New Trends in Clinical Genetics: Genomic Medicine

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LF MU 2025

1

Outline

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

2

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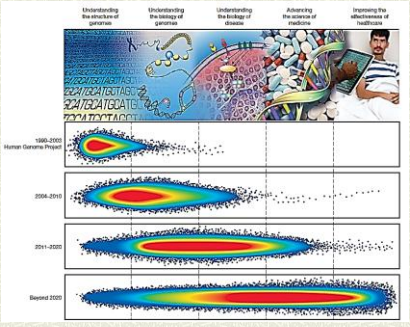
3

Genomic medicine: 2011 prediction



Charting a course for genomic medicine from base pairs to bedside

Green et al. 2011

Top of your professional career

4

Genomic medicine: clinical practice

Genetics inMedicine | REVIEW

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Implementing genomic medicine in the clinic: the future is here

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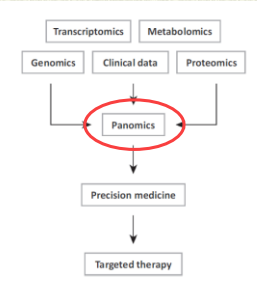
Volume 15 | Number 4 | April 2013 | GENETICS in MEDICINE

5

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.

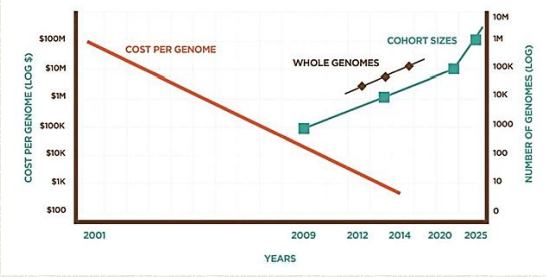
The complexity and vastness of data analysis may ultimately require the development of computational platforms to aid in the discovery of biological pathways underling health and disease.

Panomics for Precision Medicine

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

6

Genomic medicine - from theory to practice: financial aspects



S. K. DELANEY ET AL

7

Genomic medicine: clinical practice

EXPERT REVIEW OF MOLECULAR DIAGNOSTICS, 2016
VOL. 16, NO. 5, 521–532
http://dx.doi.org/10.1586/14737159.2016.1146593

Taylor & Francis

PERSPECTIVE

OPEN ACCESS

Toward clinical genomics in everyday medicine: perspectives and recommendations

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8

Recommendations for health care providers

Published in final edited form as:
Genet Med. 2016 November ; 18(11): 1075–1084. doi:10.1038/gim.2016.17.

Recommendations for the Integration of Genomics into Clinical Practice

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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

9

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10

New philosophy in medicine: genomics as a holistic approach



Slide courtesy of Prof. Jamie McLeod, UK Lexington

11

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
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


12

Tools and resources

- ✓ *DNA Sanger (1-2 kb)*
- ✓ *DNA NGS (whole genomes)*
- ✓ *DNA NGS LR: „HiFi“ (50 kb)*
- ✓ *DNA exome*
- ✓ *RNA IsoSeq: full-length cDNA*

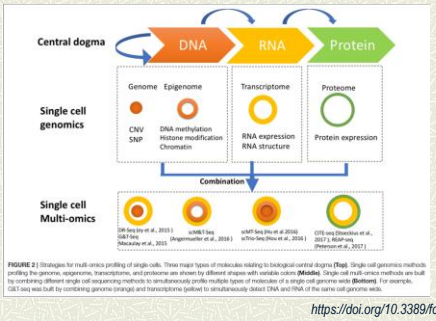
13

Recent achievements

- ✓ *T2T genome(s)*
- ✓ *Multiomics*
- ✓ *Pangenomics, pangenomes*

14

Multiomics



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

15

Multiomics

Analysis of complex phenotypes/<u>diseases</u> at all levels

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

16

Pangenomes

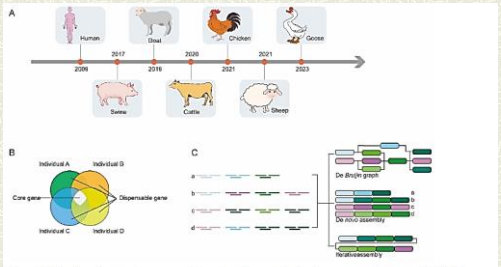


Figure 2. The development process and construction methods of pan-genomic research. (A) Numerous species have developed pan-genomes, including emiliania huxleyi. (B) Pan-genomes comprise core genes, dispensable genes, and strain-specific genes. (C) Pan-genome construction strategies include iterative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

17

Microbiome and immunogenome

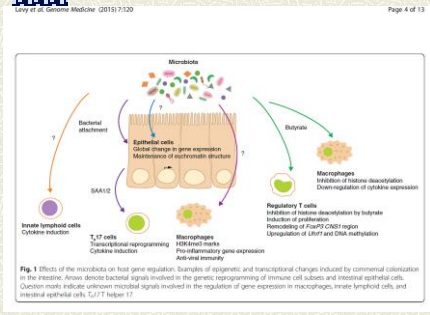
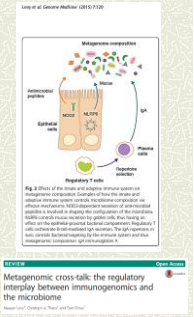


Fig. 1 Effects of the microbiota on host gene regulation. Examples of epigenetic and transcriptional changes induced by commensal colonization in the intestine. Arrows denote bacterial signals involved in the genetic reprogramming of immune cell subsets and intestinal epithelial cells. Question marks 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



18

Terminology: confusion of languages

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

Systematic and complex (holistic)
analysis of the genome

19

Genetic variability: mutations vs. polymorphisms

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

20

Genetic variability in disease: different roles

✓ *Inherited diseases: causative genes*

✓ *Genetic susceptibility/resistance to disease provoked by environmental factors*

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

21

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

22

Mutations vs. polymorphisms

✓ *Strong mutations: simple Mendelian inheritance*

✓ *Single nucleotide polymorphisms: underlie complex (quantitative) variability of traits/diseases*

23

Inherited disease: two types of inheritance

✓ Mendelian*: individual strong mutations*

✓ Complex: *interactions of multiple gene variants (SNPs) with moderate effects*

24

Reminder: individual variability of the human genome

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

cgcgcggcctcctccttgtggccatcctggtcctcctaaaccacctggac

cgcgcggcctcctccttgtggtcatcctggtcctcctaaaccacctggac

Insertions/deletions (indels)

cgcgcggcctcctccttgtggccatcctggtcctcctaaaccacctggac

cgcgcggcctcctccttgtgg-------ctggtcctcctaaaccacctggac

25

Single nucleotide polymorphisms *(SNPs)*

✓ *Nucleotide sequence*

cgcgcggcctcttgtggccatcctggtcctcctaaaccacctggac

cgcgcggcctcttgtggtcatcctggtcctcctaaaccacctggac

✓ *Alleles*

C, T

✓ *Genotypes*

CC, CT, TT

26

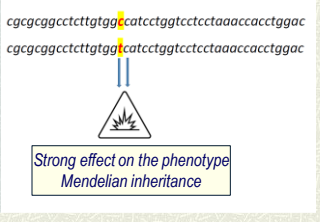
Genomic medicine - from theory to practice: technical advances

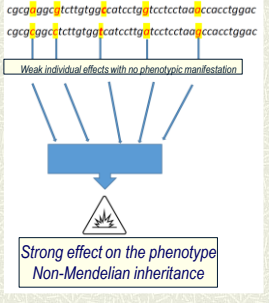
Miniaturization and automation: chips and arrays

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

27

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





28

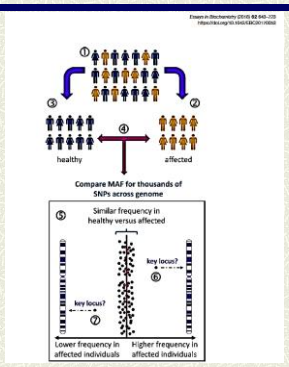
Genetics in complex diseases

Genomes in disease

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

29

A tool: Genome-wide association studies (GWAS)



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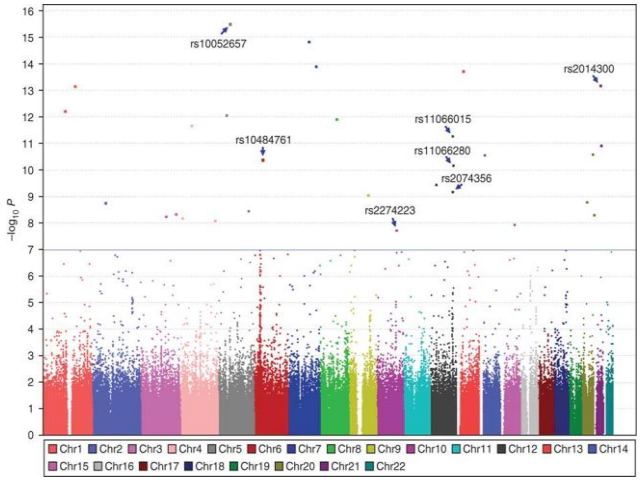
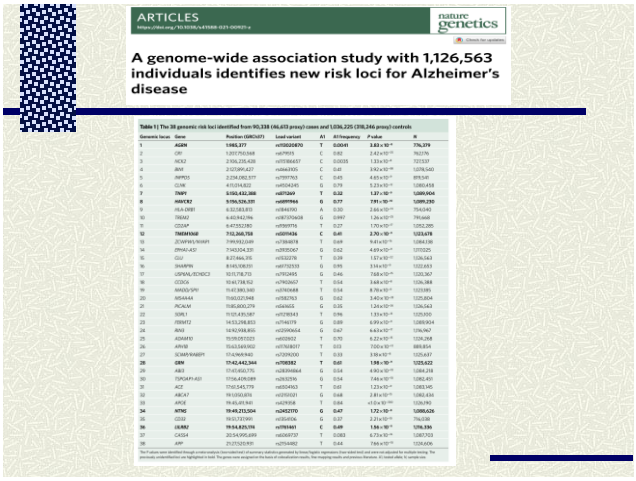


32

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

33


ARTICLES

nature genetics

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

34

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35

Applications

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

36

Genomics and diagnostics

✓Cytogenetic diagnostics
(karyotype, FISH, CGH)

✓Molecular diagnostics *(sequencing, candidate gene and GWAS markers)*

37

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

38

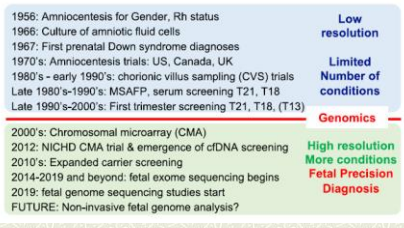
Massive molecular testing: panels

- ✓ 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)
- ✓ Whole exome sequencing

39

Prenatal genetic testing

Fig. 1 Prenatal genetic testing and screening timeline. **a** Pre-genomic era, **b** genomic era



40

Molecular diagnostics in reproductive medicine

- ✓ Fetal cell free cfDNA in maternal blood: non-invasive testing NIPT
- ✓ Karyomapping: *in vitro testing of embryos*
- ✓ High-resolution non-invasive fetal exome screening and WGS

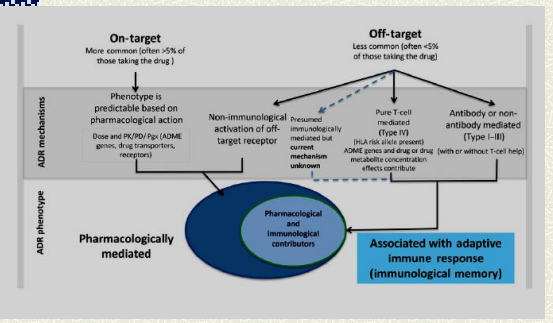
41

Preimplantation genetic diagnostics (PGD)

- ✓During assisted reproduction procedures - IVF
- ✓Diagnostics of embryos: targeted or screening
- ✓PCR and linkage analysis using STR markers
- ✓Selection of embryos
- ✓Opportunity to get rid of a familiar burden

42

Pharmacogenetics: ADR



43

Variability related to side-effects of drugs

"On-target"

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

"Off-target"

Is 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

44

Pharmacogenetics: a commercial offer

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:** Flucloxacillini (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), Ustekinumab (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)

45

The future of genome editing (?)

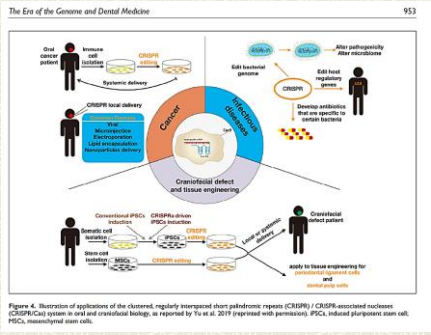


Figure 4. Illustration of applications of the clustered, regularly interspaced short palindromic repeats (CRISPR) / CRISPR-associated nucleases (CRISPR/Cas) system in oral and craniofacial biology, as reported by Yu et al. 2019 (reprinted with permission). iPSCs, induced pluripotent stem cell; MSCs,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

46

The near future in genomic medicine

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

47

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

48

Mechanisms of immunity-related diseases studied with genomic tools

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

49

A model example: genetics of susceptibility to infections

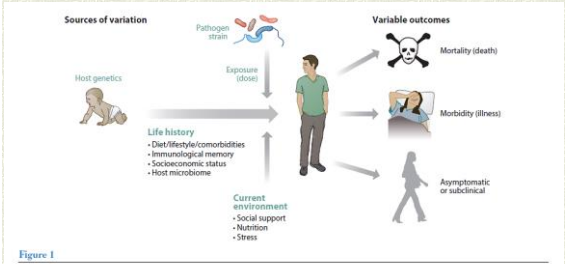


Figure 1

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.

50

Genetic susceptibility to disease as a complex trait

Leading Edge
Essay

Cell

Infectogenomics: Insights from the Host Genome into Infectious Diseases

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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.

51

Genetics of vaccination

Table 3. Heritability estimates of vaccination responses in twin studies

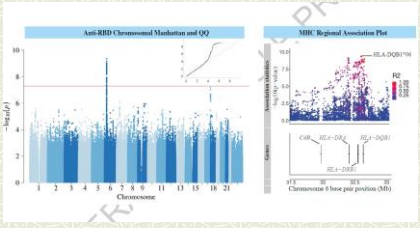
Vaccine	Parameter	DZ[a]	MZ[a]	Population	Age	Study	Heritability, %	95% CI %	References
Measles	antibody	55	45	USA[b]	2–18 years	cross-sectional	89	≥ 52[c]	18
Mumps	antibody	55	45	USA[b]	2–18 years	cross-sectional	39	≥ 2[c]	18
Rubella	antibody	55	45	USA[b]	2–18 years	cross-sectional	46	≥ 5[c]	18
HAV	antibody	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	26–70	12
Tetanus	IL-13	159	48	Gambia	5 months	prospective	64	50–75	12
Diphtheria	antibody	159	48	Gambia	5 months	prospective	49	27–77	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

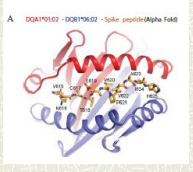
57

Genetics of vaccination: Covid-19

nature medicine
Accelerated Article Preview

Human leukocyte antigen alleles associate with COVID-19 vaccine immunogenicity and risk of breakthrough infection





58

Ethical issues: how to cope with 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

59

Outline

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

60

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*

61

Questions even at this moment?

62