	55	45	USA[b]	2–18 years	cross-sectional	39	≥ 2[c]	18
Rubella	antibody	55	45	USA[b]	2–18 years	cross-sectional	46	≥ 5[c]	18
HAV	antibody	95	96	Germany	18–65 years	prospective	36	–2–73	15
HBsAg	antibody	95	96	Germany	18–65 years	prospective	61	41–81	15
HBsAg	antibody	159	48	Gambia	5 months	prospective	77	63–85	12[d]
Polio	antibody	159	48	Gambia	5 months	prospective	60	43–73	12
Tetanus	antibody	159	48	Gambia	5 months	prospective	44	16–70	12
Tetanus	IL-13	159	48	Gambia	5 months	prospective	64	50–75	12
Diphtheria	antibody	159	48	Gambia	5 months	prospective	49	17–77	12
Hib	antibody	147	43	Gambia	5 months	prospective	51	32–66	14
Pertussis									
Pertactin	IFN-γ	159	48	Gambia	5 months	prospective	53	35–67	12
FHA	IFN-γ	159	48	Gambia	5 months	prospective	65	50–76	12
Toxin	IL-13	159	48	Gambia	5 months	prospective	57	40–71	12
BCG									
PPD	IFN-γ	159	48	Gambia	5 months	prospective	41	10–71	12
KMTB	IFN-γ	159	48	Gambia	5 months	prospective	39	3–71	
PPD	IL-13	159	48	Gambia	5 months	prospective	46	5–75	
Hsp65	IL-13	159	48	Gambia	5 months	prospective	50	29–67	

Imunogenom a precision medicine

Leading Edge

Essay

Cell

Infectogenomics: Insights from the Host Genome into Infectious Diseases

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Five years into the human postgenomic era, we are gaining considerable knowledge about host-pathogen interactions through host genomes. This "infectogenomics" approach should yield further insights into both diagnostic and therapeutic advances, as well as normal cellular function.

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Genetika infekčních nemocí u lidí

(Quintana-Murci et al. Nature Immunology 8, 2007: 1165-1171

- ✓ Klinická: definice genů a alel zodpovědných za individuální vnímavost k infekci: *PIDs*
- ✓ Epidemiologická:definice genů a alel zodpovědných za vnímavost populace k infekci: *asociace, GWAS*
- ✓ Evoluční: studium genů selektovaných předchozími infekcemi: *evoluce/speciace, diverzita populací*

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*

Odborná interpretace jako základ aplikací

Etická východiska*: jak naložit s informacemi získanými genomickými metodami*

Využitelnost v praxi

Minimální varianta

- ✓ *Kdy a kam referovat pacienta ke genetickému vyšetření - indikace a interpretace*
- ✓ *Kdy nereferovat pacienta ke genetickému vyšetření*