Klinická genetika pro mediky

Nové trendy v klinické genetice: genomická medicína

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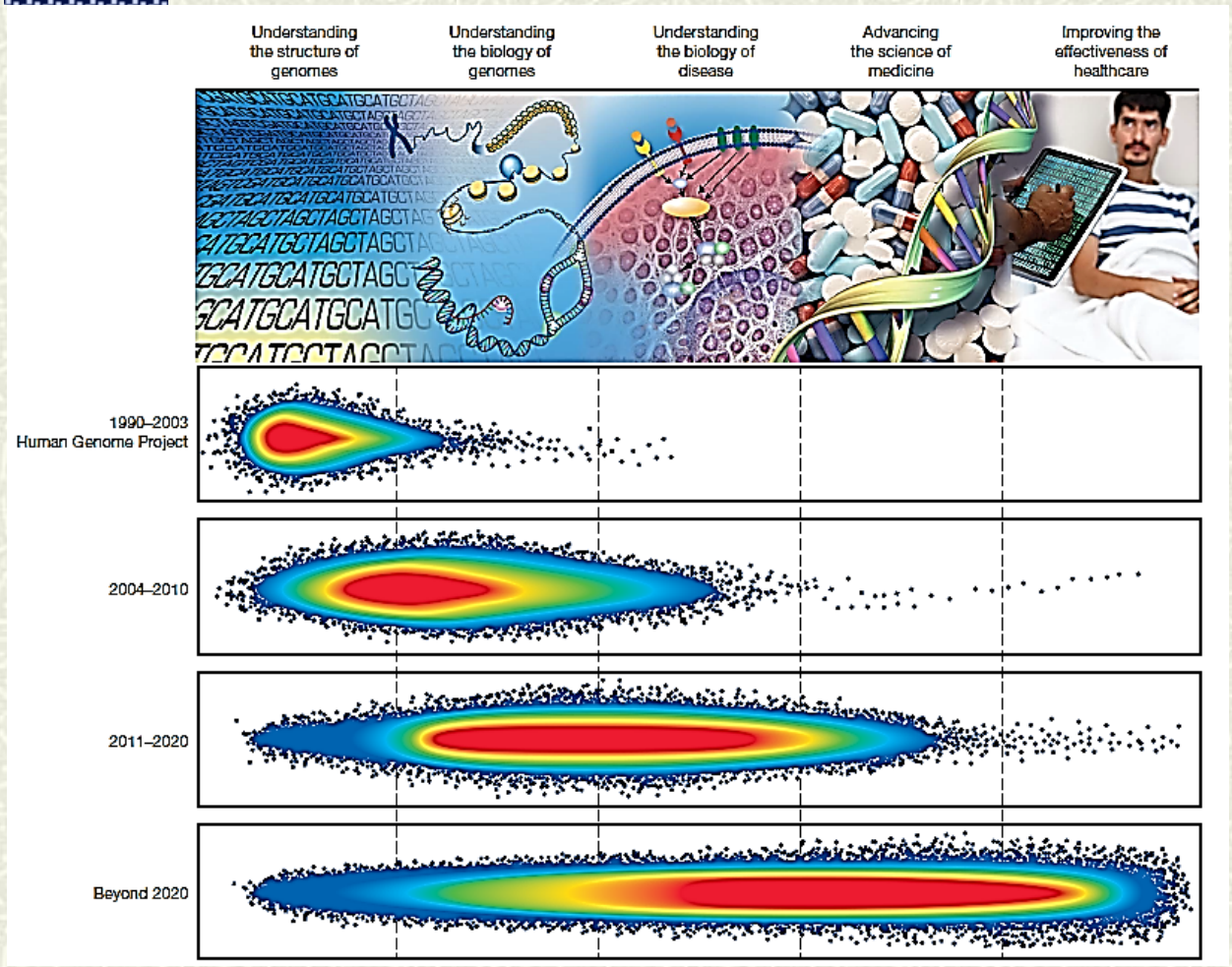
Outline

- ✓ *Genomická medicína: motivace pro lékaře*
- ✓ *Genomy, geny, genetická variabilita, nemoci*
- ✓ *Genomika a medicína: nástroje*
- ✓ *Praktické aplikace*

Genomická medicína: *predikce z roku 2011*



Charting a course for genomic medicine from base pairs to bedside

Green et al. 2011

204 | NATURE | VOL 470 | 10 FEBRUARY 2011

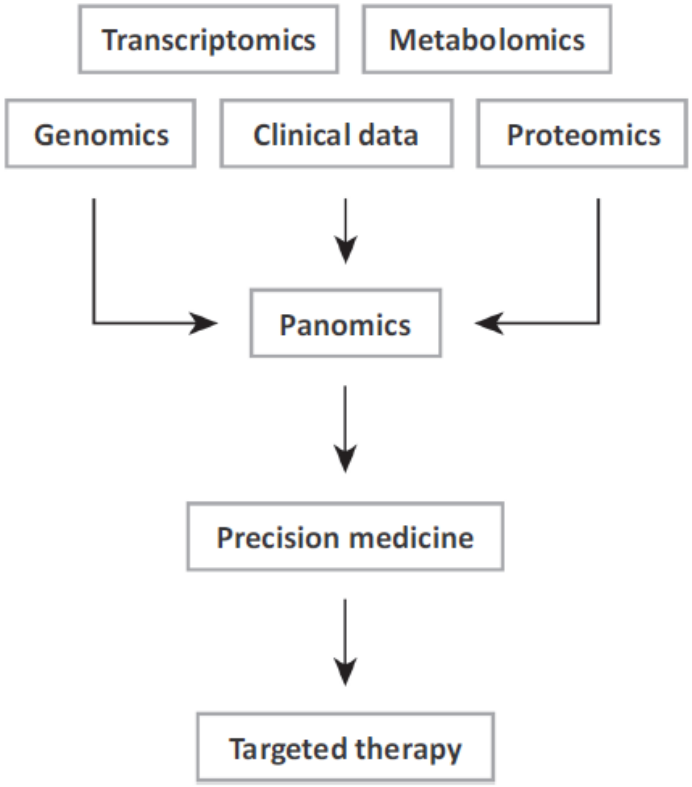
Genomická medicína v praxi

Genetics inMedicine | REVIEW

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]

Personalizovaná medicína



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 Medicine

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

Genomická medicína v praxi

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PERSPECTIVE

OPEN ACCESS

Toward clinical genomics in everyday medicine: perspectives and recommendations

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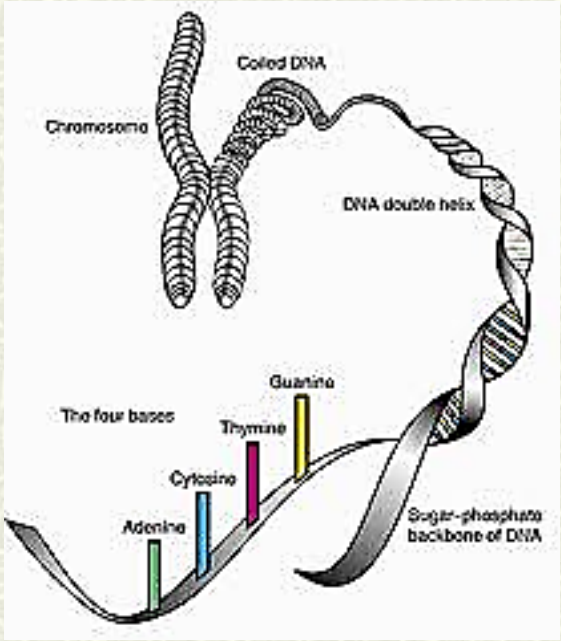
Doporučení pro lékaře

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 genomických vyšetření natolik, aby dokázali korektně interpretovat klinický význam diagnostikovaných genomických variant

Genomika:
lidský (savčí) genom



- ✓ > 1m DNA
- ✓ 24 chromosomů, mtDNA
- ✓ > 3,100,000,000 bp
- ✓ 20,000–25,000 protein kódujících genů
- ✓ (< 2% genomu)
- ✓ „Junk“ DNA: RNA, repetice, ??

Genomika a holismus

Slide courtesy of Prof. Jamie McLeod, UK Lexington

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

Postgenomic era

Kompletní sekvence lidského genomu (Human genome project 2001)

http://www.ncbi.nlm.nih.gov/Genomes/

Anotace genomu

Sekvenování dnes

- ✓ *DNA Sanger (1-2 kb)*
- ✓ *DNA NGS (až celé genomy)*
- ✓ *DNA NGS LR: „HiFi“ (50 kb)*
- ✓ *DNA exom*
- ✓ *RNA Iso seq: full-length cDNA, PacBio SMRT sekvenování*

Nová genomika

- ✓ *T2T genome(s)*
- ✓ *Multi omics*
- ✓ *Pangenomics, pangenomes*

Multiomics

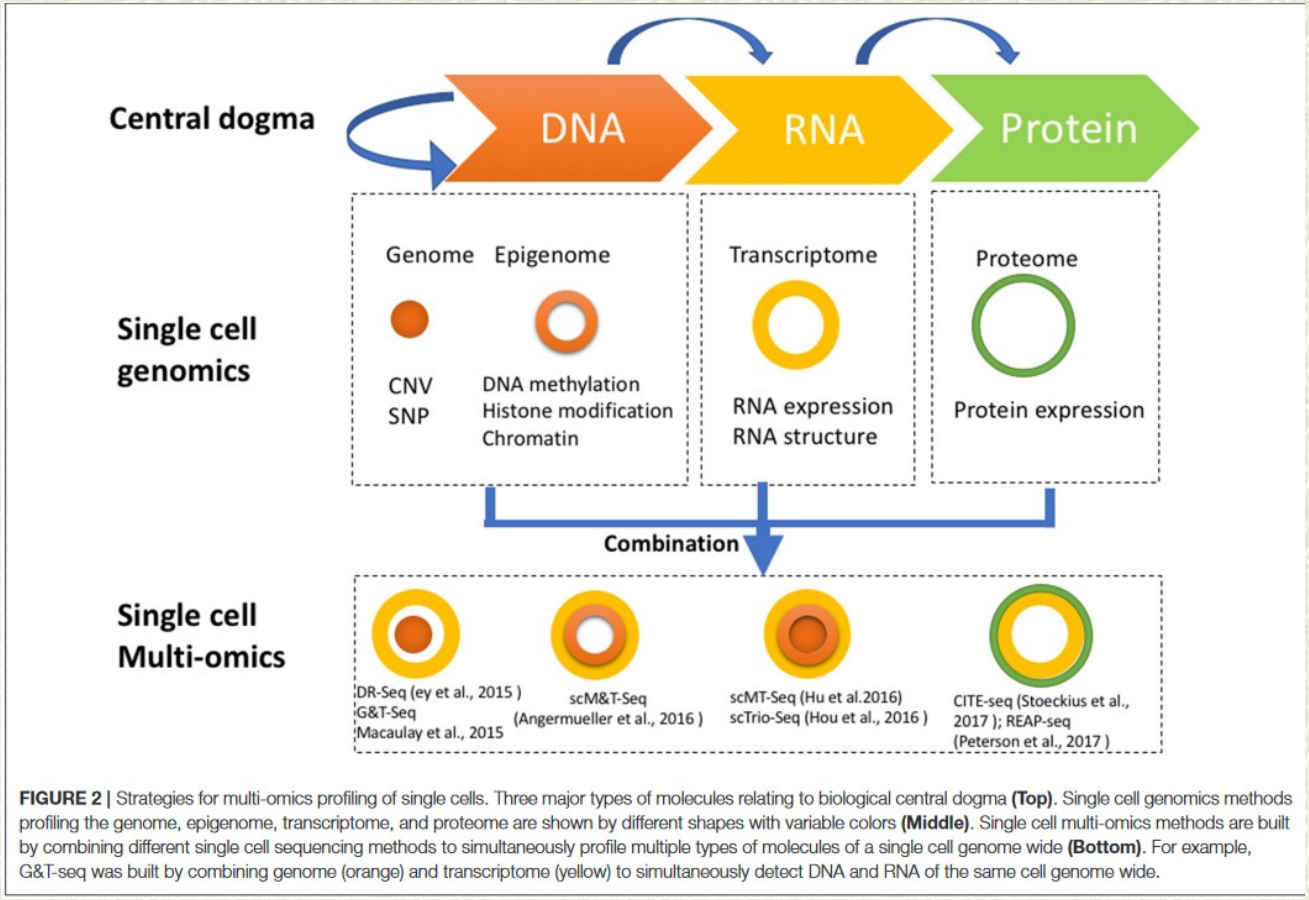


FIGURE 2 | Strategies for multi-omics profiling of single cells. Three major types of molecules relating to biological central dogma **(Top)**. Single cell genomics methods profiling the genome, epigenome, transcriptome, and proteome are shown by different shapes with variable colors **(Middle)**. Single cell multi-omics methods are built by combining different single cell sequencing methods to simultaneously profile multiple types of molecules of a single cell genome wide **(Bottom)**. For example, G&T-seq was built by combining genome (orange) and transcriptome (yellow) to simultaneously detect DNA and RNA of the same cell genome wide.

https://doi.org/10.3389/fcell.2018.00028

Multiomics:

Nemoc definována na všech úrovních

- ✓ *Genom*
- ✓ *Epigenom*
- ✓ *Transkriptom*
- ✓ *Proteom*
- ✓ *Metabolome*
- ✓ *Mikrobiom*

Regulační okruhy u komplexních fenotypů

Pangenomes

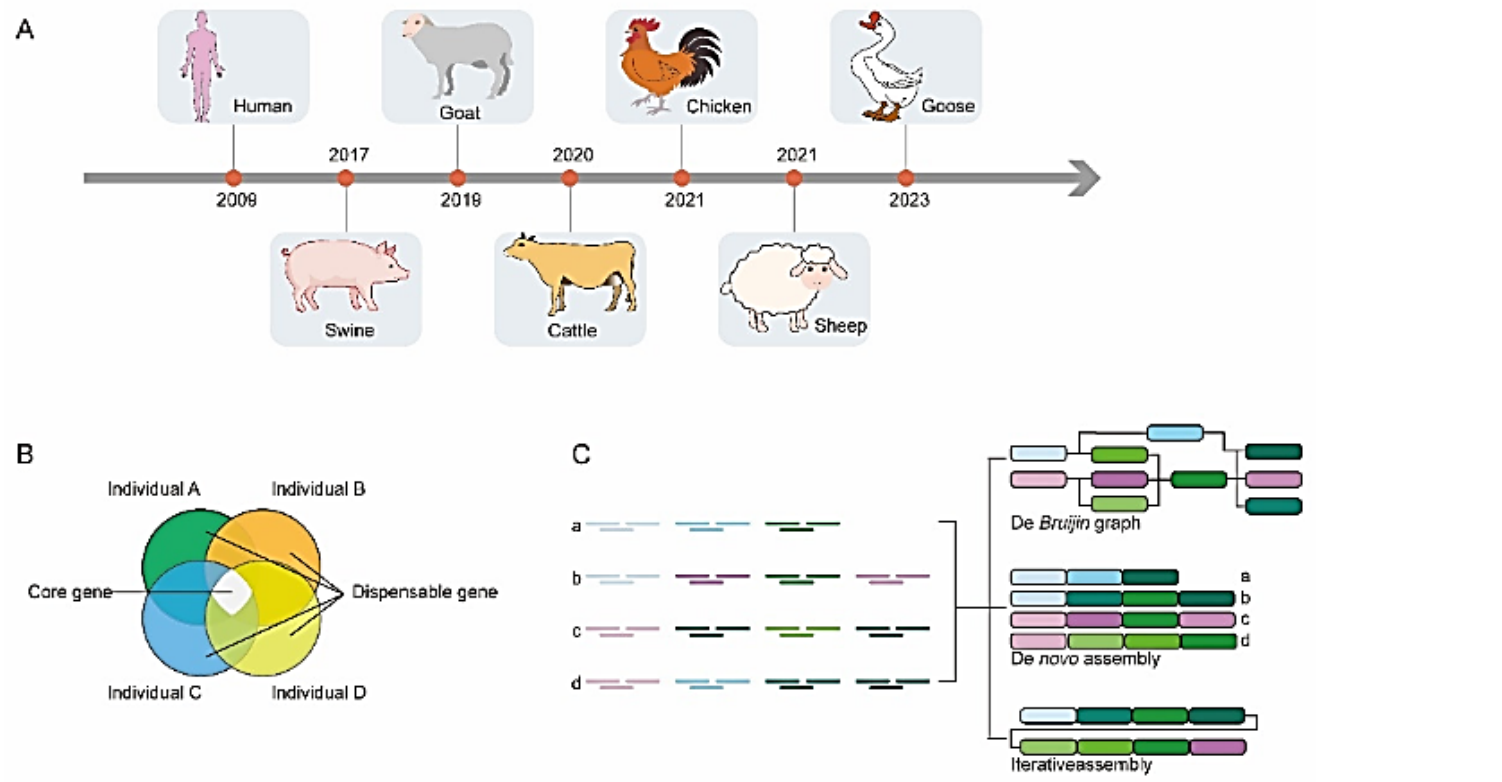


Figure 2. The development process and construction methods of pan-genomic research. (A) Numerous species have developed pan-genomes, including emiliania huxleyi. (B) Pan-genomes comprise core genes, dispensable genes, and strain-specific genes. (C) Pan-genome construction strategies include iterative assembly, de novo assembly, and graphical pan-genomes.

Microbiome and immunogenome

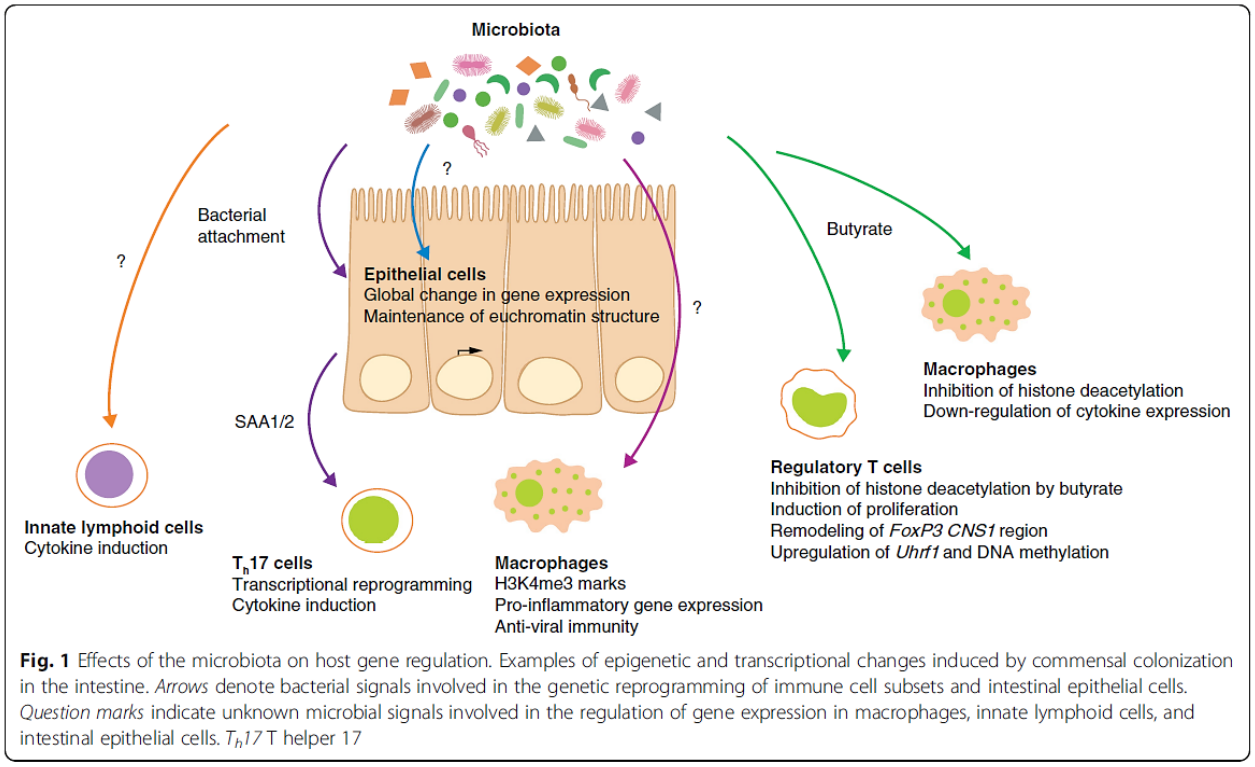


Fig. 1 Effects of the microbiota on host gene regulation. Examples of epigenetic and transcriptional changes induced by commensal colonization in the intestine. *Arrows* denote bacterial signals involved in the genetic reprogramming of immune cell subsets and intestinal epithelial cells. *Question marks* indicate unknown microbial signals involved in the regulation of gene expression in macrophages, innate lymphoid cells, and intestinal epithelial cells. T_h17 T helper 17

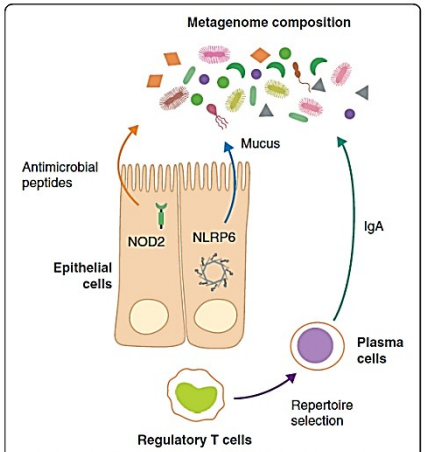


Fig. 2 Effects of the innate and adaptive immune system on metagenome composition. Examples of how the innate and adaptive immune system controls microbiome composition via effector mechanisms. NOD2-dependent secretion of anti-microbial peptides is involved in shaping the configuration of the microbiota. NLRP6 controls mucus secretion by goblet cells, thus having an effect on the epithelial-proximal bacterial compartment. Regulatory T cells orchestrate B-cell-mediated IgA secretion. The IgA repertoire, in turn, controls bacterial targeting by the immune system and thus metagenomic composition. *IgA* immunoglobin A

REVIEW Open Access

Metagenomic cross-talk: the regulatory interplay between immunogenomics and the microbiome

Maayan Levy[†], Christoph A. Thaiss[†] and Eran Elinav[*]

Nemoc:
reakce organismu na patogenní noxu

- ✓ *Návrat k homeostáze ovlivněný charakterem noxy, prostředím, aktuálním stavem organismu a jeho genetickým založením*
- ✓ *Ze své podstaty je individuálně variabilní a manifestuje se jako individuálně variabilní symptomatologie*
- ✓ *Část této variability je genetická*
- ✓ *Potřeba personalizované/precizní medicíny*

Nemoci a geny

Individuální variabilita genomu:

mutace a polymorfismus

- ✓ *Mutace jako příčina dědičných nemocí*
- ✓ *Genetický polymorfismus jako příčina variability v odolnosti a vnímavosti k nemocem*

Dědičná onemocnění

Úloha genomu ve vzniku nemocí
0.6% VCHA, 8% Mendelistická DO, 90% Multifaktoriální DO, 1.4% jiný než genetický problém

- ✓ Jednoduchá (mendelistická)
  3000 lokusů
- ✓ Komplexní
  před 10 lety 900 lokusů, dnes tisíce

Dědičnost nemocí a vnímavosti k nemocem

- ✓ Mendelistická*: jednotlivé mutace se silným účinkem na fenotyp*
- ✓ Komplexní: *interakce polymorfních variant (SNP) mnoha genů*

Molekulární podstata:
Single nucleotide polymorphisms (SNPs)

- ✓ *Nukleotidová sekvence*

*cgcgcggcctcttgtgg**c**catcctggtcctcctaaaccacctggac*

*cgcgcggcctcttgtgg**t**catcctggtcctcctaaaccacctggac*

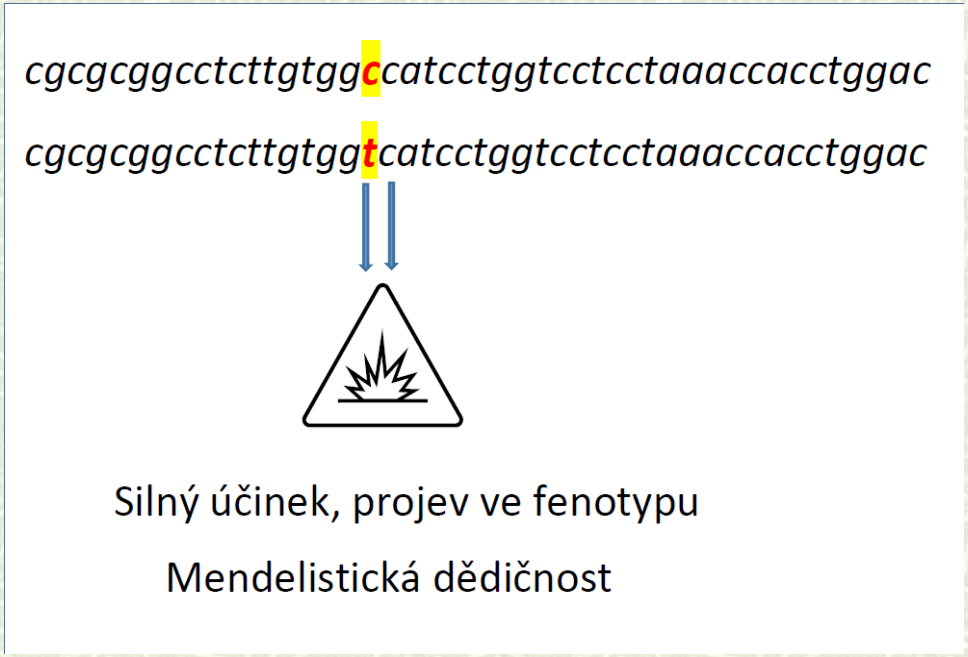
- ✓ *Alely*

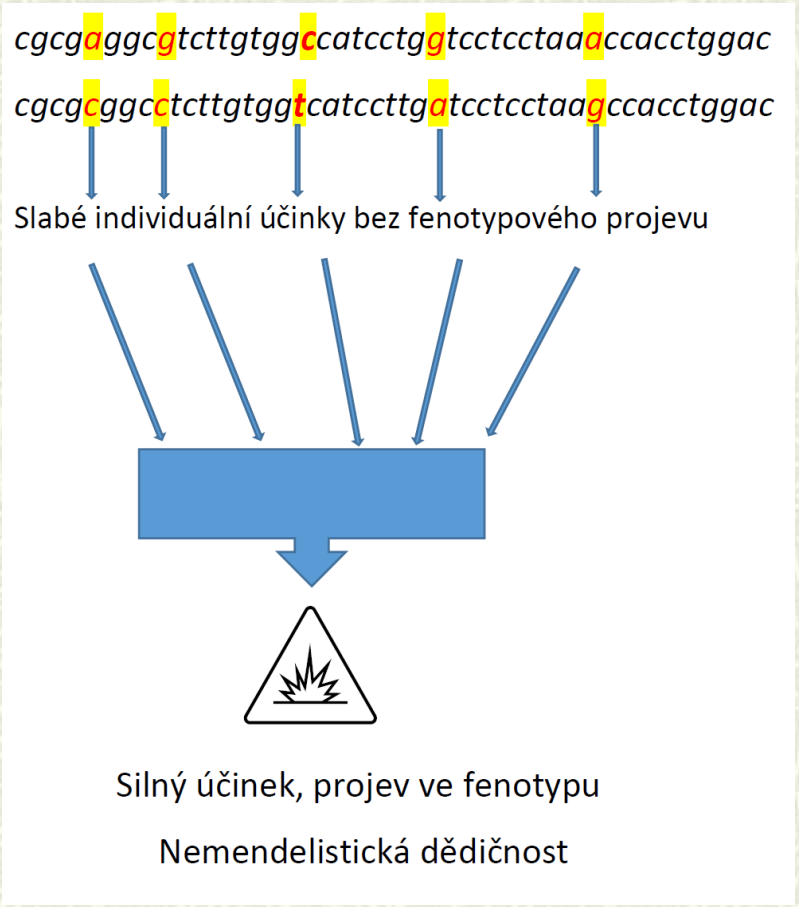
C, T

- ✓ *Genotypy*

CC, CT, TT

Mendelistická vs. nemendelistická dědičnost, jednoduché vs. komplexní znaky: molekulární podstata





Nové trendy

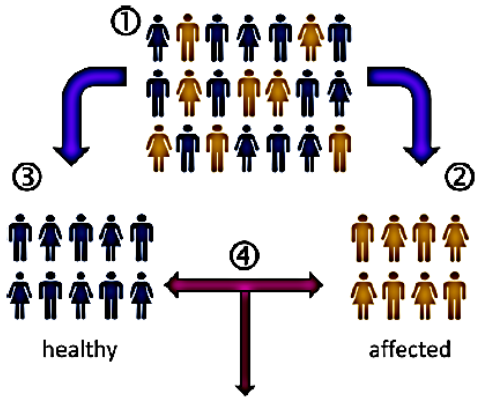
- ✓ *Genomy a nemoci: genomická medicína*
- ✓ *Mendelistická dědičná onemocnění: masivní genetická testování*
- ✓ *Komplexní znaky a jejich dědičnost v medicíně: molekulární disekce, markery*
- ✓ *Genetická odolnost/vnímavost k onemocněním: infekční choroby*

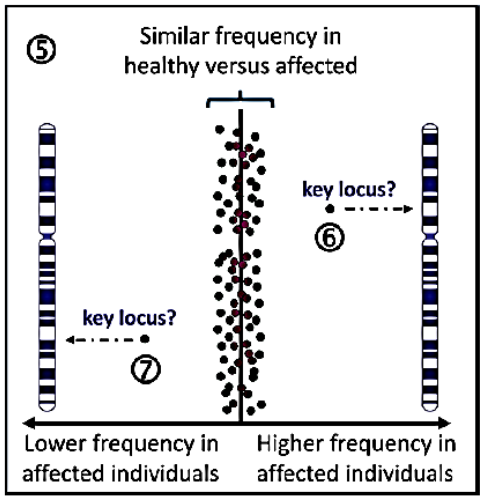
Genomická medicína: miniaturizace a automatizace

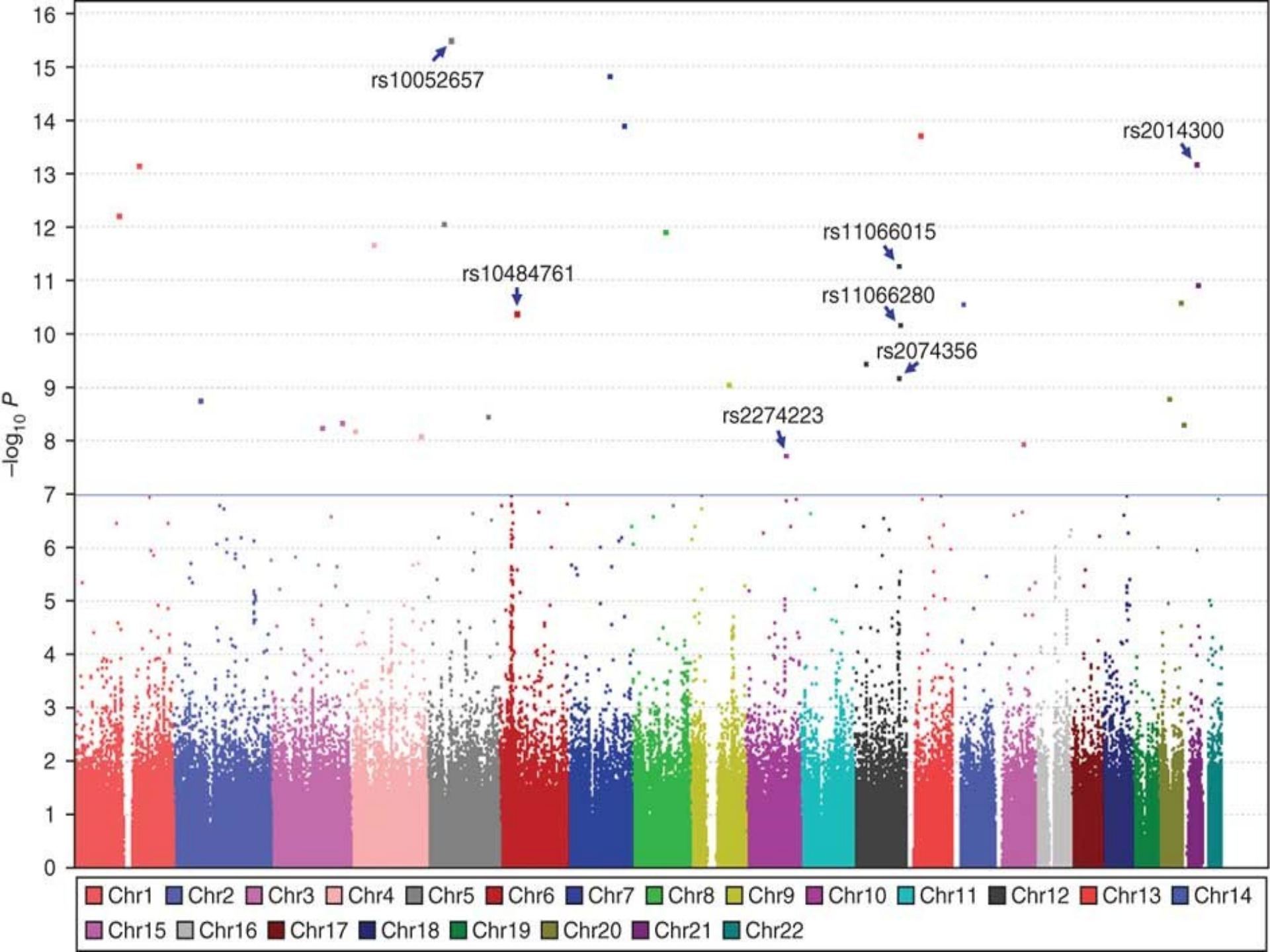
http://www.humgen.nl/SNP_databases.html

Hledání kauzálních genů a polymorfismů: GWAS

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






rs10052657
rs2014300
rs11066015
rs10484761
rs11066280
rs2074356
rs2274223
−log10 P
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Chr1 Chr2 Chr3 Chr4 Chr5 Chr6 Chr7 Chr8 Chr9 Chr10 Chr11 Chr12 Chr13 Chr14
Chr15 Chr16 Chr17 Chr18 Chr19 Chr20 Chr21 Chr22

HOLISTICKÝ PŘÍSTUP

Možnost řešení komplexních problémů:

Příčiny a patogeneze nemocí

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

Genové dráhy a mechanismus nemoci (patogeneze)

Late-onset Alzheimer's disease is a prevalent age-related polygenic disease that accounts for 50–70% of dementia cases. Currently, only a fraction of the genetic variants underlying Alzheimer's disease have been identified. Here we show that increased sample sizes allowed identification of seven previously unidentified genetic loci contributing to Alzheimer's disease. This study highlights microglia, immune cells and protein catabolism as relevant to late-onset Alzheimer's disease, while identifying and prioritizing previously unidentified genes of potential interest. We anticipate that these results can be included in larger meta-analyses of Alzheimer's disease to identify further genetic variants that contribute to Alzheimer's pathology.

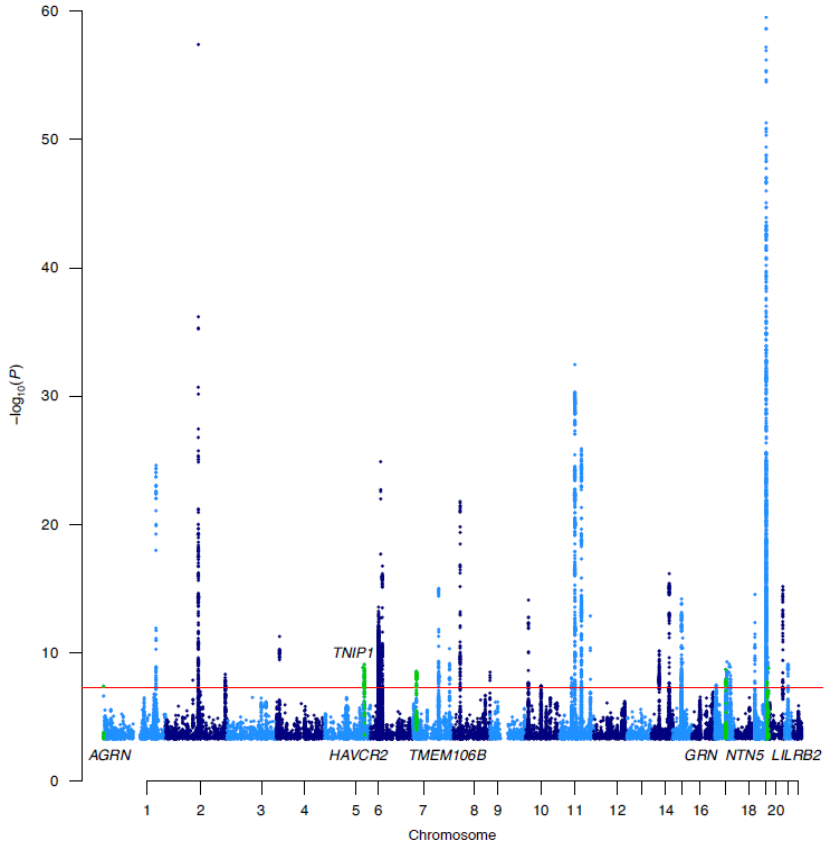


Fig. 1 | A Manhattan plot of the meta-analysis results highlighting 38 loci, including seven previously unidentified regions. Only variants with $P < 0.0005$ are displayed. The *APOE* region cannot be fully observed because the *y* axis is limited to the top variant in the second most significant locus,

ARTICLES
https://doi.org/10.1038/s41588-021-00921-z
nature genetics

A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease

ARTICLES
https://doi.org/10.1038/s41588-021-00921-z
nature genetics

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A genome-wide association study with 1,126,563 individuals identifies new risk loci for Alzheimer's disease

Table 1 | The 38 genomic risk loci identified from 90,338 (46,613 proxy) cases and 1,036,225 (318,246 proxy) controls

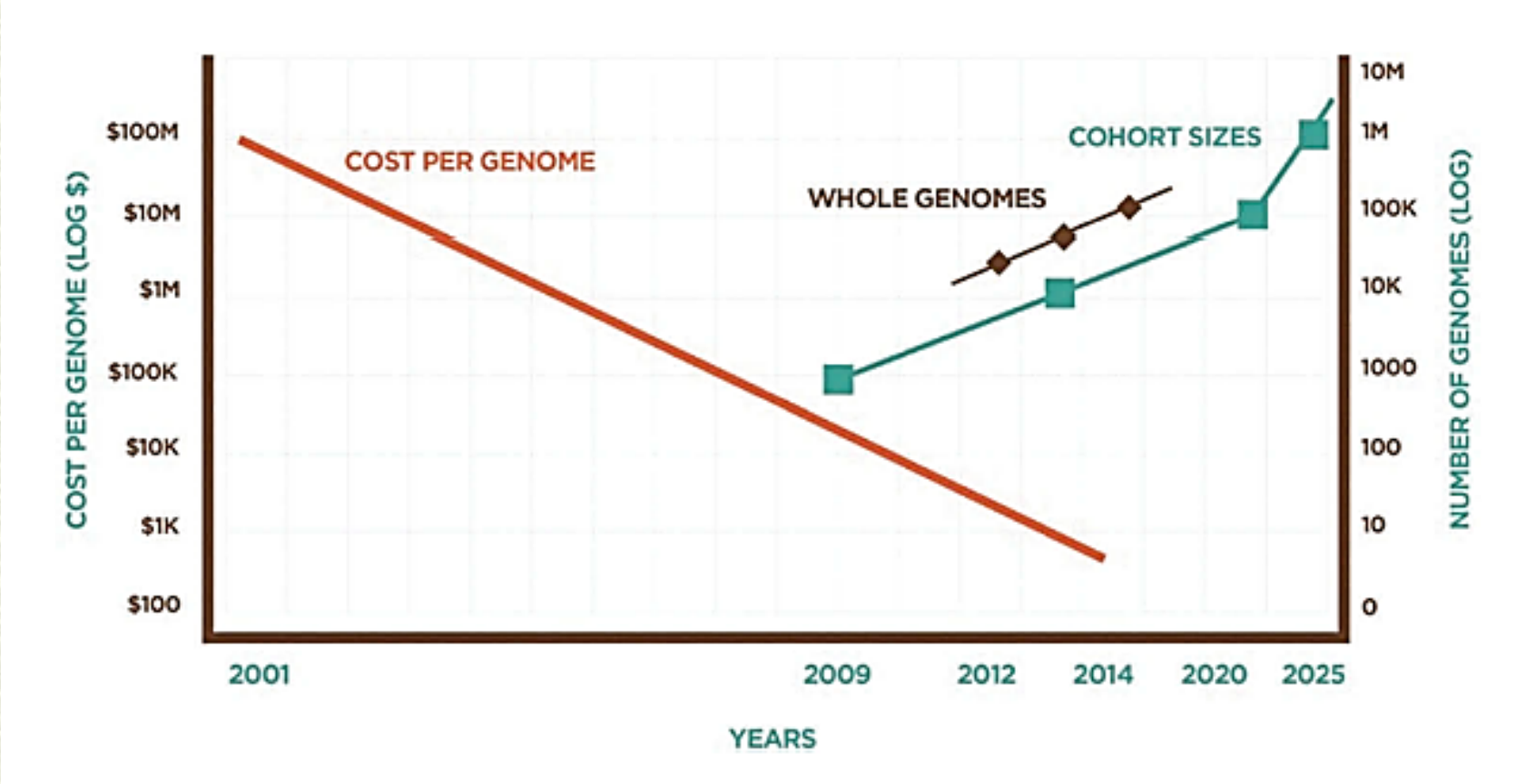
Genomic locus	Gene	Position (GRCh37)	Lead variant	A1	A1 frequency	*P* value	*N*
1	***AGRN***	**1:985,377**	**rs113020870**	**T**	**0.0041**	**3.83×10^{-8}**	**776,379**
2	*CR1*	1:207,750,568	rs679515	C	0.82	2.42×10^{-25}	762,176
3	*NCK2*	2:106,235,428	rs115186657	C	0.0035	1.33×10^{-8}	727,537
4	*BIN1*	2:127,891,427	rs4663105	C	0.41	3.92×10^{-58}	1,078,540
5	*INPPD5*	2:234,082,577	rs7597763	C	0.45	4.65×10^{-9}	819,541
6	*CLNK*	4:11,014,822	rs4504245	G	0.79	5.23×10^{-12}	1,080,458
7	***TNIP1***	**5:150,432,388**	**rs871269**	**T**	**0.32**	**1.37×10^{-9}**	**1,089,904**
8	***HAVCR2***	**5:156,526,331**	**rs6891966**	**G**	**0.77**	**7.91×10^{-10}**	**1,089,230**
9	*HLA-DRB1*	6:32,583,813	rs1846190	A	0.30	2.66×10^{-14}	754,040
10	*TREM2*	6:40,942,196	rs187370608	G	0.997	1.26×10^{-25}	791,668
11	*CD2AP*	6:47,552,180	rs9369716	T	0.27	1.70×10^{-17}	1,052,285
12	***TMEM106B***	**7:12,268,758**	**rs5011436**	**C**	**0.41**	**2.70×10^{-9}**	**1,123,678**
13	*ZCWPW1/NYAP1*	7:99,932,049	rs7384878	T	0.69	9.41×10^{-16}	1,084,138
14	*EPHA1-AS1*	7:143,104,331	rs3935067	G	0.62	4.69×10^{-11}	1,117,025
15	*CLU*	8:27,466,315	rs1532278	T	0.39	1.57×10^{-22}	1,126,563
16	*SHARPIN*	8:145,108,151	rs61732533	G	0.95	3.14×10^{-9}	1,122,653
17	*USP6NL/ECHDC3*	10:11,718,713	rs7912495	G	0.46	7.68×10^{-15}	1,120,367
18	*CCDC6*	10:61,738,152	rs7902657	T	0.54	3.68×10^{-8}	1,126,388
19	*MADD/SPI1*	11:47,380,340	rs3740688	T	0.54	8.78×10^{-9}	1,123,185
20	*MS4A4A*	11:60,021,948	rs1582763	G	0.62	3.40×10^{-33}	1,125,804
21	*PICALM*	11:85,800,279	rs561655	G	0.35	1.24×10^{-26}	1,126,563
22	*SORL1*	11:121,435,587	rs11218343	T	0.96	1.33×10^{-13}	1,125,100
23	*FERMT2*	14:53,298,853	rs7146179	G	0.89	6.99×10^{-11}	1,089,904
24	*RIN3*	14:92,938,855	rs12590654	G	0.67	6.63×10^{-17}	1,116,967
25	*ADAM10*	15:59,057,023	rs602602	T	0.70	6.22×10^{-15}	1,124,268
26	*APH1B*	15:63,569,902	rs117618017	T	0.13	7.00×10^{-12}	889,854
27	*SCIMP/RABEP1*	17:4,969,940	rs7209200	T	0.33	3.18×10^{-8}	1,125,637
28	***GRN***	**17:42,442,344**	**rs708382**	**T**	**0.61**	**1.98×10^{-9}**	**1,125,622**
29	*ABI3*	17:47,450,775	rs28394864	G	0.54	4.90×10^{-10}	1,084,218
30	*TSPOAP1-AS1*	17:56,409,089	rs2632516	G	0.54	7.46×10^{-10}	1,082,451
31	*ACE*	17:61,545,779	rs6504163	T	0.61	1.23×10^{-9}	1,083,145
32	*ABCA7*	19:1,050,874	rs12151021	G	0.68	2.81×10^{-15}	1,082,434
33	*APOE*	19:45,411,941	rs429358	T	0.84	$<1.0\times10^{-300}$	1,126,190
34	***NTN5***	**19:49,213,504**	**rs2452170**	**G**	**0.47**	**1.72×10^{-8}**	**1,088,626**
35	*CD33*	19:51,737,991	rs1354106	G	0.37	2.21×10^{-10}	716,038
36	***LILRB2***	**19:54,825,174**	**rs1761461**	**C**	**0.49**	**1.56×10^{-9}**	**1,116,336**
37	*CASS4*	20:54,995,699	rs6069737	T	0.083	6.73×10^{-16}	1,087,703
38	*APP*	21:27,520,931	rs2154482	T	0.44	7.66×10^{-10}	1,124,606

The *P* values were identified through a meta-analysis (two-sided test) of summary statistics generated by linear/logistic regressions (two-sided test) and were not adjusted for multiple testing. The previously unidentified loci are highlighted in bold. The genes were assigned on the basis of colocalization results, fine-mapping results and previous literature. A1, tested allele; *N*, sample size.

Možnosti genomiky

Mechanismy/ Dráhy → ← *Geny* → ← *Markery*

Genomická medicína: finanční dostupnost



S. K. DELANEY ET AL.

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

Etická východiska: jak naložit s informacemi získanými genomickými metodami

Genomická diagnostika

- ✓ Masivní vyšetření heterozygotnosti u AR DO (carrier test):
  Přenašečství více než 830 nejčastějších mutací 77 genů způsobujících přes 60 AR DO (cystická fibróza, spinální svalová atrofie, vrozené vady metabolismu, poruchy zraku a sluchu, choroby pohybového aparátu a kůže.
- ✓ panel „CZECANCA“ (CZEch CAncer paNel for Clinical Application 226 genů asociovaných s dědičnými nádorovými onemocněními)
- ✓ Exomové sekvenování, celogenomové sekvenování

Molekulární diagnostika: neinvazivní vyšetření plodu

- ✓ Vyšetření volné fetální DNA v mateřské krvi
- ✓ Alternativa k aminocentéze a vyšetření choriových klků na základě výsledků prenatálního skríningu
- ✓ Možnost celogenomového sekvenování plodu

Molekulární diagnostika: neinvazivní vyšetření plodu

JAMA | Original Investigation

Rapid Whole-Genomic Sequencing and a Targeted Neonatal Gene Panel in Infants With a Suspected Genetic Disorder

Jill L. Maron, MD, MPH; Stephen Kingsmore, MD; Bruce D. Gelb, MD; Jerry Vockley, MD, PhD; Kristen Wigby, MD; Jennifer Bragg, MD; Annemarie Stroustrup, MD, MPH; Brenda Poindexter, MD, MS; Kristen Suhrie, MD; Jae H. Kim, MD, PhD; Thomas Diacovo, MD, PhD; Cynthia M. Powell, MD, MS; Andrea Trembath, MD, MPH; Lucia Guidugli, PhD; Katarzyna A. Ellsworth, PhD; Dallas Reed, MD; Anne Kurfiss, MPH; Janis L. Breeze, MPH; Ludovic Trinquart, PhD; Jonathan M. Davis, MD

IMPORTANCE Genomic testing in infancy guides medical decisions and can improve health outcomes. However, it is unclear whether genomic sequencing or a targeted neonatal gene-sequencing test provides comparable molecular diagnostic yields and times to return of results.

OBJECTIVE To compare outcomes of genomic sequencing with those of a targeted neonatal

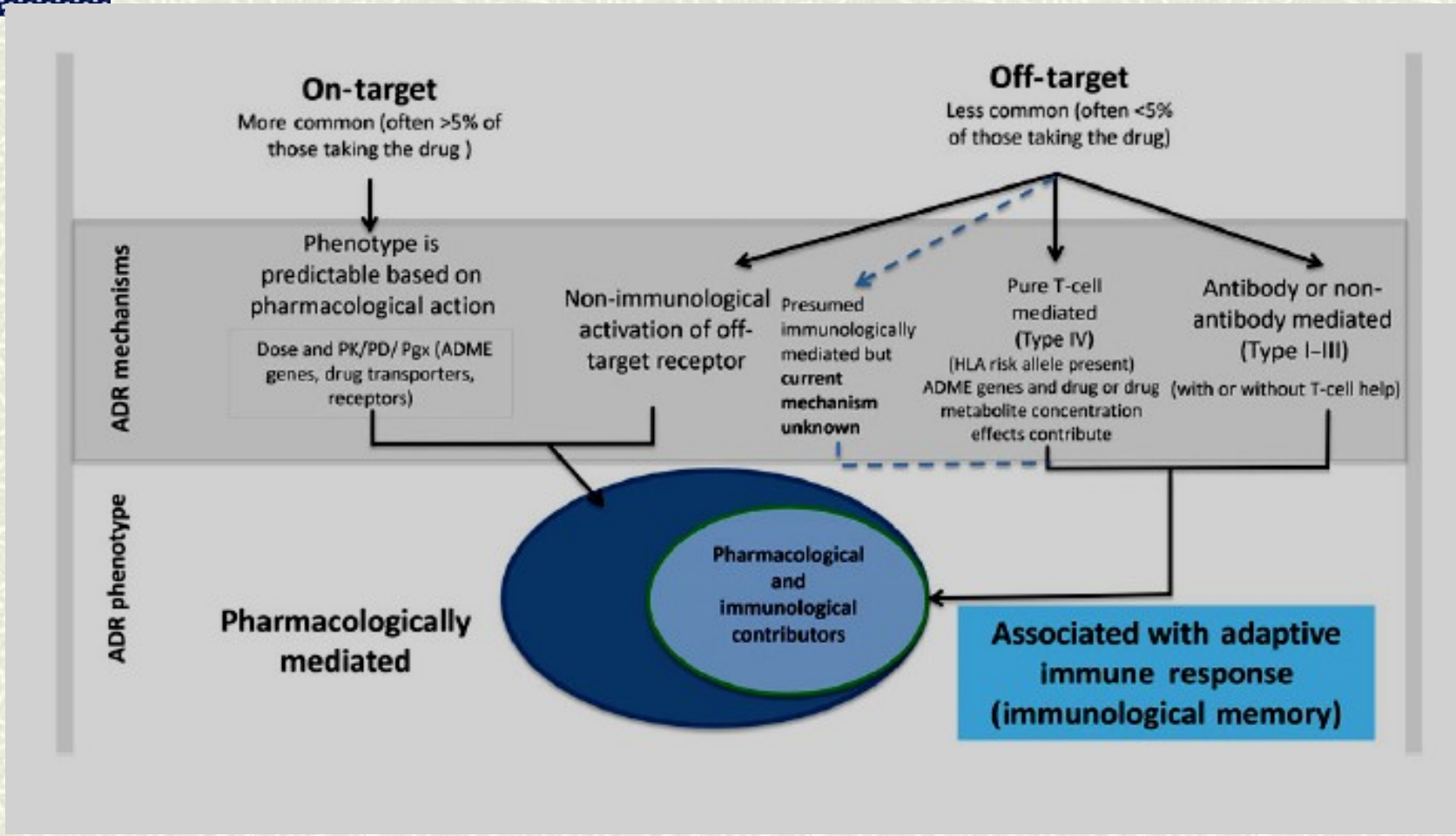
Multimedia

Supplemental content

Preimplantační genetická diagnostika

- ✓ V kontextu asistované reprodukce (punkce blastocysty po IVF)
- ✓ Diagnostika u embryí: cílená na základě rodinné anamnézy nebo skríning nejčastějších mutací u darovaných embryí
- ✓ Selekce embryí

Farmakogenetika: ADR



Farmakogenetika v praxi

Inhibitory protonové pumpy: Dexlansoprazol (A02BC06), Lansoprazol (A02BC03), Omeprazol (A02BC01), Pantoprazol (A02BC02), Rabeprazol (A02BC04); **Antiemetika:** Dronabinol (A04AD10), Metoklopramid (A03FA01), Ondansetron (A04AA01), Tropisetron (A04AA03); **Perorální antidiabetika:** Glibenklamid (A10BB01); **Antiagregancia/Antikoagulancia:** Avatrombopag (B02BX08), Klopidogrel (B01AC04), Warfarin (B01AA03); **Antiarytmika:** Flecainid (C01BC04), Propafenon (C01BC03); **Hypotenziva:** ACE Inhibitory (C09AA), Hydrochlorothiazid (C03EA01); **Inhibitory HMG-COA reduktázy (statiny):** Atorvastatin (C10AA05), Pravastatin (C10AA03), Rosuvastatin (C10AA07), Simvastatin (C10AA01); **Gynekologika:** Flibanserin (G02CX02), Hormonální antikoncepce (G03A); **Antiinfekční látky:** Flucloxacillin (J01CF05), Vorikonazol (J02AC03); **Tuberkulostatika:** Ethambutol (J04AK02), Isoniazid (J04AC01), Pyrazinamid (J04AM05), Rifampicin (J04AB03); **Antivirotika:** Abacavir (J05AF06), Efavirenz (J05AG03), Nevirapin (J05AG01), Peginterferon alfa-2a/b (L03AB11), Ribavirin (J05AP01), Telaprevir (J05AP02); **Cytostatika:** Asparaginasa (L01XX02), Erdafitinib (L01EX16), Fluorouracil (L01BC02), Gefitinib (L01EB01), Gemcitabin (L01BC05), Irinotecan (L01CE02), Kapecitabin (L01BC06), Lapatinib (L01EH01), Merkaptopurin (L01BB02), Methotrexat (L01BA01), Platinové preparáty (L01XL01X), Tamoxifen (L02BA01), Tegafur (L01BC03), Tioguanin (L01BB03); **Imunoterapeutika:** Azathioprin (L04AX01), Etanercept (L04AB01), Siponimod (L04AA42), Takrolimus (L04AD02), Takrolimus (L04AD02), Ustekinubab (L04AC05); **Nesteroidní protizánětlivé léky (NSAID):** Celekoxib (M01AH01), Flurbiprofen (M01AE09), Ibuprofen (M01AE01), Lornoxicam (M01AC05), Meloxikam (M01AC06), Piroxikam (M01AC01), Tenoxicam (M01AC02); **Urikostatika:** Allopurinol (M04AA01), Rasburicasa (V03AF07); **Inhalační anestetika:** Inhalační anestetika (N01AB), Mivacurium (M03AC10), Succinylcholin (M03AB01); **Analgetika:** Dihydrokodein (N02AA08), Fentanyl (N01AH01), Fentanyl (N01AH01), Kodein (N02AJ09), Lofexidin (N07BC04), Oxykodon (N02AA05), Tramadol (N02AX02); **Antiepileptika:** Brivaracetam (N03AX23), Fenytoin (N03AB02), Fenytoin (N03AB02), Karbamazepin (N03AF01), Oxcarbazepin (N03AF02); **Jiná psychofarmaka:** Aripiprazol (N05AX12), Brexpiprazol (N05AX16), Clobazam (N05BA09), Clozapin (N05AH02), Iloperidon (N05AX14), Thioridazin (N05AC02), Venlafaxin (N06AX16), Vortioxetin (N06AX26); **Tricyklická antidepresiva:** Amitriptylin (N06AA09), Clomipramin (N06AA04), Doxepin (N06AA12), Imipramin (N06AA02), Nortriptylin (N06AA10), Trimipramin (N06AA06); **Selektivní inhibitory zpětného vychytávání serotoninu (SSRI):** Citalopram (N06AB04), Escitalopram (N06AB10), Sertralin (N06AB06), Fluvoxamin (N06AB08), Paroxetin (N06AB05); **Jiná léčiva nervového systému:** Amifampridin (N07XX05), Atomoxetin (N06BA09), Pimozid (N05AG02), Tetrabenazin (N07XX06), Valbenazin (N07XX13); **Antimalarika:** Primachin (P01BA03), Tafenochin (P01BA07)

Zubní lékařství a genomika

JDR *Centennial Series*

The Era of the Genome and Dental Medicine

K. Divaris[1,2]

Journal of Dental Research
2019, Vol. 98(9) 949–955

DOI: 10.1177/0022034519845674
journals.sagepub.com/home/jdr

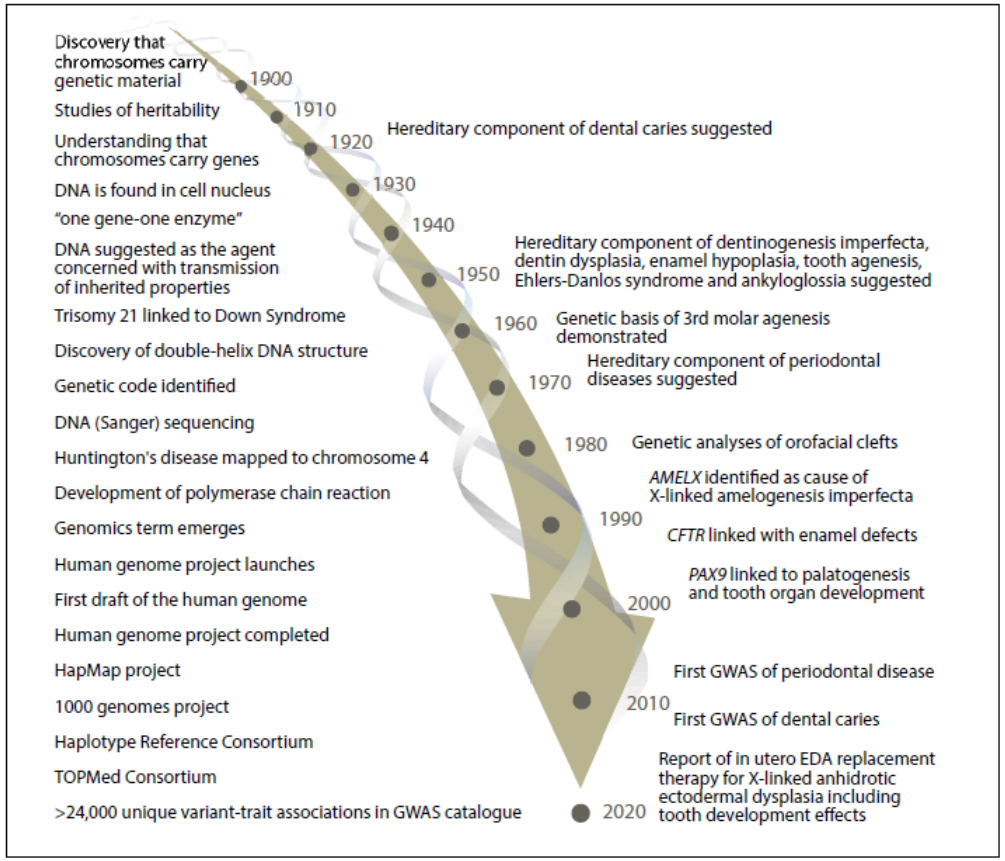


Figure 2. Timeline of genome research (left side) and oral health–specific landmark evolvements and illustrative reports (right side) since 1900.

Zubní lékařství a genomika

REVIEW ARTICLE

Periodontology 2000 WILEY

Genomics of periodontal disease and tooth morbidity

Thiago Morelli[1] | Cary S. Agler[2] | Kimon Divaris[3,4]

[1]Department of Periodontology, School of Dentistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

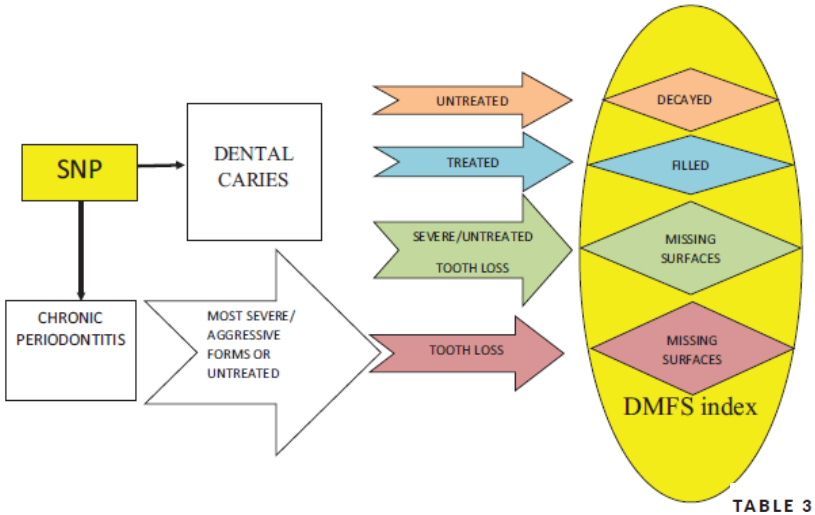


FIGURE 1 Theorized pathways contributing to the tooth morbidity (DMFS) index, emanating from dental caries and periodontitis. SNP, single nucleotide polymorphism

TABLE 3 Association results of the four loci that were prioritized from the tooth morbidity genome-wide association study with edentulousness and chronic periodontitis traits among the Atherosclerosis Risk in Communities study participants. *P* values were based on logistic regression models for the edentulous and chronic periodontitis traits, and a linear regression model for the number of remaining natural teeth

Chromosome	Locus	SNP	Edentulous vs dentate[a] (n = 8103)	Number of natural teeth[b] (0-32) (n = 5538)	Moderate chronic periodontitis vs healthy[c]	Severe chronic periodontitis vs healthy[c]
18	PMAIP1	rs11664212	0.18	0.00049	0.21	0.22
2	SPC25	rs477309	0.97	0.0087	0.26	0.06
18	MC4R	rs752720	0.22	0.00082	0.53	0.17
10	MPP7	rs1262024	0.34	0.24	0.10	0.09

Zubní lékařství a genomika

TABLE 1 Some candidate genes and loci that play roles in the etiology of non-syndromic clefts and the techniques used in their discoveries

Candidate genes and genomic loci	Technology and Methodology
SHH	Association, Mutation screen, Targeted sequencing
TP63	Mutation screen, Targeted sequencing, Whole-exome sequencing
GLI2	Targeted sequencing
MSX2	Mutation screen, Targeted sequencing, Linkage
SPRY2	Mutation screen, Targeted sequencing
SPRY1	GWAS
SULT2A1	GWAS
CTNNA2	GWAS
PDGFRA	Mutation screen, Targeted sequencing, Epigenetics
TBX1	Mutation screen, Copy number variation, Epigenetics
CTNNB1	Association, Mutation screen
PAX9	Targeted sequencing
PVRL1	Targeted sequencing, Mutation screen
TBX22	Targeted sequencing, Mutation screen
CTNND1	Mutation screen, Exome sequencing, Targeted sequencing
RARA	Association
FGF10	GWAS, Mutation screen
WNT9B	GWAS, Mutation screen
KRT18	GWAS
TFAP2A	GWAS, Mutation screen, Whole-genome sequencing
IRF6	Linkage, Association, Targeted sequencing, GWAS, Exome sequencing, Copy number variation, whole-genome sequencing
FOXE1	Linkage, Association, Targeted sequencing, GWAS
MSX1	Animal models, Targeted sequencing
BMP4	Animal models, Targeted sequencing
FGFR1	GWAS, Targeted sequencing
FGFR2	Targeted sequencing
CRISPLD2	Linkage and Association
SUMO1	FISH
TFGβ	Association
MAFB	GWAS
PAX7	GWAS
VAX1	GWAS
ARHGAP29	GWAS, Mutation Screen, Whole-exome sequencing
Chr8q.24	GWAS
Chr16p13.3	GWAS
VAX1,	GWAS
NOG	GWAS
GRHL3	Linkage, Exome sequencing
CDH1	Exome sequencing, Targeted sequencing
MGAM	Copy number variation
ADAM3A	Copy number variation
ZFHX4	Whole-genome sequencing
Chr21q22	Whole-genome sequencing
ADAM5A	Copy number variation

DOI: 10.1111/odi.14146

INVITED REVIEW

ORAL DISEASES WILEY

Genetic and epigenetic studies in non-syndromic oral clefts

Azeez Alade[1,2,3] | Waheed Awotoye[1,2] | Azeez Butali[1,2]

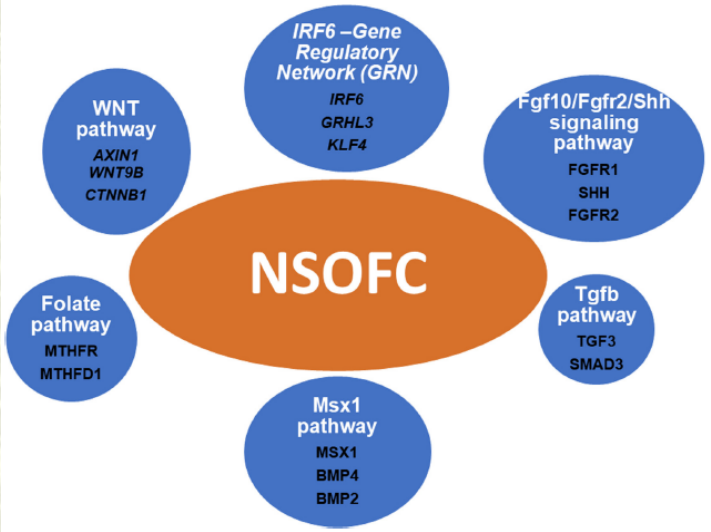


FIGURE 1 Critical pathways and the *IRF6* gene-regulatory network relevant to craniofacial development and reported for non-syndromic orofacial clefts (NSOFCs). Some cleft candidate genes in black fonts within the pathways and network. The gene list, pathways, and network are not exhaustive but represent current knowledge and a starting point for further investigations

Budoucnost genomiky a zubní lékařství: editace genomů

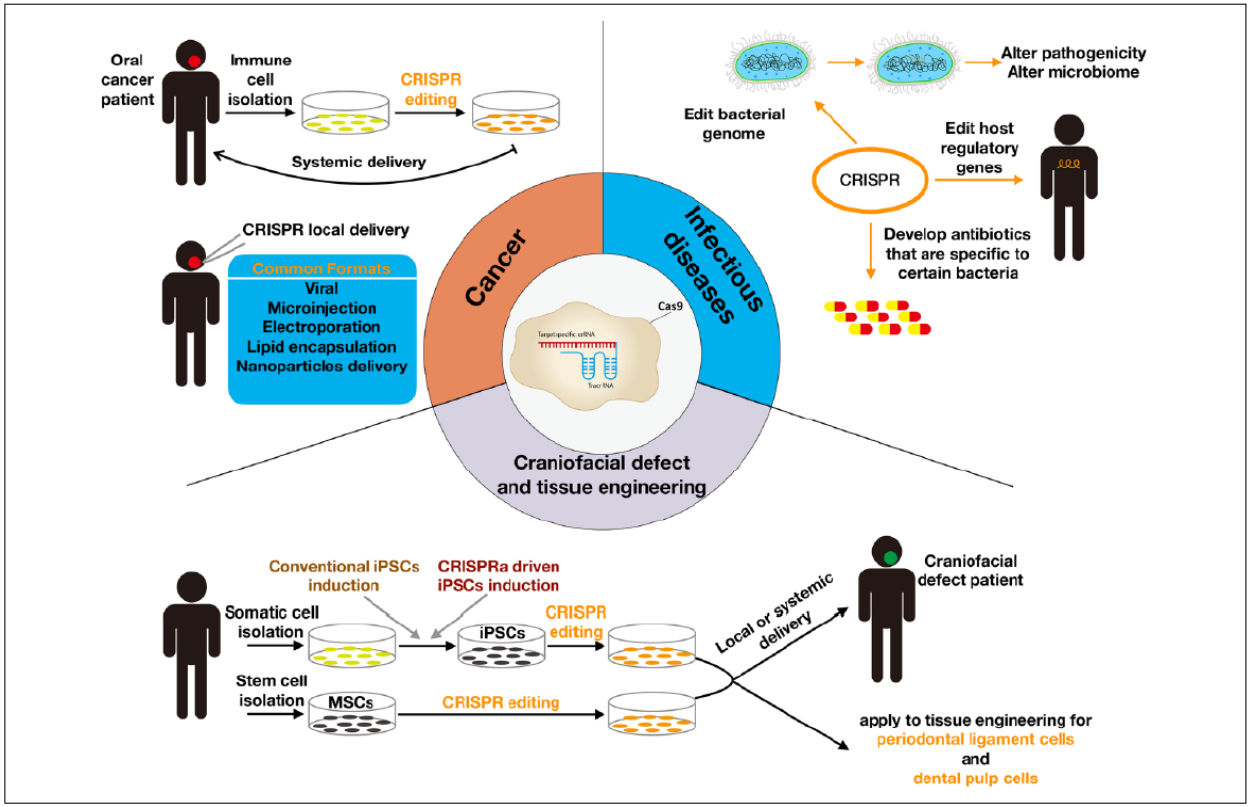


Figure 4. Illustration of applications of the clustered, regularly interspaced short palindromic repeats (CRISPR) / CRISPR-associated nucleases (CRISPR/Cas) system in oral and craniofacial biology, as reported by Yu et al. 2019 (reprinted with permission). iPSCs, induced pluripotent stem cell; MSCs, mesenchymal stem cells.

Odolnost/vnímavost k onemocněním

Modelový příklad - genetika vnímavosti k infekcím

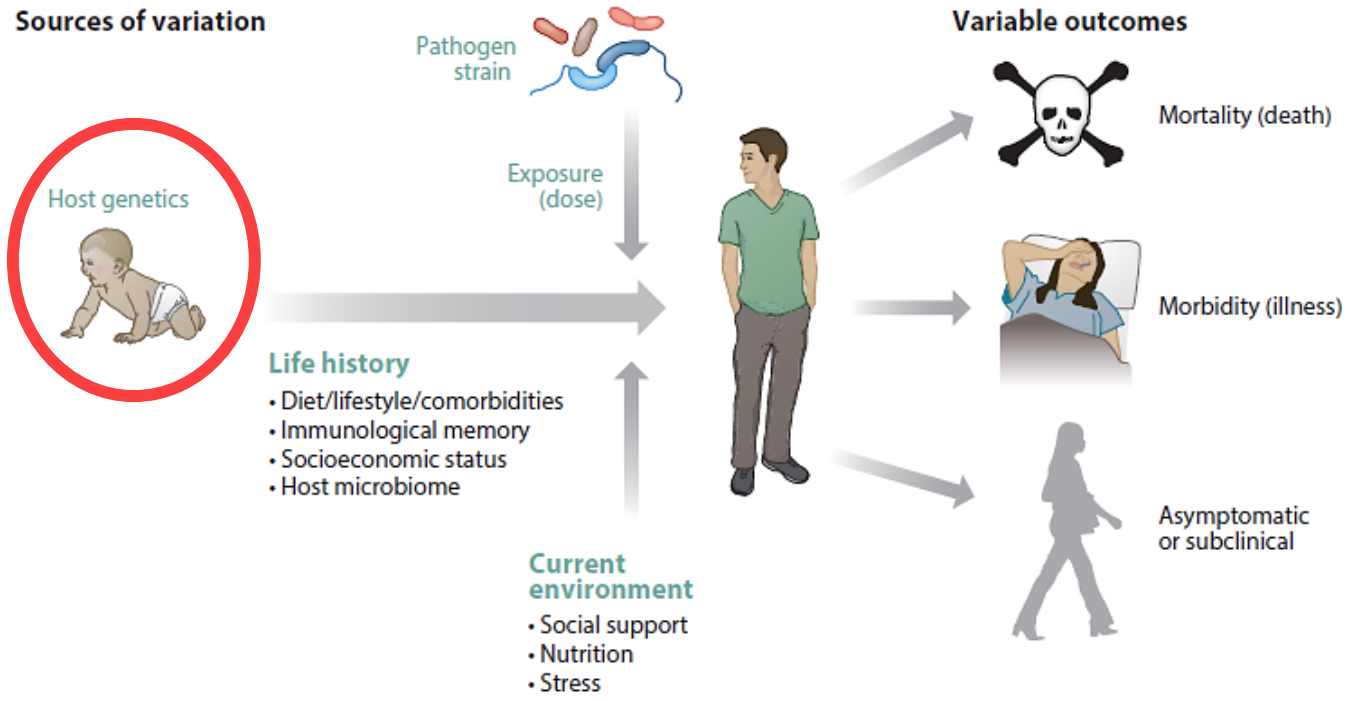


Figure 1

Sources of variable infection outcomes. Host genetics, which is fixed at conception; life history; and current environment generate differing susceptibilities in exposed individuals. Beyond host susceptibility, pathogen genetics (virulence) as well as dose also contributes to a wide range of clinical outcomes from most infectious diseases.

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., 1996

Infekční nemoc jako výsledek interakce hostitele a patogena

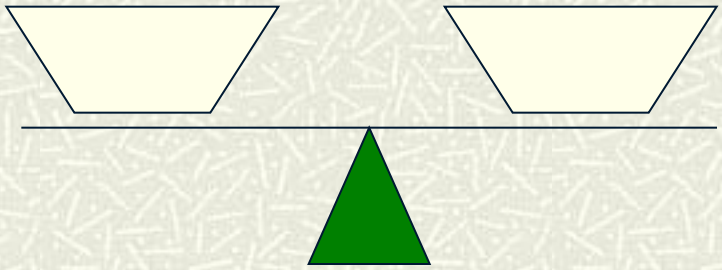
- ✓ *Nemoc jako obranná reakce*
- ✓ *Často jedinečná kombinace hostitele a patogena*
- ✓ *Individuální rozdíly v použití různých imunologických mechanismů v reakci na téhož patogena*
- ✓ *Symptomatologie určena převážně patogenem nebo převážně hostitelem*

Nejednoznačný význam variability v imunitní odpovědi: silná nebo slabá?

Skylla and Charybda
odolnosti/vnímavosti k nemocem

Protektivní imunita
Resistence k infekci

Autoimunita, alergie
Zánět



Genetika: 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

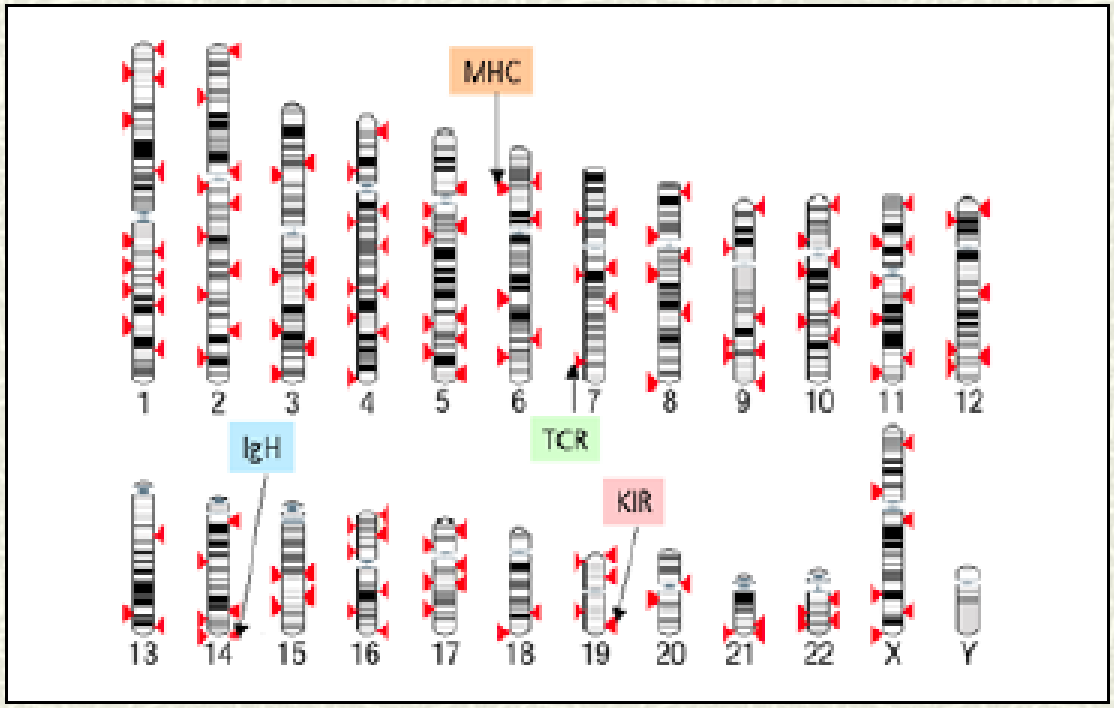
Negenetické vlivy, přírodní a umělá selekce

Geny odolnosti a vnímavosti 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*

Geny obranyschopnosti

Imunogenom: 5% genomu



Komplexní dědičnost: genomika a infekce u lidí

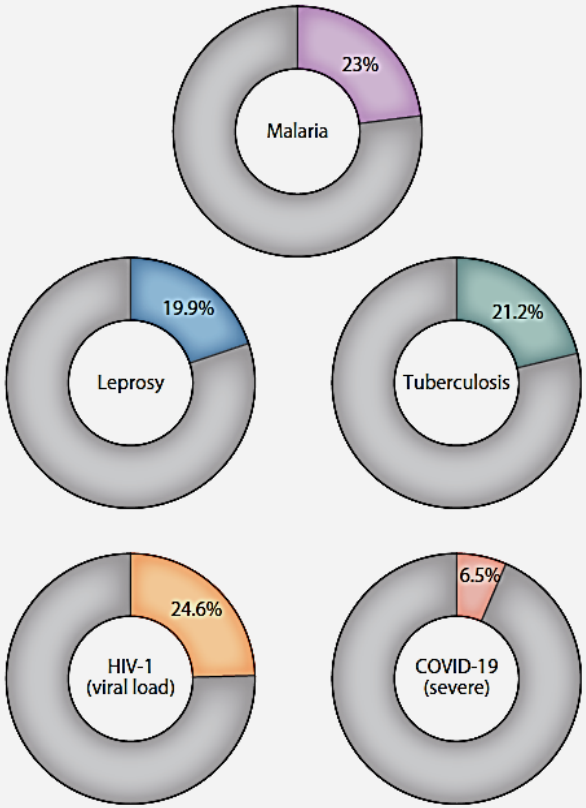
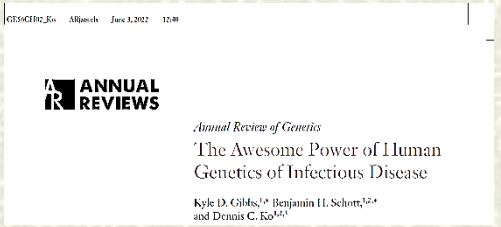


Figure 3

Heritability estimation based on genome-wide SNPs for five different infectious diseases. Estimates are for malaria (92), leprosy (141), tuberculosis (87), HIV-1 (95), and severe COVID-19 (111). Abbreviations: COVID-19, coronavirus disease 2019; HIV-1, human immunodeficiency virus 1; SNP, single-nucleotide polymorphism.


ANNUAL REVIEWS

Annual Review of Genetics

The Awesome Power of Human Genetics of Infectious Disease

Kyle D. Gibbs,[1,*] Benjamin H. Schott,[2,3,4] and Dennis C. Ko[1,5,*]

Mendelistická dědičnost vnímavosti k infekcím

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

Mechanismy nemocí

- ✓ Infekce
- ✓ Alergie, *ADR*
- ✓ Autoimunita
- ✓ Komplexní imunopatologie

Příklady

- ✓Noroviry, rotaviry (*FUT2*)
- ✓AIDS (CCR5)
- ✓Malárie (Duffy)
- ✓*COVID 19*

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

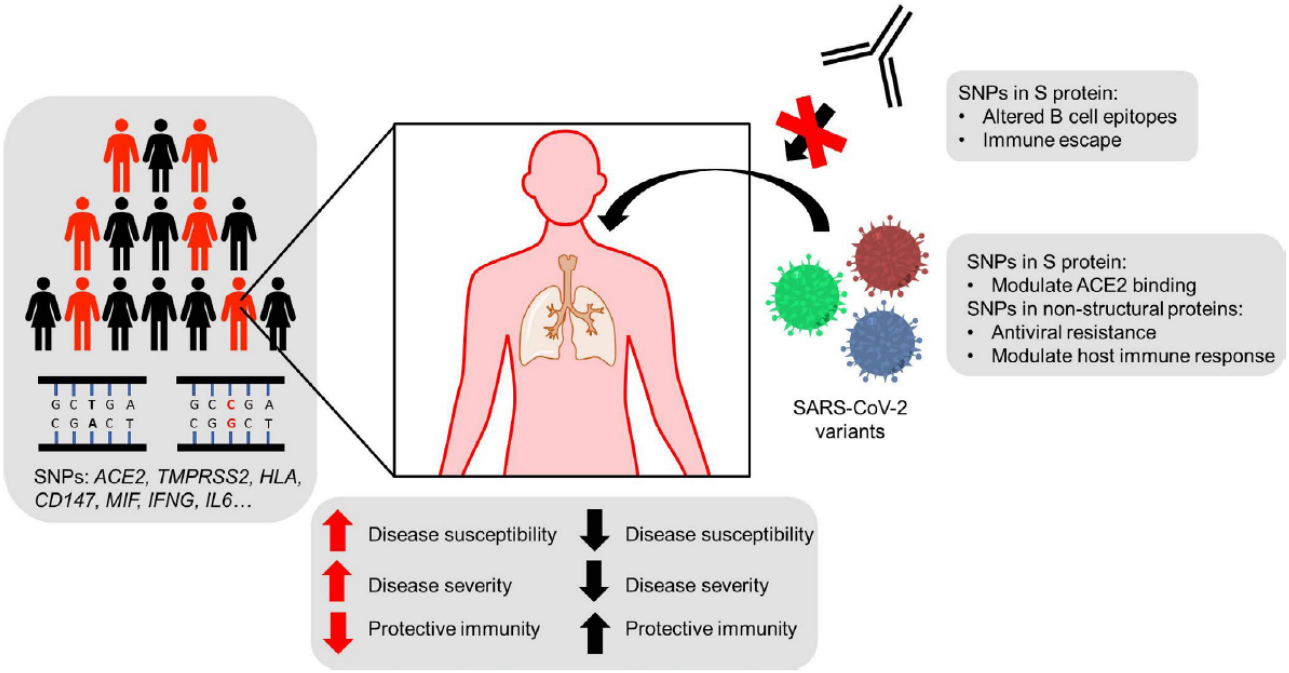


FIGURE 1 The impact of host genetics and viral variation on SARS-CoV-2 infection and COVID-19 severity. Individuals in the population harbor single nucleotide polymorphisms (SNPs) across a variety of genes (eg, *ACE2*, *TMPRSS2*, *HLA*, *CD147*, *MIF*, *IFNG*, *IL6*) that have been implicated in the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

Covid 19 a genetika hostitele

Table 3
Candidate genes, their polymorphisms and their association with COVID-19 severity and susceptibility in select populations

Gene	Polymorphism	Population	Sample size	Implication	Reference
3p21.31 cluster	rs11385942	Spain and Italy	1980	The *3p21.31* cluster was observed in patients with respiratory failure.	(The Severe Covid-19 GWAS Group, 2020)
Androgen receptor	Not mentioned	European males	1178	Androgen receptors with shorter polyQ alleles offered protection against severe COVID-19 in Italian males.	(Baldassarri et al., 2021)
BPIFB4	LAV-BPIFB4	Italy	171, 64 with COVID-19	Values of BPIFB4 were markedly lower in COVID-19-positive individuals as compared with negative patients. BPIFB4 levels in plasma are negatively correlated with SARS-CoV-2 illness severity.	(Ciaglia et al., 2021)
Complement 3	Complement 3 (S)	European, Mediterranean, and the Middle East	Not mentioned	C3 was associated with increased COVID-19-related death.	(Delanghe et al., 2021)
CCR5	rs9845542, rs12639314, rs35951367, rs34418657	Europe	6406 hospitalized COVID-19 patients and 902,088 controls	rs9845542, rs12639314, rs35951367 polymorphisms were associated with severe COVID-19 illness and low CCR5 expression	(Cantalupo et al., 2021)
CCR5	rs333	Czech Republic	416	Δ32 deletion in the *CCR5*, most found in Caucasians, could offer protection against COVID-19 illness.	(Hubacek et al., 2021)
TLL-1	rs4618569	Egypt	141 patients, 100 controls	The A allele of the *TLL-1* rs17047200 variant is associated with poor clinical outcomes.	(Agwa et al., 2021)
GOLGA3, DPP7, TMPRSS2	rs12329760 in TMPRSS2	China	332	The rs12329760 variant in *TMPRSS2* was less prevalent in severe SARS-CoV-2 patients. Loss of function mutation in *DPP7* and *GOLGA3* was observed in severe COVID-19 disease.	(Wang et al., 2020)
IFI30	rs11554159	Spain and Italy	N/A	*IFI30* polymorphisms may be a risk factor to acquiring severe COVID-19 disease	(Monticelli et al., 2021)
MEFV	rs3743930	Spain and Italy	N/A	Deleterious variants in *MEFV* could affect the severity of COVID-19.	(Monticelli et al., 2021)
IFITM3	rs12252, rs34481144	Germany	239 patients with COVID-19 and 253 controls.	There was no association between these polymorphisms and severity of COVID-19 illness.	(Schönfelder et al., 2021)
IFITM3	rs12252	China	80	Presence of the rs12252 variant of the *IFITM3* correlated with a more critical COVID-19 infection.	(Zhang et al., 2020)
LZTFL1, XCR1, CCR9, FYCO1, SLC6A20, CXCR6, HNRNPK, RMI1, IFNAR2, ABO	rs9976829 in IFNAR2-IL10RB	Italy and Spain	1,610 COVID-19 patients and 2,205 controls	All genes were strongly associated with risk of SARS-CoV-2 infection. A 16% higher chance of having SARS-CoV-2 in subjects with the G allele of rs9976829.	(Ma et al., 2021)
MBL2	rs1800450	N/A	284 patients, 100 control	Reduced MBL2 levels correlated with a more severe COVID-19 clinical course.	(Medetalibeyoglu et al., 2021)
MUC5B	rs35705950	Europe	4124 cases and 20,465 controls	rs35705950 offered protection against COVID-19 in patients with pulmonary fibrosis.	(Fadista et al., 2021)
PNPLA3, TLL-1	*PNPLA3* rs738409, *TLL-1* rs17047200,	Italy	383	Polymorphisms of *PNPLA3* and *TLL-1* were markedly associated with severe COVID-19 disease and worse outcomes.	(Grimaudo et al., 2021)
TAS2R38	Not mentioned	USA	1935, 265 tested positive	T2Rs may protect against illness by SARS-CoV-2.	(Barham et al., 2021)
DDR1	rs17047200	Egypt	141 patients, 100 controls	The AG genotype of the *DDR1* rs4618569is associated with poor outcomes in COVID-19 patients.	(Agwa et al., 2021)
TLR3	rs3775291	Spain and Italy	N/A	A missense mutation in *TLR3* (rs3775291) is associated with severe disease.	(Monticelli et al., 2021)
TLR7	rs189681811, rs147244662, rs149314023, rs200146658, rs5743781	Italy	79 cases, 77 controls	*TLR7* variants were found in 2.1% of males with severe disease, while none were found in asymptomatic males. Lower *TLR7* expression was observed in COVID-19 patients.	(Fallerini et al., 2021)
TMPRSS2	rs2298659, rs17854725, rs12329760, rs3787950	Italy	3984	Exonic variant (p.Val160Met) and two haplotypes in *TMPRSS2* showed substantial disparities between East Asians and Italians, showing increased levels of TMPRSS2 in Italians, leading to increased susceptibility to infection.	(Asselta et al., 2020)
TMPRSS2	N/A	Africa	N/A	Genetic variants in *TMPRSS2* may alter an individual's variability in susceptibility to COVID-19 infection and disease severity.	(Ortiz-Fernández and Sawalha, 2020)
TNFRSF1A	rs767455	Mexico	102 patients, 25 controls	This polymorphism is associated with increased COVID-19 disease severity.	(Palacios et al., 2021)
TNFRSF13C	p.His159Tyr	Italy	500	p.His159Tyr variant of *TNFRSF13C* was notably increased in patients with severe illness compared to asymptomatic patients.	(Russo et al., 2021)
		Serbia	120 males		(Kotur et al., 2021)

(continued on next page)

The association of COVID-19 severity and susceptibility and genetic risk factors: A systematic review of the literature

Angela Ishak [a,*], Meghana Mehendale [a], Mousa M AlRawashdeh [a,b], Cristina Sestacovschi [a], Medha Sharath [a,c], Krunal Pandav [a], Sima Marzban [a]

Table 3 (*continued*)

Gene	Polymorphism	Population	Sample size	Implication	Reference
Vitamin D (*DHCR7/ NADSYN1*), *CYP2R1*	Vitamin D (DHCR7/ NADSYN1) rs12785878, CYP2R1 rs10741657			The presence of *CYP2R1* and *DHCR7/ NADSYN1* correlated with COVID-19 increased illness severity in adults.	
IFNL3	rs12979860, rs8099917, rs12980275	Iran	750 patients with COVID-19	Frequency of these favorable variants was significantly higher in patients who survived from COVID-19 infection.	(Rahimi et al., 2021)
IFNL4	rs368234815	Iran	750 COVID-19 positive patients	Higher frequency of this variant was present in patients who survived from COVID-19 infection.	(Rahimi et al., 2021)
TMPRSS2	rs2070788	India	393 COVID-19 patients	rs2070788 may lead to worse clinical outcomes in COVID-19 patients.	(Pandey et al., 2022)
TIRAP	rs8177374	Netherlands	116 COVID-19 patients	Carriers of rs8177374 could be associated with a significantly lower COVID-19 mortality.	(Truets et al., 2022)
TMPRSS2	rs17854725/ rs75603675/ rs12329760/rs4803795	Iran	288 COVID-19 patients	These polymorphisms were associated with increased risk of COVID-19 infection and severe disease.	(Rokni et al., 2022)
IL-6	rs1800795, rs1800796, rs1800797	Iran	175 COVID-19 patients, 171 controls	No significant differences in severity of COVID-19 disease in patients with these polymorphisms.	(Falahi et al., 2022)
TMPRSS2/MX1 (21q22.3) locus	rs3787946, rs9983330, rs12329760, rs2298661, rs9985159	Italy	6,406 COVID-19 patients, 902,088 controls	These polymorphisms showed an association with severe COVID-19 disease.	(Andolfo et al., 2021)

BPIFB4: BPI fold containing family B member 4, *CCR5*: CC motif chemokine receptor 5, *CCR9*: CC motif chemokine receptor 9, *CXCR6*: C-X motif chemokine receptor 6, *DPP7*: dipeptidyl peptidase 7, *DDR1*: discoidin domain receptor tyrosine kinase 1, *GOLGA3*: Golgin A3, *TMPRSS2*: transmembrane protease, serine 2, *IFI30*: gamma-interferon-inducible lysosomal thiol reductase, *SLC6A20*: solute carrier family 6 member 20, *LZTFL1*: human leucine zipper transcription factor like 1, *XCR1*: X-C motif chemokine receptor 1, *FYCO1*: fyve and coiled-coil domain-containing protein 1, *TLR3*: toll like receptor 3, *TLR7*: toll like receptor 7, *IFNAR2*: interferon alpha and beta receptor subunit 2, *IFNL3*: interferon lambda 3, *IFNL3*: interferon lambda 3, *MUC5B*: mucin 5B, *HNRNPK*: heterogeneous nuclear ribonucleoprotein K, *IFITM3*: interferon induced transmembrane protein 3, *RMI1*: RecQ mediated genome instability 1, *MBL2*: mannose binding lectin 2, *PNPLA3*: patatin-like phospholipase domain-containing protein 3, *TLL1*: tolloid like 1, *TAS2R38*: taste receptor 2 member 38, *TNFRSF13C*: TNF receptor superfamily member 13C, *TNFRSF1A*: TNF receptor superfamily member 1A, *CYP2R1*: cytochrome P450 gamily 2 subfamily R member 1, *TIRAP*: TIR Domain Containing Adaptor Protein

Komplexní patogeneze: celiakie

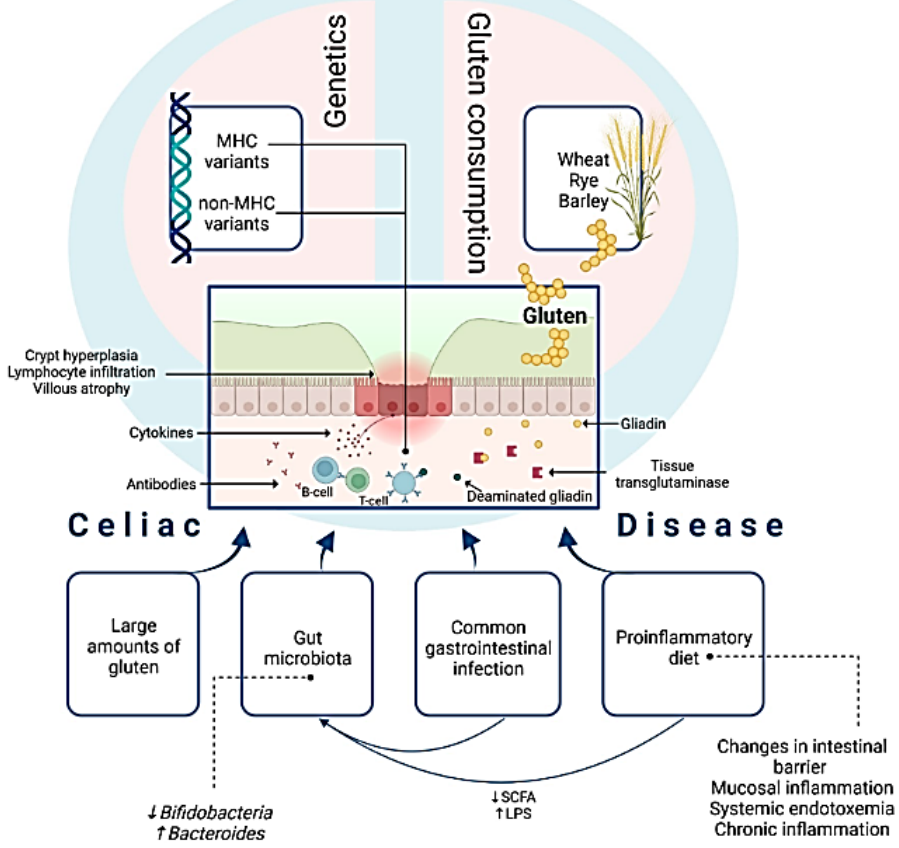


Fig. 1 Pathogenesis of celiac disease. MHC—major histocompatibility complex; HLA—human leukocyte antigen; SCFA—short-chain fatty acids; LPS—lipopolysaccharide. Exposure to gluten may activate cell-mediated and humoral immune response in genetically predisposed individuals leading to the crypt hyperplasia, lymphocyte infiltration and villous atrophy in the small intestine. Tissue transglutaminase deaminates gliadin, resulting in greater proliferative response of gliadin-specific T-cells, leading to mucosal inflammation and B-cell activation

Zubní lékařství - příklady

Table 1: Candidate genes studied for erosion in humans.

Genes	Function	Results and conclusion	Reference
Enamelin (ENAM) rs12640848	Enamel formation gene. Mineralization and structural organization of the enamel [16].	Analysis based on differences in allele frequency showed a statistically significant association with dental erosion and the ENAM rs12640848 marker. The frequency of the G allele of ENAM rs12640848 was significantly higher in the erosion group than in the nonerosion group.	Sovik et al. [31]
Amelogenin (AMELX) rs946252	Enamel formation gene. Mineralization during tooth enamel development [16].	When erosion severity was considered, statistically significant differences in allele frequency were observed for the AMELX rs946252 marker, with the C allele suggesting a protective role. An over-representation of the TT genotype of the AMELX marker was seen in cases with severe erosion. AMELX was also associated with severe erosion when the recessive model was considered; the TT genotype was significantly more frequent in the affected group than in the unaffected group. Association with severe dental erosion and the AMELX rs946252	Sovik et al. [31]
		When analyzing the terciles, significant associations were found between enamel loss and the AMELX rs946252. When comparing allele and genotype distributions between individuals more and less susceptible to enamel loss, no statistically significant differences were found.	Uhlen et al. [28]
Ameloblastin (AMBN) rs4694075	Enamel formation gene. Involved in enamel matrix formation and mineralization [16].	No evidence of association	Sovik et al. [31]

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Review Article

Genetic Aspects of Dental Erosive Wear and Dental Caries

Amela Tulek,[1] Aida Mulic,[2] Maria Runningen,[1] Jannike Lillemo,[1] Tor Paaske Utheim,[1,3] Qalbi Khan,[4] and Amer Sehic[1,3]

Table 2: Candidate genes studied for dental caries in humans.

Genes	Function	Results and conclusion	Reference
Enamelin (ENAM)	Mineralization and structural organization of the enamel	Associated with higher caries experience	Patir et al. [54]; Shimizu et al. [49]; Jeremias et al. [55]; Gerreth et al. [56]; Wang et al. [57]
		Associated with higher caries experience	Deeley et al. [58]; Kang et al. [53]; Shimizu et al. [49]; Jeremias et al. [55]
Amelogenin (AMELX)	Mineralization during tooth enamel development	Associated with lower caries experience	Kang et al. [53]
		No evidence of association	Slayton et al. [59]; Olszowski et al. [60]; Ergoz et al. [61]; Gasse et al. [62]
		Associated with higher caries experience	Patir et al. [54]; Shimizu et al. [49]; Ergoz et al. [61]
Ameloblastin (AMBN)	Involved in enamel matrix formation and mineralization	Protective effect for caries	Gerreth et al. [63]
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Netranslatovaný genom a vnímavosť k infekcím

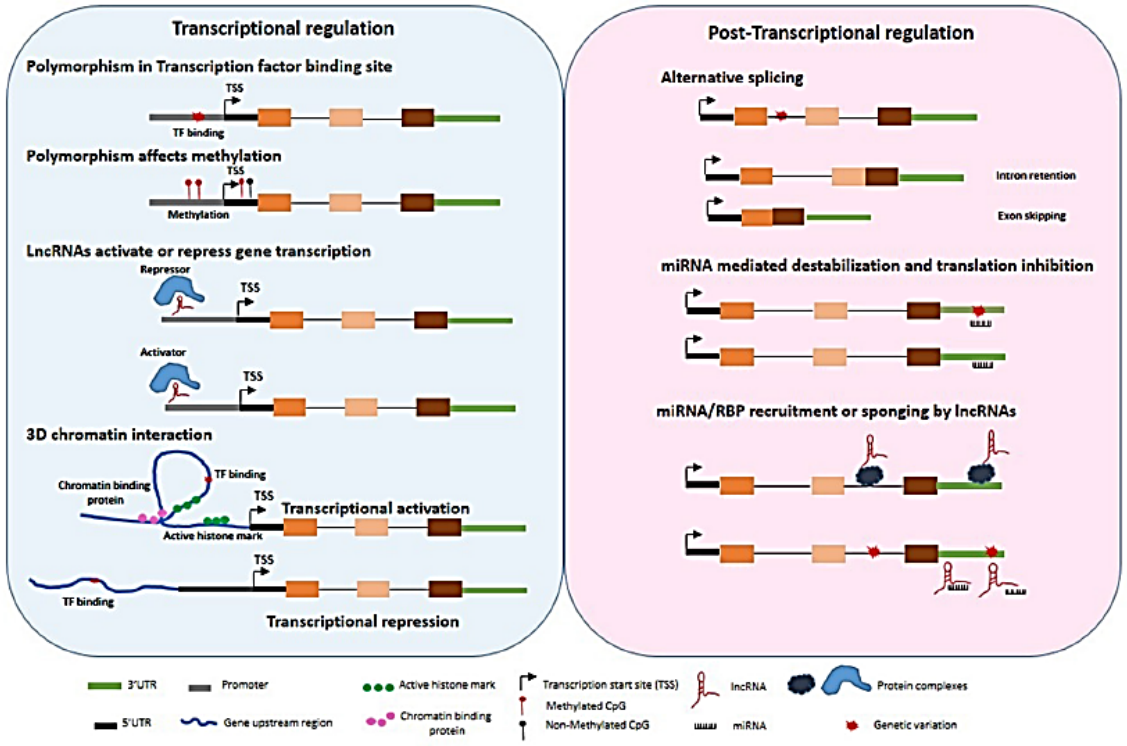

FIGURE 1 | Untranslated gene variations influence regulation of gene expression. Disease associated polymorphisms may alter methylation, transcription factor binding in the gene promoter regions, recruitment of repressor or activators, 3 dimensional chromatin structure, splicing, miRNA binding to 3′UTR,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

Zubní lékařství - příklady

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Emerging role of long non-coding RNAs in the pathogenesis of periodontitis

Arezou Sayad[a], Sara Mirzajani[a,b], Leila Gholami[c], Parnian Razzaghi[d], Soudeh Ghafouri-Fard[e,*], Mohammad Taheri[f,*]

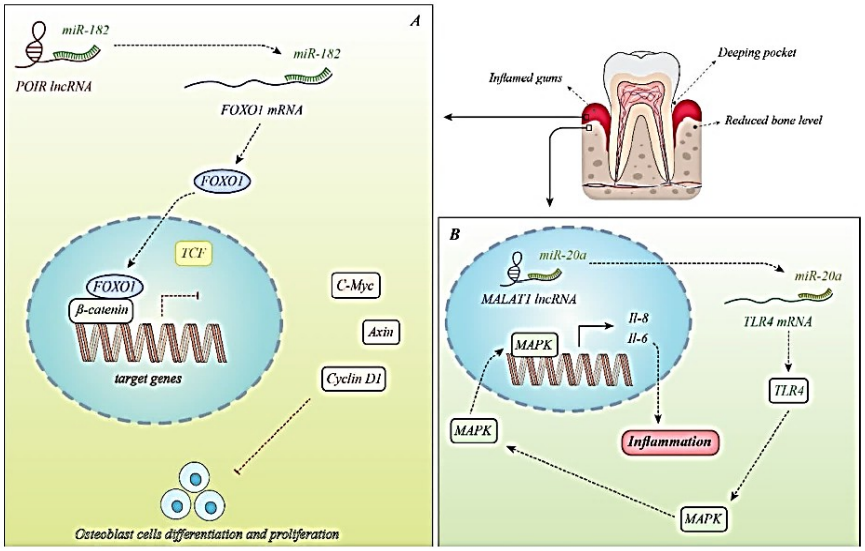


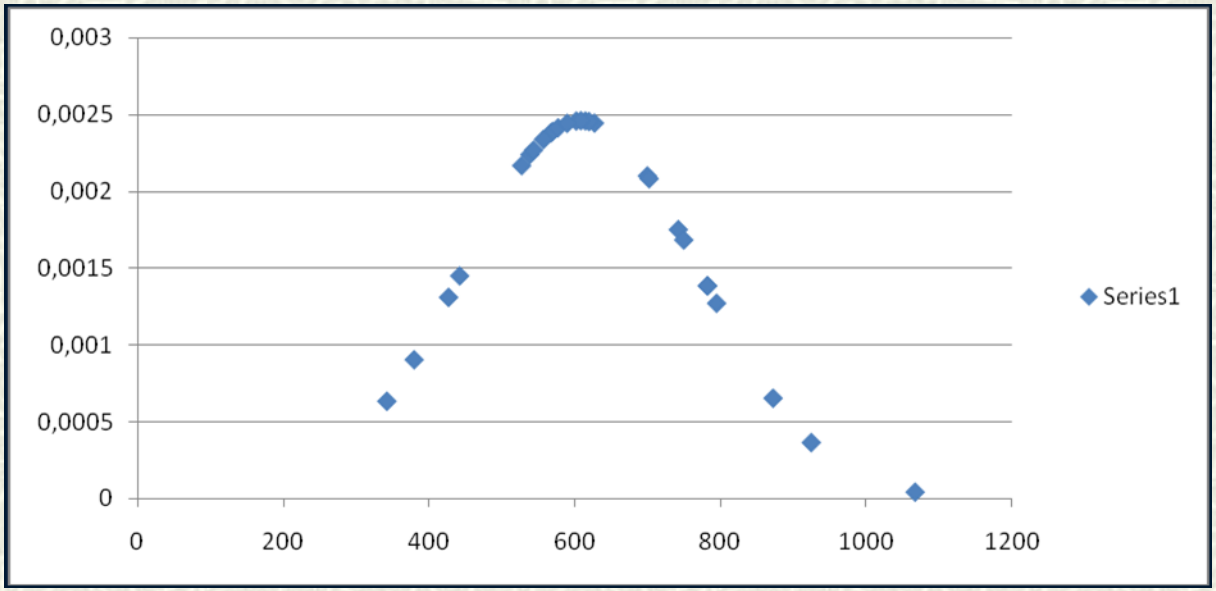
Fig. 1. (A) POIR lncRNA is decreased in periodontitis. This lncRNA acts as a sponge for miR-182. miR-182 binds with the 3′ UTR of FOXO1. FOXO1 inhibits canonical Wnt, thus supressing expression of Cyclin D1, Axin and c-Myc. Suppression of canonical Wnt inhibits proliferation and differentiation of osteoblasts [23]. (B) In the nucleus, MALAT1 binds with miR-20a, thus inhibiting its export from the nucleus and its effects on TLR4. Therefore, MALAT1 enhances expression of TLR4. TLR4 promotes expression of inflammatory cytokines [22].

Vakcinace a genetika

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

Vakcinace a genetika

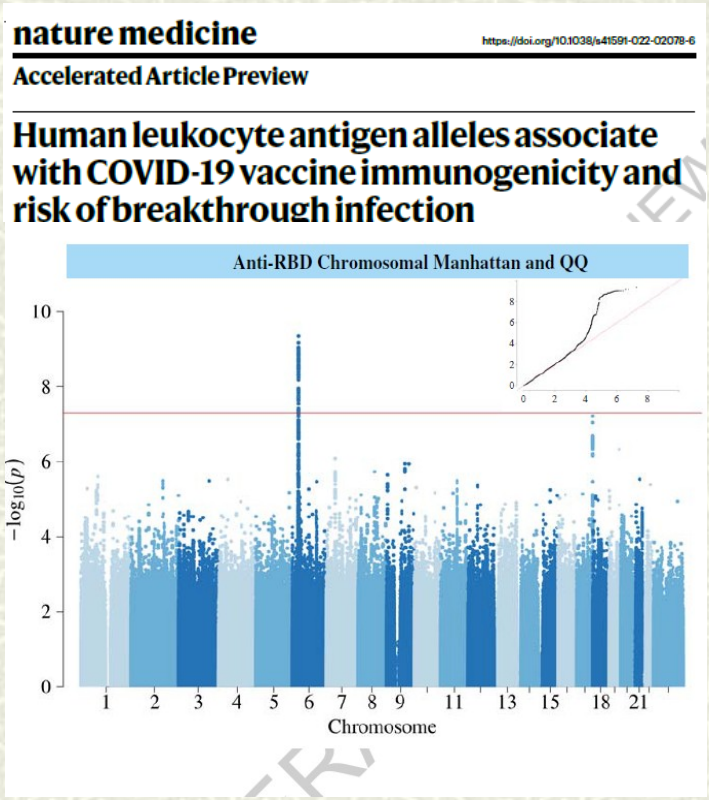
Individuální variabilita imunitní odpovědi po vakcinaci



Genetika vakcinace a personalizovaná medicína

Table 3. Heritability estimates of vaccination responses in twin studies

Vaccine	Parameter	DZ[a]	MZ[a]	Population	Age	Study	Heritability, %	95% CI %	References
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	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



Doporučení pro lékaře a využitelnost v praxi

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 genomických vyšetření natolik, aby dokázali korektně interpretovat klinický význam diagnostikovaných genomických variant

Využitelnost v praxi: odborná interpretace jako základ aplikací

- ✓ Pochopení podstaty používaných přístupů: *umět třídit informace a soustředit se na podstatu*
- ✓ 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*

Dotazy i v tomto stavu?