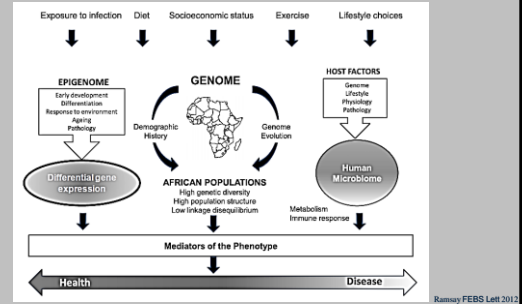


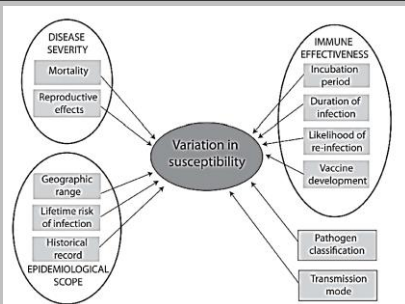
Molekulární disekce imunity

- ✓ Identifikace genů a drah
- ✓ Mechanismy nemoci
- ✓ Farmakogenetika, farmakogenomika
- ✓ Genetika vakcinace, vakcinomika

Genetika vnímavosti k infekcím

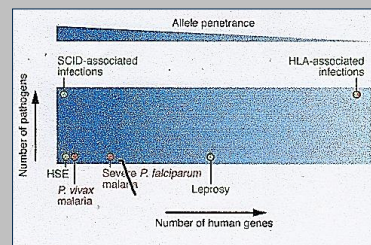


Vnímovost k infekci jako komplexní znak



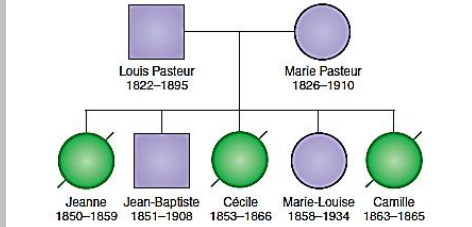
Baker, Antonovics 2012

Imunogenom a infekce



Alcais et al. J Clin Invest 2009

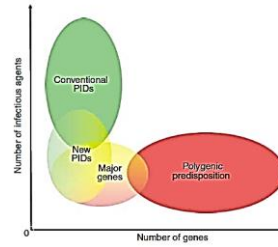
Dědičnost vnímavosti k infekci



Quintana-Murci et al. 2007

Typy dědičnosti vnímavosti k infekcím

Genetics of infectious diseases
J-L Casanova and L Abel



Casanova, Abel EMBO J 2007

Mendelistická dědičnost

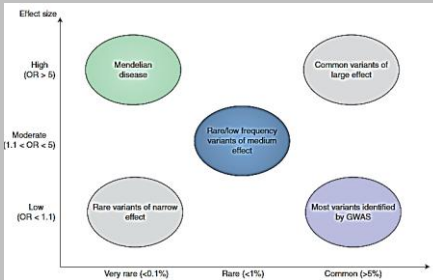
Nízkočetné varianty s velkým účinkem

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

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

Picard et al Curr Opin Immunol 2006

Power of GWAS



Jeremy Mamy and Luis Quintana-Murci
Cold Spring Harb Perspect Med 2013; doi: 10.1101/cshperspect.a012400

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 (<i>HLA-B-HLA-C</i>), <i>CCR5</i>	Acquired immunity, deletion of viral co-receptor
Hepatitis B ²	Hepatitis B virus (HBV)	Major histocompatibility complex, class II (<i>HLA-DP</i>)	Acquired immunity
Hepatitis C ^{3,4}	Hepatitis C virus (HCV)	<i>IL28B</i>	Innate immunity
Leprosy ⁵	<i>Mycobacterium leprae</i>	Major histocompatibility complex, class II (<i>HLA-DP-DQ</i>), <i>RGD2</i> , <i>TNFSF15</i> , <i>RIPK2</i> , <i>CCDC122</i> and <i>C13orf33</i>	Acquired and innate immunity, and unknown mechanisms
Tuberculosis ⁶	<i>Mycobacterium tuberculosis</i>	19q11.2 (<i>GATA6</i> , <i>CTAGE1</i> , <i>BBBP8</i> , <i>CABLES1</i>)	Unknown
Meningococcal disease ⁷	<i>Neisseria meningitidis</i>	<i>CFH</i> , <i>CFHR3</i> , <i>CFHR1</i>	Innate immunity

De Bakker, Telenti 2010

Příklady kandidátních genů: chřipka a Mx



- ✓ Interferon-induced members of the dynamin superfamily of large GTPases
- ✓ Key mediators of innate antiviral resistance induced in cells by type I (a/b) and type III (I) interferons
- ✓ They inhibit a wide range of viruses by blocking an early stage of the replication cycle
- ✓ Present in most vertebrate species

(Haller et al. Microbes Infect 2007)

Příklady kandidátních genů: flaviviry a OAS1

- ✓ Coding for 2' - 5' - oligoadenylate synthase, activated by dsRNA
- ✓ Identified in mice as flavivirus resistance gene
- ✓ Exon 4 mutation leading to a STOP codon causes susceptibility to infection
- ✓ In the horse, SNPs within the gene associated with anti-WNV antibody production (Rios et al., 2009)

Cave: Příklady kandidátních genů: NRAMP1 a TB

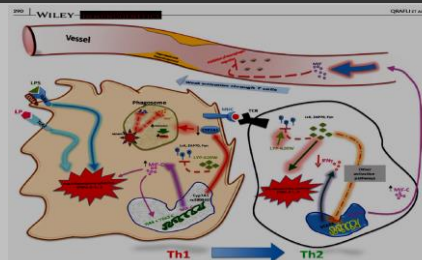


FIGURE 2 Schemata contrasting current key candidate genes of the susceptibility to TB development in African population. After TB infection, macrophages are equipped by innate immune cells, such as dendritic macrophages. In dendritic macrophages, they are recognized by TLRs (TLR1, TLR2, TLR4), TLR engagement activates signaling cascades leading to the expression of inflammatory cytokines, including TNF, which the secret levels is increased in infectious TB patients. In addition, TNF-induced cytokine responses are produced by CD4+ Th1 cells. The administration is associated with proinflammatory Th2 responses leading to a downregulation of TB disease. Th2s Th2s that release IL-4, IL-5, IL-6, IL-10, IL-13, IL-17, IL-22, IL-25, IL-27, IL-31, IL-33, IL-35, IL-36, IL-37, IL-38, IL-39, IL-40, IL-41, IL-42, IL-43, IL-44, IL-45, IL-46, IL-47, IL-48, IL-49, IL-50, IL-51, IL-52, IL-53, IL-54, IL-55, IL-56, IL-57, IL-58, IL-59, IL-60, IL-61, IL-62, IL-63, IL-64, IL-65, IL-66, IL-67, IL-68, IL-69, IL-70, IL-71, IL-72, IL-73, IL-74, IL-75, IL-76, IL-77, IL-78, IL-79, IL-80, IL-81, IL-82, IL-83, IL-84, IL-85, IL-86, IL-87, IL-88, IL-89, IL-90, IL-91, IL-92, IL-93, IL-94, IL-95, IL-96, IL-97, IL-98, IL-99, IL-100, IL-101, IL-102, IL-103, IL-104, IL-105, IL-106, IL-107, IL-108, IL-109, IL-110, IL-111, IL-112, IL-113, IL-114, IL-115, IL-116, IL-117, IL-118, IL-119, IL-120, IL-121, IL-122, IL-123, IL-124, IL-125, IL-126, IL-127, IL-128, IL-129, IL-130, IL-131, IL-132, IL-133, IL-134, IL-135, IL-136, IL-137, IL-138, IL-139, IL-140, IL-141, IL-142, IL-143, IL-144, IL-145, IL-146, IL-147, IL-148, IL-149, IL-150, IL-151, IL-152, IL-153, IL-154, IL-155, 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Příklady: FCoV/FIP

- ✓ Coronaviry jako model proměnlivých patogenů
- ✓ Coronavirové infekce lidí a zvířat: SARS, MERS
- ✓ Kočičí model komplexní etiopatologie

Ke všem příkladům: [viz Modelové nemoci](#)

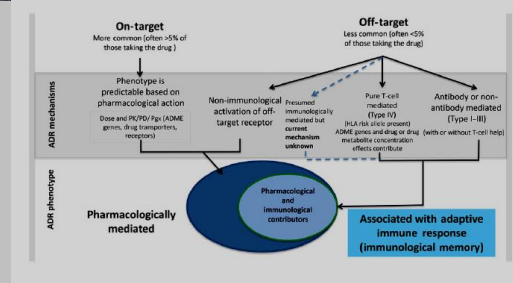
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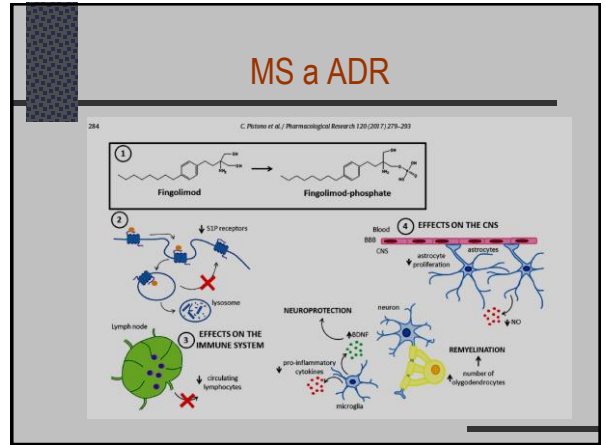
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Farmakogenetika: ADR



Drug	DIR	HLA risk alleles	PPV	NPV	Populations
Abacavir	R57, D95	B*57:01 ^{HLA-B*57:01}	55%	100%	European, African
Carbamazepine	S5, T55	B*15:02 ^{HLA-B*15:02}	3%	100% in Han Chinese	Han Chinese, Thai, Malaysian, Indian
		B*15:11 ^{HLA-B*15:11}			Korean, Japanese
		B*15:18, B*59:01 and C*9:04 ^{HLA-B*15:18, HLA-B*59:01, HLA-C*9:04}			Japanese
MS, DRB1, DRESS		A*11:01 ^{HLA-A*11:01}	0.89%	99.99%	Japanese, northern European, Korean, Caucasians
		A*11:01	0.89%	99.87%	Chinese
		A*11:01	0.89%	99.87%	Northern European, Japanese, and Korean
		A*11:01 (break) ^{HLA-A*11:01}	94.9%	96.7%	Japanese
MFE	Any DRB	A*11:01	94%	96.7%	
		A*11:01	94%	100% in Han Chinese	Han Chinese, Thai, European, Indian, Korean
Alogliptin	S5, T55, D95, D95S	B*58:01 (or B*58 haplotype) ^{HLA-B*58:01}	9%	100% in Han Chinese	Han Chinese, Thai, European, Indian, Korean
		S, MFE	B*15:02 and B*15:18 ^{HLA-B*15:02}	15.02 - 0.73%	15.02 - 99.97
Rizatriptan	S5, T55	B*15:02 (break) ^{HLA-B*15:02}			Han Chinese
		B*15:02 (no association) ^{HLA-B*15:02}			Han Chinese
Fluvoxotin	S5, T55, D95S, MFE	B*15:02 (break) ^{HLA-B*15:02}			Han Chinese
		B*15:02 (no association) ^{HLA-B*15:02}			Han Chinese
Nevirapine	S5, T55, R57, D95, D95S	C*9A:01 ^{HLA-C*9A:01}	18%	96%	Malawian
		DRB1*01:01 & DRB1*01:02 (haplotypes and low CD4) ^{HLA-DRB1*01:01, HLA-DRB1*01:02}	18%	96%	Australian, European and South African
		C*9A:01, C*9B:01, B*14 haplotype ^{HLA-C*9A:01, HLA-C*9B:01, HLA-B*14}			Indian and Japanese
Delayed rash	DRB1*01:01	B*15:01 ^{HLA-B*15:01}	16%	97%	Asian
		B*15:02 ^{HLA-B*15:02}			French
Etoposide	S55	B*15:01 ^{HLA-B*15:01}	7.8%	99.8%	African, Asian, European, and Thai
		B*15:02 ^{HLA-B*15:02}			French
Eflornithin	S5, T55	DRB1*01:01 ^{HLA-DRB1*01:01}			European
		DRB1*15:01 ^{HLA-DRB1*15:01}			European
Sulfamethoxazole trimethoprim	D91	A*02:01 ^{HLA-A*02:01}			
		DQB1*06:02 ^{HLA-DQB1*06:02}			
Lamivudine	D91	DRB1*15:01-DQB1*06:02-DREB1*01:01-DQA1*01:02 haplotype ^{HLA-DRB1*15:01, HLA-DQB1*06:02, HLA-DREB1*01:01, HLA-DQA1*01:02}			International, multi-center
		DRB1*15:01 and DQA1*01:02 ^{HLA-DRB1*15:01, HLA-DQA1*01:02}			Swedish
Indinavir	D91	B*44:03 ^{HLA-B*44:03}			European



MS a ADR

Table 2
HLA alleles related to a different response to the injectable drugs employed in MS treatment. NAb = neutralizing anti-drug antibodies; OR = Odds Ratio.

Drug	Genes	Alleles	Response to treatment	OR	Studied populations	References
Natalizumab	HLA-DQB1	DRB1*13	Higher risk of developing natalizumab-related myelitis/encephalomyeloid reactions	4.06	French, Spanish, German	[141]
		DRB1*14	Protective effect on the development of myelitis/encephalomyeloid reactions	0.2		
Catastrophic uveitis	HLA-DQB1	DRB1*1501	Positive response	-	Italian	[142]
		DRB1*1501	Positive response	-	American	[143]
		DRB1*1501	Positive response	-	American	[144]
		DQ2	Positive response	-		
Interferon β	HLA-DQB1	DRB1*01	No response	-		
		DQ2	No response	-		
		DRB1*01	Increased risk to produce NAb	5.158/6	German	[151]
		DRB1*08, DRB1*04, DRB1*01	Increased risk to produce NAb	-	German	[152]
HEA-DQB1	DQB1*15	DRB1*15	Risk to produce biologically relevant NAb times following intramuscular IFNβ-1a administration	4.36	Swedish	[153]
		DRB1*15	High risk to produce NAb times following intramuscular IFNβ-1a administration	4.15		
		DRB1*15	Risk to produce biologically relevant NAb times following intramuscular IFNβ-1a administration	8.16		
HLA-DQA1	DQA1*05	DQA1*05	Decreased risk to produce biologically relevant NAb times following intramuscular IFNβ-1a administration	0.29		
		DQA1*05	High risk to produce NAb times following intramuscular IFNβ-1a administration	3.53		

Zmatení pojmů

➤ *Farmakogenetika*

➤ *Farmakogenomika*

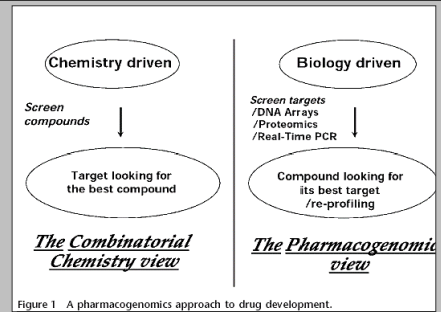
Farmakogenomika a farmakogenetika

Table 1 Terminology.

- Pharmacogenetics
 - Differential effects of a drug – *in vivo* – in different patients, dependent on the presence of inherited gene variants
 - Assessed primarily genetic (SNP) and genomic (expression) approaches
 - A concept to provide more patient-/disease-specific health care
 - One drug – many genomes *i.e.*, different patients)
 - Focus: patient variability
- Pharmacogenomics
 - Differential effects of compounds – *in vivo* or *in vitro* – on gene expression, among the entirety of expressed genes
 - Assessed by expression profiling
 - A tool for compound selection/drug discovery
 - Many “drugs” (*i.e.*, early-stage compounds) – one genome (*i.e.*, “no imitative” genome [database, technology platform])
 - Focus: compound variability

Lindpaintner, 2003

Farmakogenomika v produkci léčiv

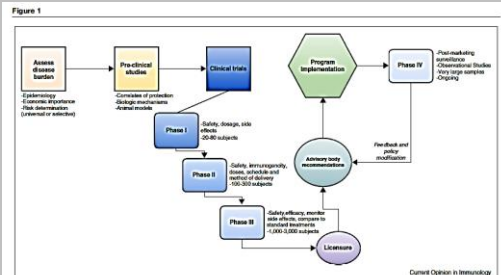


Grenet, 2002

Farmakogenomika a transgenoze

- Rekombinantní produkty mikroorganismu
- DNA vakcíny
- Transgenní savci

Infekční onemocnění: vakcinace



Current Opinion in Immunology

Vakcinace a genetika

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

PRINCIP VAKCÍN

Odstranění patogenity při zachování imunogenity

TYPY VAKCÍN

- # 1. generace
- # 2. generace (*rekombinantní*)
- # 3. generace (*DNA*)

VAKCÍNY 1. GENERACE

- # Živé *atenuované*
- # Inaktivované (*usmrcené*)

PRINCIP ATENUACE VAKCÍNY

M U T A C E

*v genu/genech pro
patogenitu*

VAKCÍNY 2. GENERACE

- # *Podjednotkové*
- # *Deleční*
- # *Deleční markerové*
- # *Živé chimérické*
- # *Antiidiotypové*

PODJEDNOTKOVÉ VAKCÍNY

*Gen kódující antigenní protein je
vložen do bakterie, která následně
produkuje čistý antigen*

DELEČNÍ VAKCÍNY

*Cílenou mutagenezí je odstraněn
gen/genová oblast zodpovědná
za patogenní efekt*

DELEČNÍ MARKEROVÉ VAKCÍNY

Cílenou mutagenézí je odstraněn/vložen/ nejen gen/genová oblast zodpovědná za patogenní efekt, ale i gen pro dobře zjištělý antigenní protein (marker)

Lze tedy odlišit postinfekční a postvakcinační imunitu

ŽIVÉ CHIMÉRIČKÉ VAKCÍNY

Do genomu vektoru je vložen gen/genová oblast kódující antigenní protein(y)

VAKCÍNY 3. GENERACE

DNA vakcíny: do organismu se nevpravuje antigen, ale gen, který jej kóduje

*DNA ==> RNA ==> Protein (cizí)
==> Imunizace in vivo*

DNA VAKCÍNY

Indikovány k využití když:

- ‡ *je antigenní protein obtížně purifikovatelný nebo je purifikací zničen*
- ‡ *antigenní protein není znám, i když známe gen*
- ‡ *protilátky produkované po DNA imunizaci mohou sloužit k purifikaci proteinu*
- ‡ *slabě imunogenní proteiny získají imunogenitu po fúzi s genem pro vysoce imunogenní protein*

MODULACE IMUNITNÍ ODPOVĚDI PŘI DNA IMUNIZACI

- # *Geny pro cytokiny*
- # *Adjuvantní efekt DNA*

Farmakogenomika a transgenoze

- *Transgenní savci*

TRANSGENNÍ SAVCI

- # *Genové konstrukty*
- # *Genové konstrukty s tkáňově specifickými promotory*

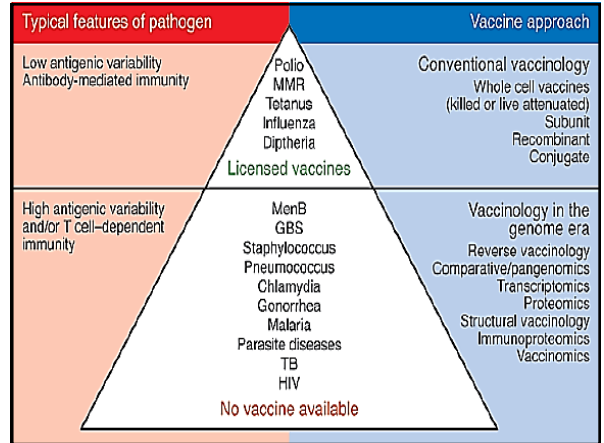
TRANSGENNÍ SAVCI

- #
- # *Genové konstrukty s tkáňově specifickými promotory*

TRANSGENNÍ SAVCI

s tkáňově specifickými promotory:

BIOREAKTORY

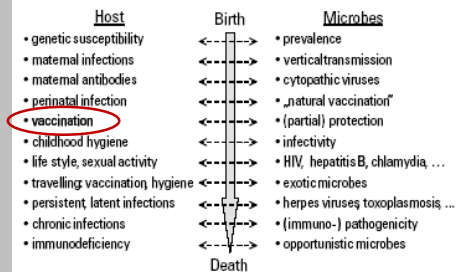


Vakcinace a genetika

➤ Využití genetických principů při produkci nových vakcín, farmakogenomika

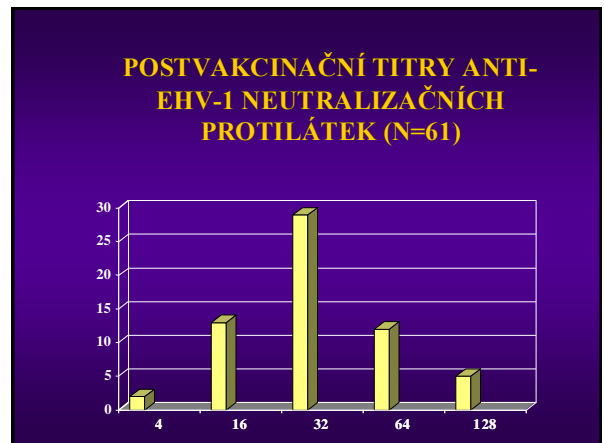
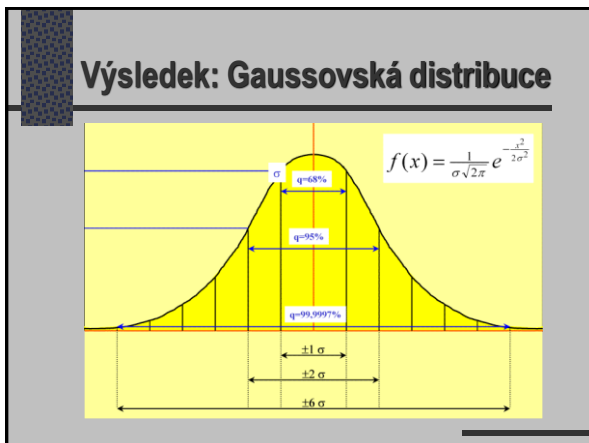
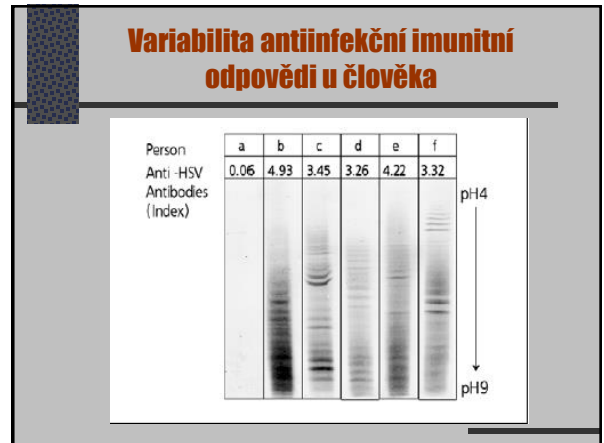
➤ Individuální variabilita imunitní odpovědi po vakcinaci

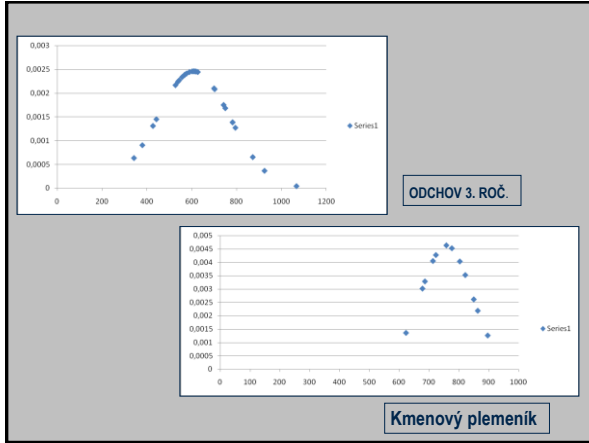
Člověk a infekce



Příčiny selhání účinku vakcinace proti chřipce

- ◆ Druh vakcíny a její kvalita
- ◆ Změna viru
- ◆ Nereaktivita hostitele





Genetics of vaccination

Table 1. Host mechanisms involved in vaccine-induced immune responses

Function	Genes (examples)
Attachment, entry, replication (live vaccines)	CD150/SLAM
Antigen recognition	Toll-like receptors
Antigen uptake by and activation of innate immune system	HLA class III genes (complement proteins C3 and C4), costimulatory molecules (CD80, CD86), CD21, CD35, killer Ig-like receptors
Antigen processing and presentation	HLA class I/II genes, TAP, CD21, CD35
B/T lymphocyte function	CD40, CD40 ligand, B/T cell receptors, G proteins
Immune regulation	Cytokines, monokines, C-C chemokines (and receptors)
Effector and accessory cell function	Fc receptors

SLAM = Signaling lymphocyte activation molecule, identified as measles virus receptor.

Infekční onemocnění: vakcinace

Molecular & Systems Immunology

The genetic regulation of infant immune responses to vaccination

Molecular & Systems Immunology

Table 1. Summary of studies that have investigated heritable immune responses to vaccines.

Study	Study site and age group	Vaccine	Immune response studied	Heritability (h ²) (95% CI)
Reaper et al. 10	The Gambia, school leavers	BCG	IFN-γ	41 (32-51)
			IL-10	48 (36-59)
			IFN-γ/IFN-β	30 (20-41)
			IL-10/IFN-β	30 (20-41)
			IL-10/IFN-β ratio	71 (60-82)
			Anti-IFN-β autoantibodies	44 (33-55)
			IL-10/IFN-β	44 (33-55)
			IFN-γ/IFN-β	44 (33-55)
			IFN-γ/IFN-β ratio	44 (33-55)
			IFN-γ/IFN-β ratio	44 (33-55)
Hollander et al. 38	Germany, adult twins	Hepatitis B	Anti-HBs Ab titer	31 (20-41)
			Anti-HBe Ab titer	31 (20-41)
			Anti-HBc Ab titer	31 (20-41)
			Anti-HBc IgG titer	31 (20-41)
			Anti-HBc IgM titer	31 (20-41)
			Anti-HBc IgA titer	31 (20-41)
			Anti-HBc IgE titer	31 (20-41)
			Anti-HBc IgG/IgM ratio	31 (20-41)
			Anti-HBc IgG/IgM ratio	31 (20-41)
			Anti-HBc IgG/IgM ratio	31 (20-41)

Table 2. Genetic regulation of infant immune responses to vaccination.

Study	Study site and age group	Vaccine	Immune response studied	Heritability (h ²) (95% CI)
Reaper et al. 10	The Gambia, school leavers	BCG	IFN-γ	41 (32-51)
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Genetics of vaccination

Table 3. Heritability estimates of vaccination responses in twin studies

Vaccine	Parameter	DZ ²	MZ ²	Population	Age	Study	Heritability, %	95% CI	References
Measles	antibody	55	45	USA ^a	2-18 years	cross-sectional	89	≥ 52 ^b	18
Mumps	antibody	55	45	USA ^a	2-18 years	cross-sectional	39	≥ 2 ^b	18
Rubella	antibody	55	45	USA ^a	2-18 years	cross-sectional	46	≥ 5 ^b	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
PHA Toxin	IFN-γ	159	48	Gambia	5 months	prospective	65	50-76	12
PHA 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	12
PPD	IL-13	159	48	Gambia	5 months	prospective	46	5-75	12
Hsp65	IL-13	159	48	Gambia	5 months	prospective	50	29-67	12

HLA a spalničky

Associations between HLA gene polymorphisms and humoral (IgG antibody) and cellular (lymphoproliferation) immune responses to measles vaccine

HLA gene	Variant	Effect	Reference
Class I allele	B*8, B*13, B*44	Decreased antibody (single dose)	[14]
Class I allele	B*7	Increased antibody (single dose)	[15]
Class II allele	DRB1*03, DQA1*0301	Increased antibody (single dose)	[15]
Class II allele	DRB1*08, DQA1*0304, DRB1*0202	Increased antibody (single dose)	[15]
Class I supertype	B7	Increased antibody (two doses)	[17]
Class I supertype	B44	Decreased antibody (two doses)	[17]
Class I supertype	B58	Decreased antibody (two doses)	[17]
Class I haplotype	A*24-C*03-B*15	Decreased antibody (two doses)	[18]
Class II haplotype	DRB1*07-DQA1*03-DRB1*04	Decreased antibody (two doses)	[18]
Class II haplotype	DRB1*07-DQA1*02-DRB1*02	Decreased antibody (two doses)	[18]
Class II haplotype	DRB1*1516-DQB1*05-DRB1*04	Increased antibody (two doses)	[18]
Class I haplotype	A*35-C*12-B*38	Increased cellular (two doses)	[18]
Class II haplotype	DRB1*04-DQA1*03-DRB1*03	Increased cellular (two doses)	[18]
Class II haplotype	DRB1*03-DQA1*02-DRB1*04	Increased cellular (two doses)	[18]

Cytokine and cytokine receptor SNP associations with humoral (IgG antibody) and cellular (lymphoproliferation) immune responses to measles vaccine

Gene	SNP ID	Genotype	Phenotype
IL-2	rs2059962	GG/TC/TT	Antibody ^{low} /Cellular ^{high}
	rs2059963	GG/TC/TT	Antibody ^{high} /Cellular ^{low}
IL-10	rs1800889	AA/TA/TT	Antibody ^{high} /Cellular ^{low}
	rs1800874	AA/CA/GC	Antibody ^{low} /Cellular ^{high}
	rs1800572	AA/GA/CC	Antibody ^{high} /Cellular ^{low}
IL-12RB	rs13740567	AA/GA/GC	Antibody ^{high} /Cellular ^{low}
	rs272889	AA/GA/GC	Antibody ^{high} /Cellular ^{low}

No. of measles vaccine doses (MMR 5)	HLA class I allele	HLA class II allele
1 dose	B*8, B*13, B*44	DRB1*03, DQA1*0301
2 doses	B*44:B1	None

