Human sequence variation and our diseases

International Commission on the Clinical Use of Human Germline Genome Editing
US National Academy of Science
Washington, DC
August 13, 2019

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Outline

1. Patterns of human sequence variation
2. Genomics of Mendelian disorders
3. Genomics of multifactorial disorders

Patterns of human sequence variation

Types of sequence variation

SNVs (single nucleotide variants): 88%

AAGTCGATTGACCGAATTAATTAATTGCGGT

AAGTCGATTGATCGAATTAATTAATTGCGGT

1 in 1,000 bases or 3 million differences in a pair of genomes

INDELs (insertions/deletions <50nt), small CNVs (copy number variants): 7%

AAGT- GATTGACCGAATTAATTAATTGCGGT

AAGTCGATTGACCG ------ AATTAATTGCGGT

Inversions, segmental rearrangements: 5%

1) Short read sequencing technology misses many variants;
2) There are many structurally complex loci across the genome.

Sequence variation in 53,831 humans (TOPMed): 410m variants*

*European, African, Asian & Native American ancestry; Hispanic & non-Hispanic ethnicity; ~40% individuals admixed

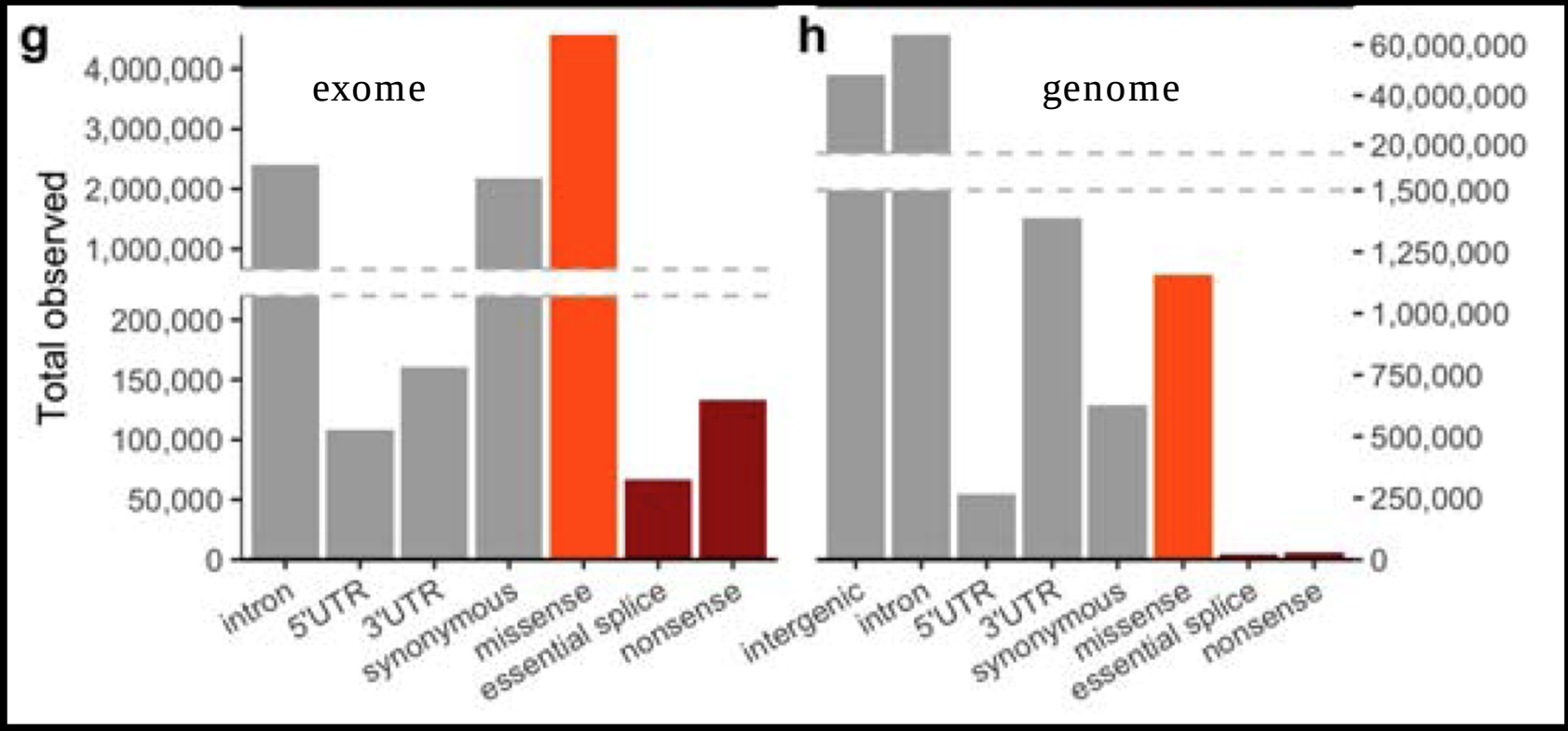
Variant type	Total #	# per individual
single nucleotide variants	381,343,078	3,383,710
insertions/deletions	28,980,753	183,759
coding: synonymous	1,525,971	11,073
non-synonymous	3,172,551	10,875
stop/± 2nt splice	105,042	456
frameshift	113,805	127
in-frame deletions	55,806	99

~50% of variation is unique to individuals

Taliun et al *bioRxiv* 2019

Sequence variation in 141,456 exomes and genomes (gnomAD): 270m variants*

*diverse ethnicities and ancestries; includes admixed individuals



443,769 loss-of-function (protein) variants in 16,694 genes…
genes vary considerably in tolerance to such variants

Karczewski *bioRxiv* 2019

Genomics of Mendelian disorders

The molecular basis of rare and severe disorders

- 5,048 of 7,926 Mendelian phenotypes have known genes (*Mendelian Inheritance in Man*);
- Exome/genome sequencing (22,742 families) revealed 1,430 known genes, 470 phenotypic expansions and 1,767 new genes (*Centers for Mendelian Genomics)*;
- 70% of known Mendelian phenotypes have associated genes and 24% of these are pleiotropic;
- 20% of human genes have an associated Mendelian disorder and 30% likely involve embryonic lethality.

1) ~50% of causal variants can be recognized today;
2) functional analysis of pathogenic alleles in a cellular context is severely lagging;
3) deleterious alleles can be beneficial in some contexts (Fy^0 protection for *P vivax*).

Chong et al *Am J Hum Genet* 2015; Posey et al *Genet in Med* 2019

Clinical genetics of rare and severe disorders

- In clinical genetic testing laboratories, the fractions of autosomal dominant/recessive and X-linked dominant/recessive cases are 53, 31, 3 and 13%, respectively

- ...but, exome/genome sequencing of 6,040 families (proband, parents) with an undiagnosed rare disorder reveals 46% are from *de novo* coding mutations, 3.6% are recessive but rising to 31% in inbred families (*Deciphering Developmental Disorders*).

The 50% 'gap' in undiagnosed disorders is owing to our inability to recognize all coding pathogenic alleles or they are non-coding, have reduced penetrance or are polygenic (synthetic lethals).

Farwell et al *GIM* 2014; Retterer e al *GIM* 2015;Martin et al *Science* 2018

Mutation-Selection balance

- Pathogenic alleles in humans are rare and at equilibrium between their elimination by natural selection and occurrence through *de novo* mutations (DNM, μ);

- autosomal/X-linked recessive/dominant disorders with large fitness reductions have *incidence* proportional to the mutation rate (μ) of the underlying gene (3-fold difference);

- $\mu = 1.29 \times 10^{-8}$ /base/generation in humans but depends on gene sequence, particularly CpG transitions, and increases with paternal (1.47 DNM/yr) and less so with maternal (0.37 DNM/yr) age.

1) $\mu \sim 5 \times 10^{-5}$ /gene (median) and varies 100-fold;
2) μ depends on demographic/reproductive/environmental factors.

Jonsson et al *Nature* 2017

Pathogenic alleles of high frequency

- Some pathogenic alleles have arisen to high frequency (>1%) in some populations;

- the usual cause is genetic drift in geographic, cultural or religious isolates with or without consanguinity;

- less frequently, mutant alleles have heterozygote advantage (fitness advantage over either homozygote, e.g., malarial protection in sickle cell trait);

Genetic testing together with community education and counseling have reduced/eliminated some disorders in some populations (β-thalassemia in Cyprus, Sardinia; Tay-Sachs disease in the Ashkenazim; several recessive disorders in the Orthodox Jewish community: Dor Yeshorim).

Cao & Kan *Cold Spr Harb Pers* 2013

Genetic modifiers of pathogenic alleles

- Evolutionary arguments suggest that alleles at genes that can reduce the pathogenicity of a disease allele or delay its onset will be positively selected;

- genetic 'modifiers' are expected but contrary to model organisms can be heterogeneous or polygenic in humans;

- this is one genetic scenario by which complex inheritance can arise.

1) Pathogenic alleles identified in "affected" families have high penetrance (an ascertainment bias);
2) the same allele found by screening may have lower penetrance ...genetic background effect.

Haldane *J Genet* 1941; Van Driest et al *JAMA* 2016

Implications for families

- Most Mendelian disorders are dominant, usually arise from *de novo* mutations and do not recur in a family except when a parent is a gonadal mosaic (unfortunately recognized through recurrence);

- Recessive disorders are infrequent in outbred but frequent in inbred families and can be recognized through segregating pathogenic variants, as in some dominant families;

- X linked recessives are somewhat intermediate because 1/3 of all affected males are from *de novo* mutations with recurrence from segregating variants and some gonadal mosaics.

1) Many families can benefit from sequence-based diagnosis;
2) Despite the *ClinVar* database assessing variant pathogenicity is challenging...many variants of unknown significance.

Disease prevention

- With increased sequencing in affected families and in the general population, plus education and counseling, many cases of single gene high penetrance disorders can be avoided;

- couples at high-risk today choose prenatal testing, selective termination, adoption, use of sperm/egg or embryo donors, *in vitro* fertilization followed by prenatal genetic testing (IVF/PGT) of embryos to mitigate risk;

- couples with 100% risk in their children are exceptional but are rare: expected frequency of q^4 for a recessive and ~$2q^2$ for a dominant disease (q, mutant allele frequency), respectively, or ~1 per 10^{10} couples...unless q is very high.

Lander et al *Nature* 2019

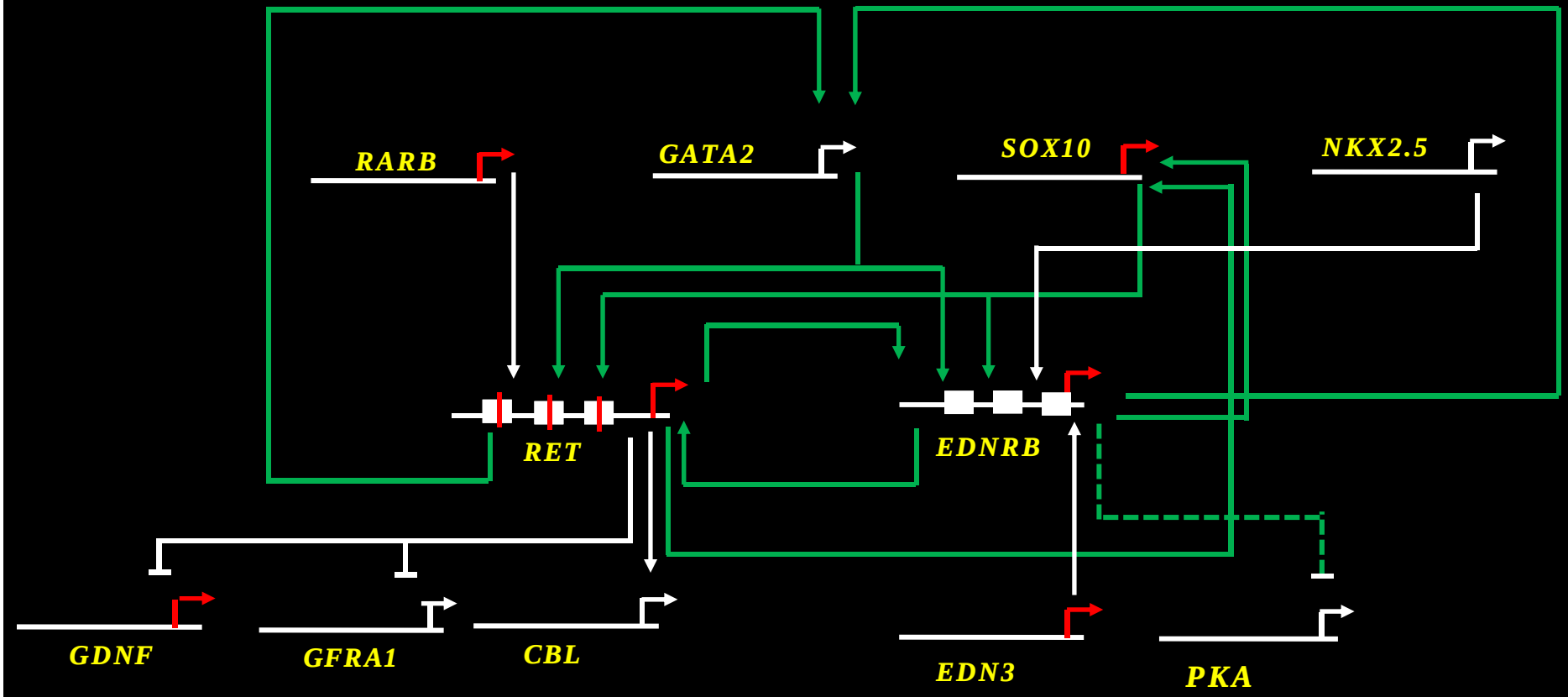
Genomics of multifactorial disorders

Genomic properties of complex phenotypes

- Multigenic inheritance is the rule rather than the exception;
- great progress in mapping complex trait loci (~72,000 replicated associations from >1,000 traits) (GWAS and sequencing phenotypic extremes/diseases);
- additive contributions from 100s to 1000s of common variants with small-to-modest effects allow polygenic risk prediction in those highly susceptible or protected;
- functional bases of these disorders are largely unknown...although regulatory defects are suspected, and demonstrated in some cases, this is an emerging but important area.

Buniello et al *NAR* 2019

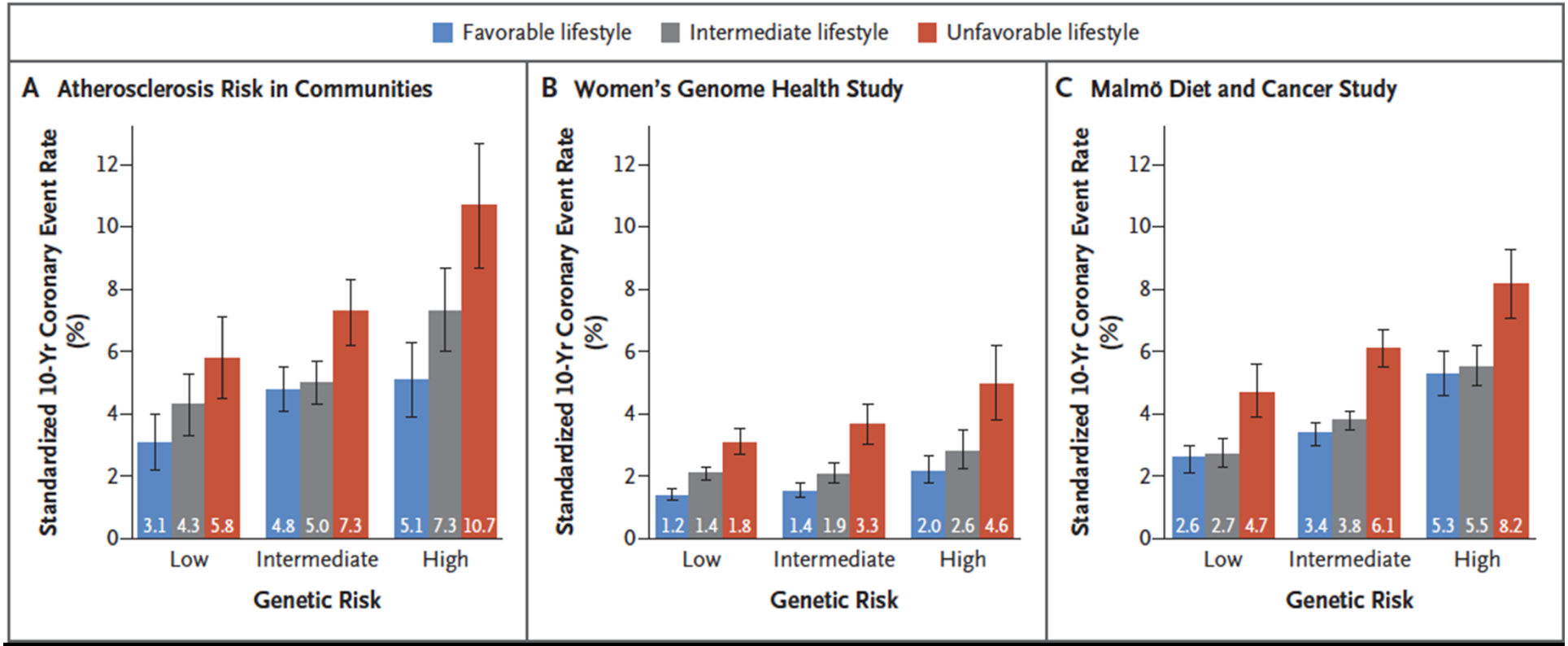
Genes for a complex disease do interact in the relevant cell-type: Hirschsprung disease



HSCR associated mutation/enhancer variant
Genetic interactions

Chatterjee et al *Cell* 2016,
Hum Mol Genet 2019

Gene-environment interactions may be pervasive: coronary artery disease



55,685 subjects across 3 studies; 50 genome-wide significant CAD GWAS SNPs; 4 healthy lifestyle factors from the AHA

Khera et al *NEJM* 2016

Challenges in elucidating complex disorders

- Despite progress, we have not achieved complete genetic, epigenetic and environmental dissection of even one phenotype;

- individual causal variants/genes are neither necessary nor sufficient for trait expression...mechanisms for explaining this feature and the disease are largely absent;

- gene interactions are important but unknown;

- environmental interactions can occur through the same transcriptions factors (thalidomide embryopathy by inactivating SALL4), chromatin regulators (O2 sensing by KDM6A) or enhancers (effects of 2-OGDD dioxygenase on *HIF1*α responsive elements) variant in disease.

Disease prevention

- Variants/genes for complex disorders have largely been used to identify individuals at high risk from single variants or polygenic scores (coronary artery disease, breast cancer, Alzheimer's, etc.);

- despite many genes contributing to high risk, drugs against single proteins (HMG CoA reductase, PCSK9, etc.) can reduce risk because its effect is usually larger than a common variant at the same gene;

- lifestyle changes are also necessary to reduce risk;

- gene editing in a complex disease is unpredictable because of the multiplicity of factors but likely to have a minor effect because the allelic effect is small.

Thank you!!