



Linking Disease Models and Human Phenotypes: The Clinical Geneticist Perspective

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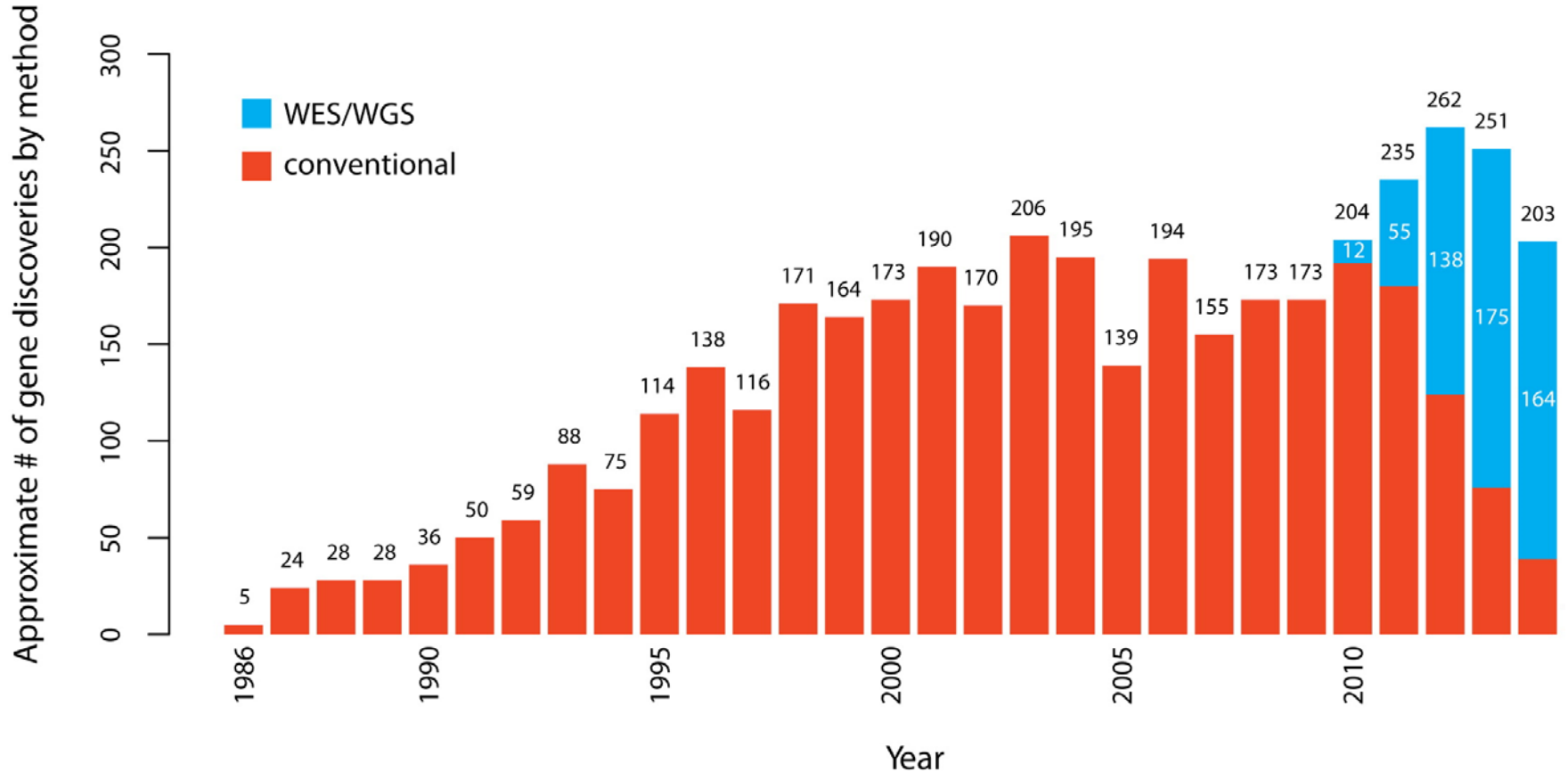
Disclosures

- Past-President of the American College of Medical Genetics and Genomics (ACMG)
- Funded research on
 - Genetics of autism spectrum disorders (DoD)
 - Mouse models for human developmental disorders of cholesterol synthesis (NIH)

Precision Medicine

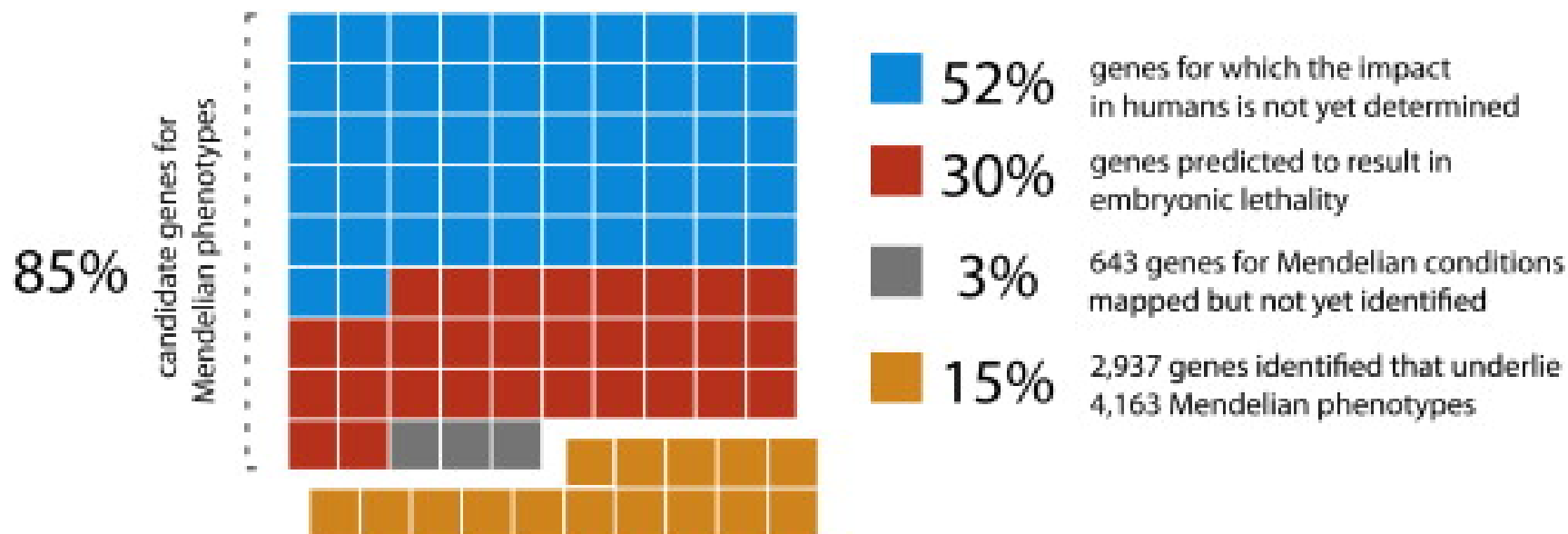
- Possible through disruptive technology of NGS and advances in computational biology
- Clinical utility currently
 - Cancer diagnosis and personalized therapeutics
 - Diagnosis of rare Mendelian disorders
- Future expected clinical utility
 - Pharmacogenomics
 - Multifactorial disorders

Human Gene Discovery for Mendelian Phenotypes



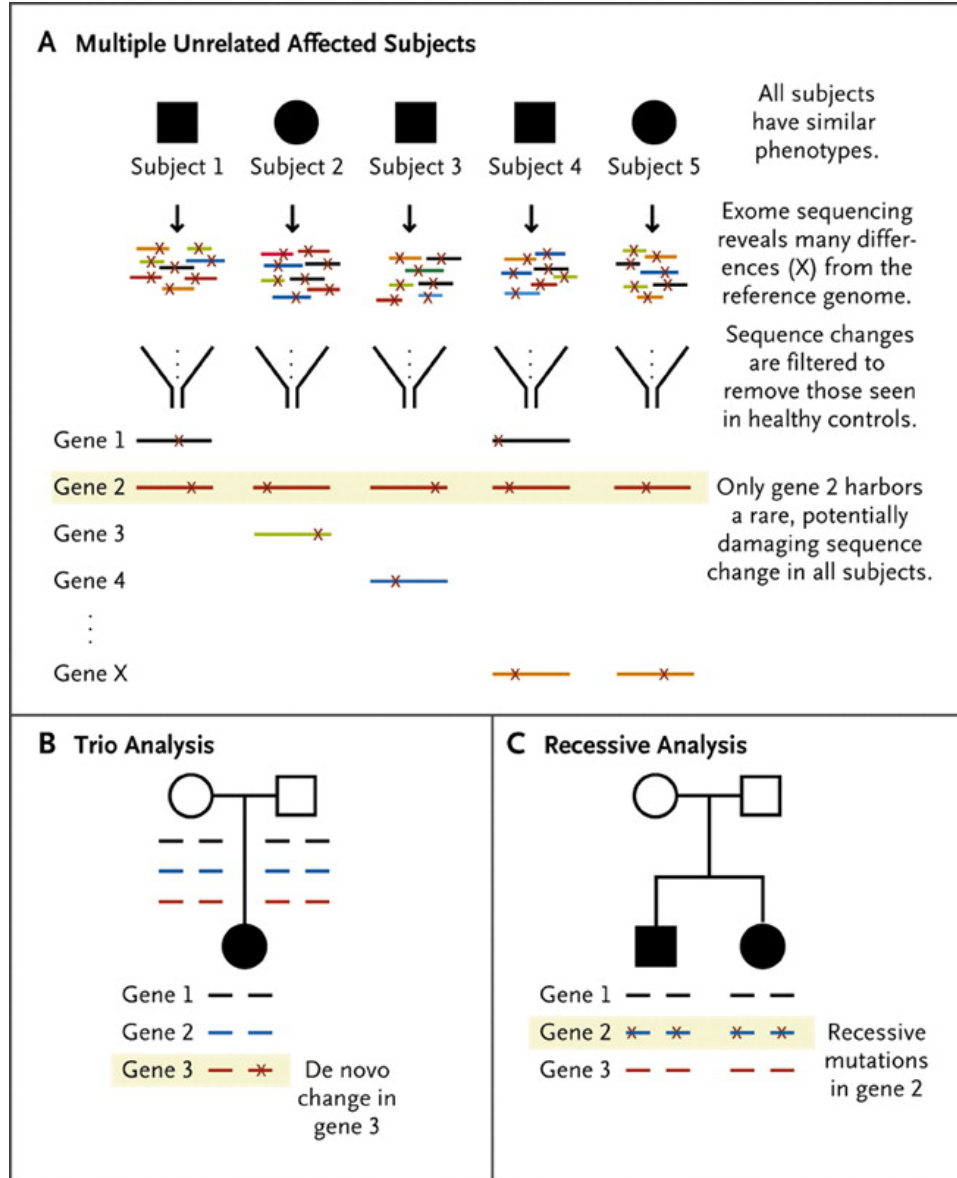
Bamshad et al., *The Genetic Basis of Mendelian Phenotypes: Discoveries, Challenges, and Opportunities*, Amer J Hum Genet, 97: 199-215, 2015

Protein Coding Genes and Mendelian Phenotypes



Bamshad et al., *The Genetic Basis of Mendelian Phenotypes: Discoveries, Challenges, and Opportunities*, Amer J Hum Genet, 97: 199-215, 2015

Strategies for Exome Sequencing in Pediatrics



Secondary Findings - Definitions

- Primary Finding – pathogenic alterations in gene(s) relevant to the diagnostic indication for which sequencing was ordered
- Secondary Finding – results of a deliberate search for pathogenic or likely pathogenic alterations in genes that are apparently unrelated to a diagnostic indication for which sequencing was ordered (also called incidental findings)

Secondary Findings in Clinical Sequencing

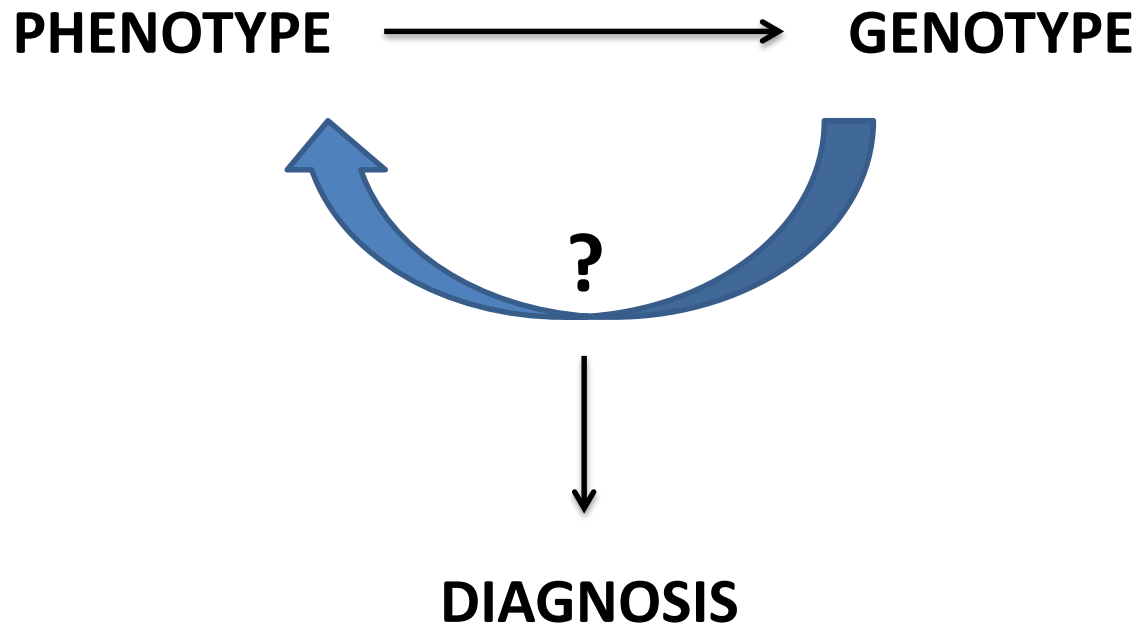
- Recommendations of ACMG & President's Commission on Bioethics (2013)
- “Minimum list” of 56 **actionable** genes and specific mutations
 - Hereditary cancer genes, Marfan and related syndromes, inherited cardiomyopathies & arrhythmias, familial hypercholesterolemia, malignant hyperthermia
- Pathogenic variants in this gene list should be reported regardless of indication for clinical exome sequencing
 - Additional genes may be analyzed for incidental variants
 - Minimal list should be reported regardless of patient age
 - Patients/parents may “opt out” at time of consent

Secondary Findings

- Labs should seek and report only the types of variants listed (pathogenic)
 - Low prior likelihood of disease for secondary findings
 - Labs should list quality of coverage/data which may be lower than for diagnostic genes
- Clinician/team has responsibility to provide appropriate pre- and post-test counseling [should include qualified genetics professional(s)]
- List should be refined and updated at least annually
- No consensus or recommendations on reporting of 2ary findings in research WES/WGS sequencing

Clinical Exome Sequencing

- High diagnostic yield (~25-40%)
 - Frequent de novo heterozygous mutations, some recurrent
 - Broadening of phenotypic spectrum for some classic syndromes; ≥ 1 phenotype ass'd with a single gene
- Importance of studying trios – higher yields in trios of ~40% vs ~25% if study DNA from proband only
- VUS and actionable secondary findings are common (the latter in ~1-5% of cases depending on lab)
- Requires team to interpret results, including clinicians



Types of Information on the Clinical Exome Report

- Variants/mutations likely or possibly related to the patient's clinical phenotype
- Medically actionable variants in disease genes unrelated to the patient's clinical phenotype (secondary findings)
- Carrier status for recessive Mendelian disorders
- Pharmacogenetic results

Who are the Best Candidates for Clinical Exome Sequencing?

- Specific phenotypes/disorders should lead to specific genetic testing (single gene, gene panel)
 - May be less coverage of specific genes/regions on WES
 - Longer TAT; ?higher cost; lower % reimbursement
- Testing prior to exome
 - Microarray analysis - MCA, intellectual disability (IDD), severe szs, severe ASD (low IQ, dysmorphic)
 - Low cost screening tests where appropriate

Utility of a Genetic Diagnosis

- Prevents additional unnecessary testing
- May help predict future medical complications
- May help tailor specific interventions
- May help predict function as an adult
- Will often provide better guidance concerning recurrence risks
- Will occasionally permit specific medical therapies that may significantly improve the outcome



 NATIONWIDE CHILDREN'S

Clinical Exome Sequencing Results at NCH Through 2/10/15

Exomes Completed	131
Cause Identified (Pathogenic variant found related to disease)	55 (42%)
Likely Cause Identified (awaiting confirmation)	0
Questionable Results (VUS, pathogenicity unclear)	2
Actionable Secondary Findings (BRCA1, MEN I, BRCA2)	3

Exome Sequencing Results at NCH – Implications for Management on 1st 100 Cases

- 19/41 (46%) with positive result had change in management beyond reproductive risk
 - 16/41 change in surveillance, including increased cancer risk (DKC)
 - 3/41 specific rx such as medication, diet (Lesch-Nyhan, AR disorder of creatine synthesis, novel sz/movement disorder)
- 20/41 clearly de novo – dramatic reduction in recurrence risk (?25% to <1%)
- 3 novel genes identified (PURA, VARS2, one pending)

Trends in Clinical Sequencing

- Expansion to carrier and population screening
- Move from gene identification to validation of variant pathogenicity; Need rapid, robust tools to validate potential disease-causing variants, particularly missense variants
- Move toward WGS, with assessment of chr rearrangements included in analysis; increased complexity of assessing non-coding variants

Acknowledgements

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