New Trends in Clinical Genetics: Genomic Medicine

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LF MU 2022

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Outline

- ✓ *Genomic medicine: motivation for MDs*
- ✓ *Genomes, genes, genetic variability, disease*
- ✓ *Genomics and disease*
- ✓ *Importance for MDs and dentistry*

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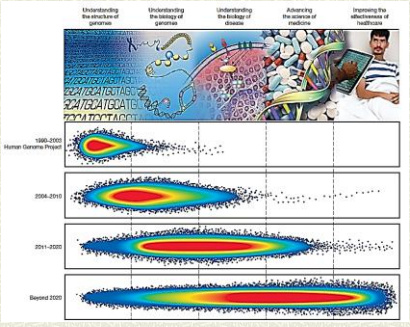
Genomic medicine: 2011 prediction



Charting a course for genomic medicine from base pairs to bedside

Green et al. 2011

Top of your professional career

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Genomic medicine: clinical practice

Genetics inMedicine | REVIEW

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Implementing genomic medicine in the clinic: the future is here

Teri A. Manolio, MD, PhD[1], Rex L. Chisholm, PhD[2], Brad Ozenberger, PhD[3], 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[13], James R. Lupski, MD, PhD[12], 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]

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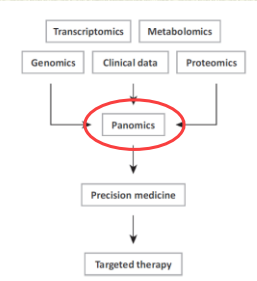
Precision medicine



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,*] Ala Qureshi,[2] and Andrew Emili[1]

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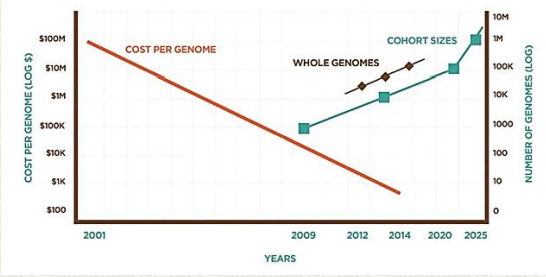
Genomic medicine - from theory to practice: financial aspects



S. K. DELANEY ET AL

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Genomic medicine: clinical practice

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Taylor & Francis

PERSPECTIVE

OPEN ACCESS

Toward clinical genomics in everyday medicine: perspectives and recommendations

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Genomic medicine: recommendations for health care providers

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Recommendations for the Integration of Genomics into Clinical Practice

Sarah Bowdin, M.D.[2], Adel Gilbert, M.S.[2], Emma Bedoukian, M.S.[3], Christopher Carew, M.B.A.[4], Margaret P Adam, M.D.[4], John Belmont, M.D., Ph.D.[5], Barbara Bernhardt, M.S.[6], Leslie Biesecker, M.D.[7], Hans T. Bjornsson, M.D., Ph.D.[8], Miriam Blitzer, Ph.D.[9], Lisa C. A. D'Alessandro, M.D.[28], Matthew A. Deardorff, M.D., Ph.D.[3,27], Laurie Demmer, M.D.[10], Alison Elliott, Ph.D.[11], Gerald L. Feldman, M.D., Ph.D.[12], Ian A. Glass, M.B.Ch.B., M.D.[1], Gail Herman, M.D., Ph.D.[13], Lucia Hindorff, Ph.D.[7], Fuki Hisama, M.D.[28], Louanne Hudgins, M.D.[14], A. Micheil Innes, M.D.[15], Laird Jackson, M.D.[16], Gail Jarvik, M.D., Ph.D.[28], Raymond Kim, M.D., Ph.D.[1], Bruce Korf, M.D., Ph.D.[17], David H. Ledbetter, Ph.D.[18], Mindy Li, M.D.[19], Eriskay Liston, M.S.[1], Christian Marshall, Ph.D.[20], Livija Medina, M.S.[1], M. Stephen Meyn, M.D., Ph.D.[1,2], Nasim Monfared, M.Sc.[1], Cynthia Morton, Ph.D.[28], John J. Mulvihill, M.D.[21], Sharon E. Plon, M.D., Ph.D.[29], Heidi Rehm, Ph.D.[20], Amy Roberts, M.D.[22], Cheryl Shuman, M.S.[1,2], Nancy B. Spinner, Ph.D.[19], D. James Stavropoulos, Ph.D.[20], Kathleen Valverde, M.S.[23], Darrel J. Waggoner, M.D.[24], Alisha Wilkens, M.S.[3], Ronald D. Cohn, M.D.[1,2,*], and Ian D. Krantz, M.D.[3,27,*]

Translating and realizing the comprehensive clinical benefits of genomic medicine remains a key challenge for the current and future care of patients. With the increasing application of CGES, it is necessary for geneticists and other health care providers to understand its benefits and limitations, in order to interpret the clinical relevance of genomic variants identified in the context of health and disease. Establishing new, collaborative working relationships with specialists across diverse

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Terminology: confusion of languages

- ***Genetics***
- ***Genomics***

Systematic and complex (holistic)
analysis of the genome

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Holistic approaches



Slide courtesy of Prof. Jamie McLeod, UK Lexington

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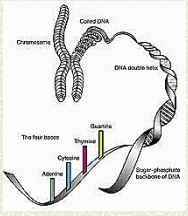
Reminder: the GENOME



- > 1m DNA
- 24 chromosomes, mtDNA
- > 3,100,000,000 bp
- 20,000–25,000 protein coding genes (< 2% of the genome)
- > 5 MG SNPs
- „Junk" DNA: RNA coding sequences, repeats, ??

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Holism and genomics:
Genome is more than the sum of its genes

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
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tctggatgag 481 aacatgctga cagccattga caagctgatg caggccctga
acttcaacag tgagactgtg 541 ccacaaaagc cctcccttga aggactggat
ttttataaaa ctaaagtcaa gctctgcatc 601 cttcttcatg ccttcagaat
ccgcgcagtg accatcaaca ggatgatggg ctatctgaat 661 gcttcctaa

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NA sequencing today

- ✓ DNA Sanger (1-2 kb)
- ✓ DNA NGS (whole genomes)
- ✓ DNA NGS LR: „HiFi" (50 kb)
- ✓ DNA exome
- ✓ RNA IsoSeq: full-length cDNA, PacBio, Single molecule real time

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Postgenomic era

Full genome sequences determined (human genome 2001)

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

Annotation of genomes

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Genomics today

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

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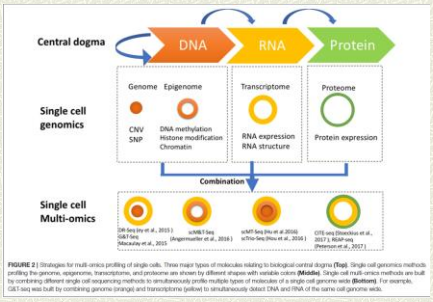
Multiomics



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

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Multiomics:

- ✓ *Genome*
- ✓ *Epigenome*
- ✓ *Transcriptome*
- ✓ *Proteome*
- ✓ *Metabolome*
- ✓ *Microbiome*

Regulatory pathways underlying complex phenotypes defined on all levels

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Pangenomes

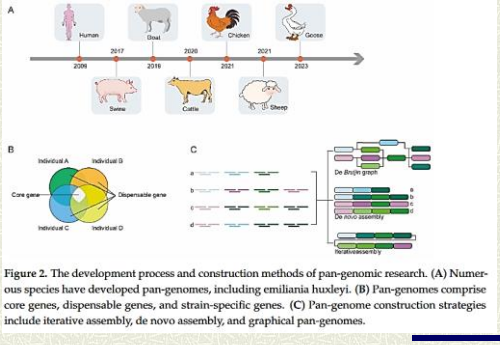

Figure 2. The development process and construction methods of pan-genomic research. (A) Numerous species have developed pan-genomes, including emiliania huxleyi. (B) Pan-genomes comprise core genes, dispensable genes, and strain-specific genes. (C) Pan-genome construction strategies include iterative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

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Genetic variability: mutations vs. polymorphisms

- ✓ *Polymorphisms as "established" mutations*
- ✓ *Mutations as causes of disease*
- ✓ *Genetic polymorphisms as causes of the variability in susceptibility/resistance to disease*

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Genetic variability in disease: different roles

- ✓ *Inherited diseases: causative genes*
- ✓ *Genetic susceptibility/resistance to disease provoked by environmental factors*

Both can be inherited in the Mendelian and/or non-Mendelian way

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Reminder: individual variability of the human genome

Single nucleotide polymorphisms (SNPs): 10 M throughout the genome

cgcgcggcctcctccttgtggccatcctggtcctcctaaaccacctggac

cgcgcggcctcctccttgtggtcatcctggtcctcctaaaccacctggac

Insertions/deletions (indels)

cgcgcggcctcctccttgtggccatcctggtcctcctaaaccacctggac

cgcgcggcctcctccttgtgg-------ctggtcctcctaaaccacctggac

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Single nucleotide polymorphisms *(SNPs)*

- ✓ *Nucleotide sequence*

cgcgcggcctcttgtggccatcctggtcctcctaaaccacctggac

cgcgcggcctcttgtggtcatcctggtcctcctaaaccacctggac

- ✓ *Alleles*

C, T

- ✓ *Genotypes*

CC, CT, TT

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Genomes in disease

- ✓ *0.6% chromosome abnormalities*
- ✓ *8% Mendelian diseases (> 3000 loci)*
- ✓ *90% Multifactorial (complex) disease*
- ✓ *1.4% other than genetic problem*

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Inherited disease: two types of inheritance

- ✓ Mendelian*: individual strong mutations*
- ✓ Complex: *interactions of multiple gene variants (SNPs) with moderate effects*

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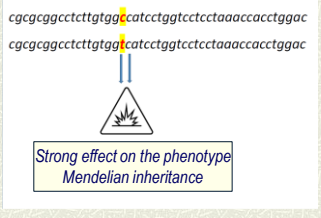
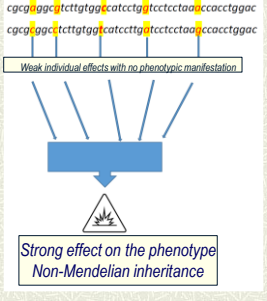
Mendelian vs. non-Mendelian inheritance, simple vs. complex traits





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An example: infectious diseases

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

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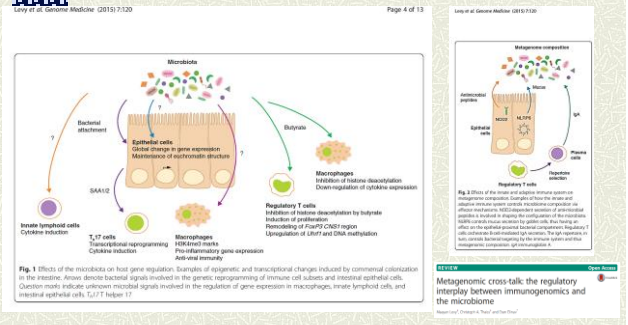
Microbiome and immunogenome



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Microbiome and immunogenome

Table 2 Examples of reprogramming of the immunogenome by the microbiota

Cell type	Influence	Microbial signal(s)	References
Macrophages	Deposition of activating histone marks, enhanced cytokine expression	Unknown	[40, 132]
Macrophages	HDAC inhibition, reduced cytokine expression	Butyrate	[41]
Regulatory T cells	HDAC inhibition, acetylation of *FoxP3* CNS1 region, induction of proliferation, upregulation of *Ufnl1*	Butyrate	[42–45]
T helper 17 cells	Transcriptional reprogramming through epithelially produced SAA1 and SAA2	Epithelial attachment	[47, 48]
Neutrophils	Induction of neutrophil aging, steady-state granulopoiesis, stimulation of migration through SAA1 and SAA2	TLR ligands	[133–135]
Innate lymphoid cells	Transcriptional reprogramming, cytokine induction	Unknown	[133–135]
Natural killer T cells	Mucosal recruitment via CXCL16, cytokine production	Glycosphingolipids	[52, 136, 137]
γδ T cells	Transcriptional reprogramming	Unknown	[51]

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Identification of causative genes and polymorphisms: genomics

- ✓ Theory
- ✓ Medical applications: *genomic medicine*

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- ✓ Theory
- ✓ Medical applications: *genomic medicine*

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Simple Mendelian traits

Identification of causative mutations

- ✓ Genealogy, comparative genomics
- ✓ Candidate genes, whole genome screens

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Complex traits

- ✓ Quantitative phenotypes
- ✓ Small additive effects of individual polymorphisms, mostly SNPs, composing the complex phenotype
- ✓ Gene-gene interactions identified by analysis of composed genotypes
- ✓ Genes/genotypes with major effects can be used as genetic markers

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Complex traits: genomic medicine - from theory to practice

Miniaturization and automation

Chips and arrays

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High Density (HD) Single Nucleotide Polymorphism (SNP) chips

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

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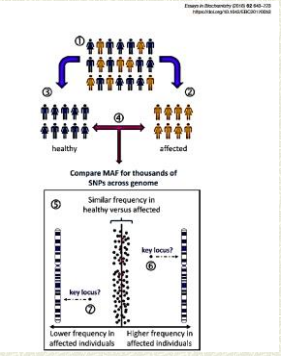
How to find markers -a genomic tool: Genome-wide association studies (GWAS)



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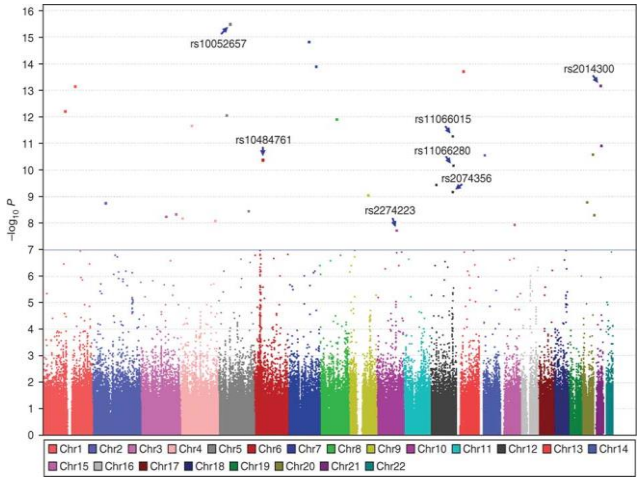

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Example of a really complex disease: Genes associated with atherosclerosis/hypercholesterolemia and Alzheimer's disease

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

http://www.pharmgkb.org/

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Phenotypes, genes and mechanisms of disease

Mechanisms/ Pathways → Genes → Markers

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Identification of causative genes and polymorphisms: genomics

- ✓ Theory
- ✓ Medical applications: *genomic medicine*

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Genomics in Mendelian diseases: Examples of practical applications

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

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Examples of practical applications: Inherited diseases

- ✓Genetic prevention: prenatal screening
- ✓Genetic counselling
- ✓Genetic diagnostics

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Laboratory diagnostics

- ✓Cytogenetic diagnostics *(karyotype, FISH, CGH)*
- ✓Molecular diagnostics *(sequencing, candidate gene and GWAS markers)*

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Molecular diagnostics: individual testing for ARD

- ✓ Identification of carriers
- ✓ Most common mutations in the (Czech) population: *Cystic fibrosis (1/25), spinal muscular atrophy (1/30), pre-lingual deafness (1/40)*
- ✓ Further diseases (1/40): phenylketonuria, adrenogenital syndrome – curable, therefore prenatal screening is performed

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Massive molecular testing: panels

- ✓ The carrier status (heterozygosity)
- ✓ Infertility, donors of sexual cells and embryos
- ✓ More than 830 most common mutations in 77 genes causing more than 60 AR DO
- ✓Oncological panel „CZECANCA“ (CZEch CAncer paNel for Clinical Application: 226 genes associated with inherited predisposition (population specific again)

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Molecular diagnostics in reproductive medicine

- ✓ Cell-free cf-DNA in maternal blood: *noninvasive molecular testing (NIPT)*
- ✓ Karyomapping: *technique used to test in vitro embryos for genetic mutations (PGD, PGT-M/PGT-A)*
- ✓ New: *high-resolution and noninvasive fetal exome screening, WGS*

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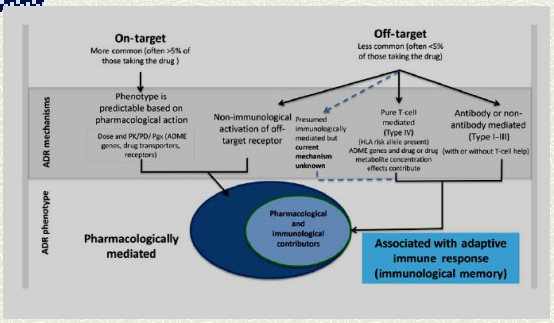
Pharmacogenetics: ADR



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Variability related to side-effects of drugs

„On-target“

Due to polymorphisms in genes encoding proteins involved in mechanisms of drug action, e.g. signaling molecules and/or cell metabolism pathways

„Off-target“

Due to polymorphisms in genes affecting reactions of the organism to a drug. However, these reactions are not related to its curative effects. They are mostly represented by undesirable immune reactions (hypersensitivity) to the drug and associated with underlying immune response genes

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Drug	DHR	HLA risk alleles	PPV	NPV	Populations
Abacavir	HSS/DRHS	B*57:01[99,113,114]	55%	100%	European, African
Carbamazepine	SJS/TEN	B*15:02[76-80]	3%	100% in Han Chinese	Han Chinese, Thai, Malaysian, Indian
		B*15:11[113,114]			Korean, Japanese
		B*15:18, B*59:01 and C*07:04[83]			Japanese
		B*15:21[117]			
		A*31:01[116,118-120]			Japanese, northern European, Korean
	HSS/DIHS/ DRESS	8.1 AH (HLA A*01:01, Cw*07:01, B*08:01, DRB1*03:01, DQA1*05:01, DQB1*02:01)[121]			Caucasians
		A*31:01[122]	0.89%	99.98%	Europeans
		A*31:01[122]	0.59%	99.97%	Chinese
		A*31:01[116,118-120]			Northern Europeans, Japanese, and Korean
		A*11 and B*S 1 (weak)[120]			Japanese
	MPE	A*31:01[123]	34.9%	96.7%	
	Any ADR	A*31:01[124]			
Allopurinol	SJS/TEN/DIHS/DRES S/MPE	B*58:01 (or B*58 haplotype)[80,125-131]	3%	100% in Han Chinese	Han Chinese, Thai, European, Italian, Korean
Oxcarbazepine	SJS/TEN	B*15:02 and B*15:18[132-136]	15:02 - 0.73%	15:02 -99.97	Han Chinese, Taiwanese
Lamotrigine	SJS/TEN	B*15:02 (positive)[133]			Han Chinese
		B*15:02 (no association)[135,136]			Han Chinese
Phenytoin	SJS/TEN	B*15:02 (weak), Cw*08:01 and DRB1*16:02[72,7,137]			Han Chinese
	DRESS/MPE	B*15:01 (weak) B*S101 (weak)[137]			Han Chinese
Nevirapine	SJS/TEN	C*04:01[138]			Malawian
	HSS/DIHS/DRESS	DRB1*01:01 & DRB1*01:02 (hepatitis and low CD4+)[92,139]	18%	96%	Australian, European and South African
		Cw*8 or Cw*5-B*14 haplotype[140]			Italian and Japanese
		Cw*4[83,141]			Blacks, Asians, Whites, Han Chinese
		B*35[71] B*35:01[126] B*35:05[142]	16%	97%	Asian
	Delayed rash	DRB1*01[143]			French
		Cw*04[143]			African, Asian, European, and Thai
		B*35:05[142]			Thai
Dapsone	HSS	B*13:01[144]	7.8%	99.8%	
Efavirenz	Delayed rash	DRB1*01[143]			French
Sulfamethoxazole	SJS/TEN	B*38[88]			European
Amoxicillin-clavulanate	DILI	DRB1*15:01 A*02:01 DQB1*06:02, and rs3135388, a tag SNP of DRB1*15:01-DQB1*06:02			European
		DRB1*07 and HLA-A1 (protective)[145-147]			
Lumiracoxib	DILI	DRB1*15:01-DQB1*06:02-DRB5*01:01-DQA1*01:02 haplotype[148]			International, multi-center
Ximelagatran	DILI	DRB1*07 and DQA1*02[149]			Swedish
Diclofenac	DILI	HLA-A11[150]			European

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Pharmacogenetics/pharmacogenomics

Table 1 Candidate genes for pharmacogenetic implementation with available practice guidelines and recommendation statements

Gene(s)	Drug	Organization	Practice guidelines/ recommendation statements
CFTR	Ivacaftor	CPIC	Clancy et al. 2014[139]
CYP2C9/VKORC1	Warfarin	ACMG	Flockhart et al. 2008[140]
		CPIC	Johnson et al. 2011[141]
CYP2C19	Clopidogrel	CPIC	Scott et al. 2011,[142] 2013[143]
		ACCF/AHA	Holmes et al. 2010[144]
	TCAs	CPIC	Hicks et al. 2013[145]
CYP2D6	Codeine	CPIC	Crews et al. 2012[146]
	SSRIs	CPIC	In preparation; 2014[a]
		EGAPP	EGAPP Working Group, 2007[147]
	Tamoxifen	ACMG	Lyon et al. 2012[148]
	TCAs	CPIC	Hicks et al. 2013[145]
CYP3A	Tacrolimus	CPIC	In preparation; 2014[a]
DPYD	Fluoropyrimidine	CPIC	Caudle et al. 2013[149]
HLA-B	Abacavir	CPIC	Martin et al. 2012[150]
	Allopurinol	CPIC	Hershfield et al. 2013[151]
	Carbamazepine	CPIC	Leckband et al. 2013[152]
	Phenytoin	CPIC	In preparation; 2014[a]
IFNL3 (IL28B)	Interferon-α	CPIC	Muir et al. 2014[153]
SLCO1B1	Simvastatin	CPIC	Wilke et al. 2012[154]
TPMT	Azathioprine/6-mercaptopurine	CPIC	Relling et al. 2011,[155] 2013[156]
UGT1A1	Irinotecan	EGAPP	EGAPP Working Group, 2009[157]
Multiple (eleven genes)	Multiple (53 drugs)	KNMP-PWG	Swen et al. 2011[158]

Note: [a]Based on information available from Pharmacogenomics Knowledge Base website (http://www.pharmgkb.org/cpicpair/), and F. Caudle, CPIC Coordinator, personal communication.

Abbreviations: TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; ACCF, American College of Cardiology Foundation; ACMG, American College of Medical Genetics and Genomics; AHA, American Heart Association; CPIC, Clinical Pharmacogenetics Implementation Consortium; EGAPP, Evaluation of Genomic Applications in Practice and Prevention; KNMP-PWG, Royal Dutch Association for the Advancement of Pharmacy-Pharmacogenetics Working Group.

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Pharmacogenetics/pharmacogenomics

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:** Fibanserin (G02CX02), Hormonální antikoncepce (G03A); **Antiinfekční látky:** Flucloxacilin (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), Ustekinzubab (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); **Trieyklická 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)

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Genetics of vaccination

- ✓ *Individual variation in post-vaccination IRs*
- ✓ *Pharmacogenomics*

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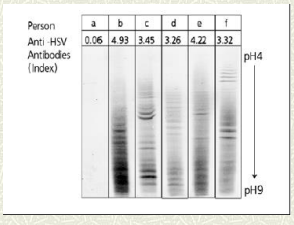
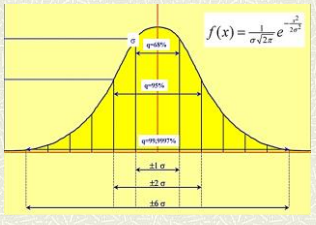
Individual variation in antibody responses





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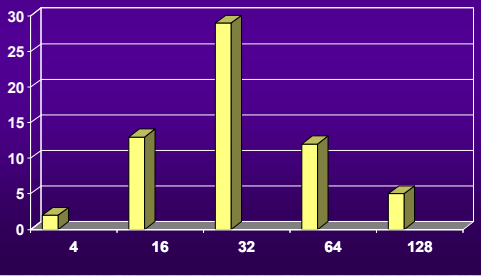
Titers of post-vaccination antibodies in a real experiment (N=61)



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Genetics of vaccination

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	53–85	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

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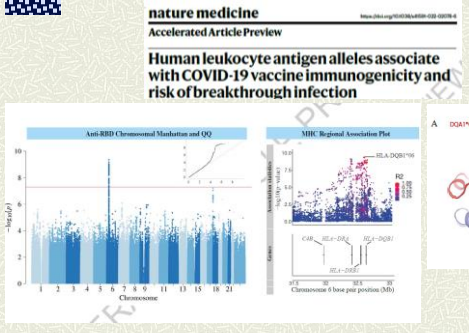
Vaccination: Covid, IR genes



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Genetics of vaccination

- ✓ *Individual variation in post-vaccination IRs*
- ✓ *Pharmacogenomics*

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Pharmacogenomics of vaccination (vaccinomics)

Generation 1

Generation 2 (recombinant vaccines)

Generation 3 (DNA, RNA vaccines)

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Genomics and dental medicine

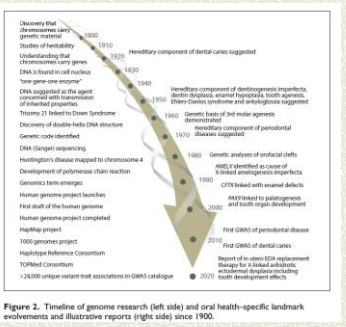

Figure 2. Timeline of genome research (left side) and oral health–specific landmark evolvements and illustrative reports (right side) since 1900.

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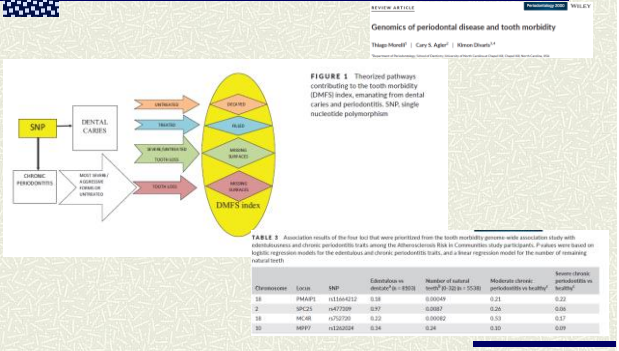
Genomics and dental medicine



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Genomics and dental medicine

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Genomics and dental medicine: the future - genome editing

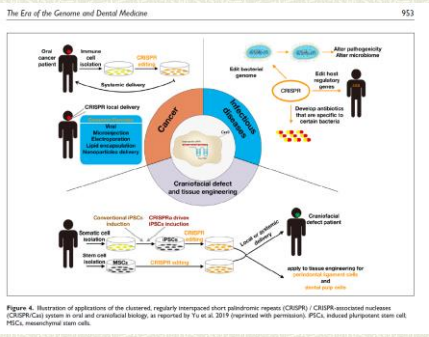

Figure 4. Illustration of applications of the clustered, regularly interspaced short palindromic repeats (CRISPR) / CRISPR-associated nucleases (CRISPR/Cas) system in oral and craniofacial biology, as reported by Yu et al. 2019 (reprinted with permission). iPSCs, induced pluripotent stem cell; MSCs,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

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Ethical issues: how to handle information generated by genomic techniques

Examples

- ✓ Mendelian diseases:
  e.g. carrier tests, PGD
- ✓ Complex diseases
  e.g. interpretation of GWAS, DTC

Only people understanding principles can cope with this problem

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Practical applications

Minimum variant for you

- ✓ *To know, when and where to refer a patient for a genetic consultation*
- ✓ *To know how to interpret clinical geneticist's reports*
- ✓ *To know when not to refer a patient for a genetic consultation*

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Questions even at this moment?

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The near future in genomic medicine

- ✓ *Inherited diseases: causative genes*
- ✓ *Genetic susceptibility/resistance to disease provoked by environmental factors*

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Disease

Reaction of an organism to pathogenic insults

Affected by the nature of the insults, environmental factors, current condition of the organism and its genetic make-up

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Genetics of susceptibility to disease

- ✓ *Genes affecting health*
- ✓ *Their polymorphisms do not cause the disease, but they affect the organism´s reaction to the pathogen(s)*
- ✓ *Relative value of the phenotypes: more/less susceptible/resistant than average*

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A model example: genetics of susceptibility to infections

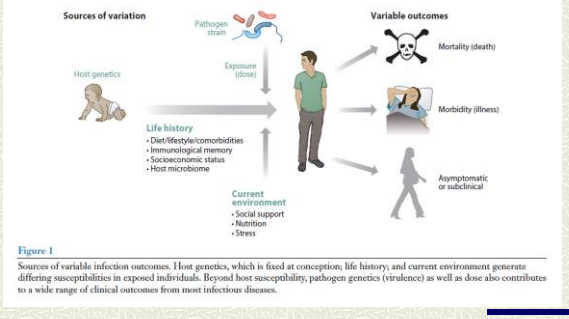

Figure 1
Sources of variable infection outcomes. Host genetics, which is fixed at conception; life history; and current environment generate differing susceptibilities in exposed individuals. Beyond host susceptibility, pathogen genetics (virulence) as well as dose also contributes to a wide range of clinical outcomes from most infectious diseases.

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Genetic susceptibility to disease as a complex trait

Leading Edge
Essay

Cell

Infectogenomics: Insights from the Host Genome into Infectious Diseases

Paul Kellam[1] and Robin A. Weiss[1,*]
[1]MRC/UCL Centre for Medical Molecular Virology, Division of Infection & Immunity, University College London, London W1T 4JF, UK
*Contact: rweiss@ucl.ac.uk
DOI 10.1016/j.cell.2006.02.003

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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Genetic resistance, susceptibility and tolerance

***Susceptibility/Resistance*: (in)ability to reduce pathogen replication in the host**

vs.

***Tolerance*: ability to maintain homeostasis in the presence of replicating pathogen**

Susceptibility	*Tolerance, carrier status, shedding*	*Resistance*

environmental (non-genetic) factors, selection

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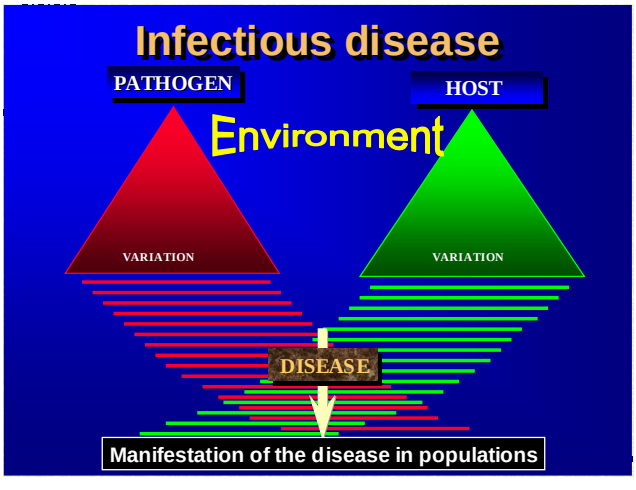

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Infectious disease as a result of host-pathogen interactions

„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

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Infectious disease as a result of host-pathogen interactions

- ✓ *Disease as a defense reaction of the host*
- ✓ *Often unique host/pathogen combinations*
- ✓ *Individual variability in using different immunological mechanisms against the same pathogen*
- ✓ *Symptomatology determined mostly by the pathogens or by the host*

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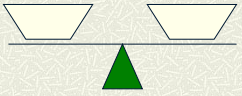
Scylla and Charybdis of immune responses: genetic variation

The dilemma:
too high/too low immune responses?

Protective immunity
Resistance to infection

Autoimmunity
Inflammation



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Immunity-related (IR) genes: the immunogenome

- ✓*Genes involved in host immune reactions*
- ✓ *Immunome: products of IR genes*
- ✓ *Despite the same biological importance, IR genes underlie many different functions in all branches of immunity*

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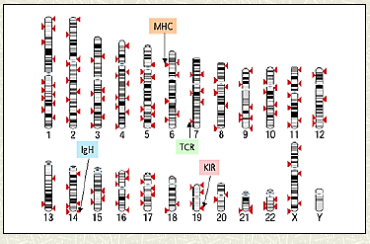
Immunogenome and immunome

5% of the mammalian genome (~1,000 human genes) are protein coding genes related to immune mechanisms



Ortutay et al. Immunogenetics 2007

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Immunity-related (IR) genes and disease

- ✓ *Immune functions as simple and/or complex traits (Mendelian vs. complex inheritance)*
- ✓ *Immune functions in mechanisms of infectious diseases*

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Genetic resistance/susceptibility to infections: a summary

- ✓ Genes affecting health (interactions with environmental factors)
- ✓ Their polymorphisms are not causative for diseases, but they influence reactions of the host to environmental pathogens
- ✓ Pathogens as a driving force of evolution: IR genes/immunogenome have been shaped by evolutionary interactions with pathogens,
- ✓ In practical terms, resistance/susceptibility are usually relative to a population average

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Mendelian inheritance

- ➢ Major effects
- ➢ Expected to result from low-frequency variants
- ➢ Less knowledge than for complex traits

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

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GWAS and infections in humans

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[6]	*Mycobacterium tuberculosis*	18q11.2 (*GATA6, CTAGE1, RBBP8, CABLES1*)	Unknown
Meningococcal disease[7]	*Neisseria meningitidis*	*CFH, CFHR3, CFHR1*	Innate immunity

De Bakker, Telenti Nature Genet 2010

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Genetic resistance/susceptibility to infections: untranslated genome

- ✓*Most GWAS hits observed in (protein) non-coding regions*
- ✓*Many SNPs found in regulatory regions of protein coding genes*
- ✓*Effects on expression and consequently on diseases, including infections*

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Mechanisms of immunity-related diseases studied with genomic tools

- ✓ Infections
- ✓ Allergies
- ✓ Autoimmunity
- ✓ Complex immunopathologies

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Examples of genetic susceptibility to infections

- ✓Norovirus, rotavirus (*FUT2*)
- ✓AIDS (CCR5)
- ✓Malaria (Duffy)
- ✓*COVID 19 (AB0, IFN type 1)*

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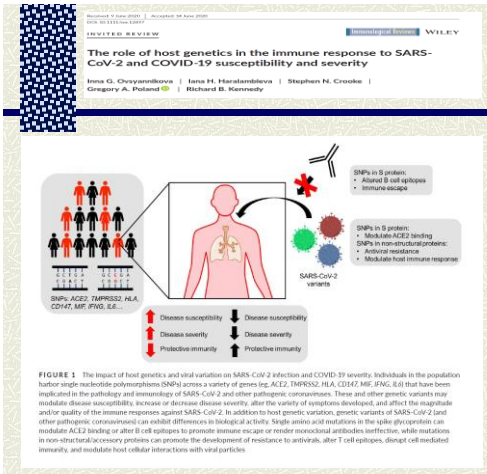

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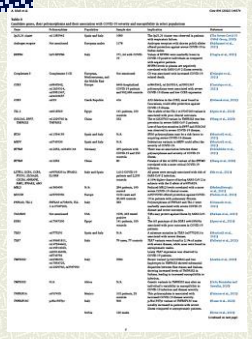
Covid 19 and host genetics: 2022



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

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

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Evolutionary aspects

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

- ✓ *Migrations and sympatry of hominoid populations, sharing different infections*
- ✓ *Lower overall genome diversity and mostly lower IR gene in Neanderthals*
- ✓ *Higher MHC gene diversity*
- ✓ *Archaic Neanderthal haplotypes TLR6-TLR1-TLR10*
- ✓ *Chromosomes 3 and 12: risk vs. protection from Neanderthals*
- ✓ *Susceptibility to COVID 19, ethnic differences*

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Examples from dental medicine

Hindawi
International Journal of Dentistry
Volume 2021, Article ID 5566733, 14 pages
https://doi.org/10.1155/2021/5566733

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]

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

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

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Examples from dental medicine

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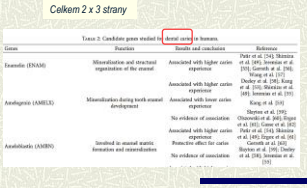

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Examples from dental medicine

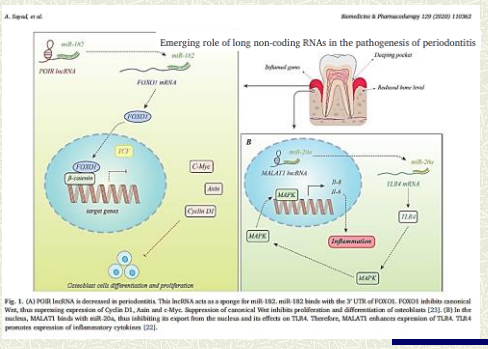

Fig. 1. (A) POIR lncRNA is decreased in periodontitis. This lncRNA acts as a sponge for miR-182. miR-182 binds with the 3′ UTR of FOXO1. FOXO1 inhibits canonical Wnt, thus supressing expression of Cyclin D1, Axin and c-Myc. Suppression of canonical Wnt inhibits proliferation and differentiation of osteoblasts [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].

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