Hôpital général juif
Jewish General Hospital

McGill

Discovering the Genomic Bases of Mendelian Diseases

NHGRI Workshop
July 28, 2014

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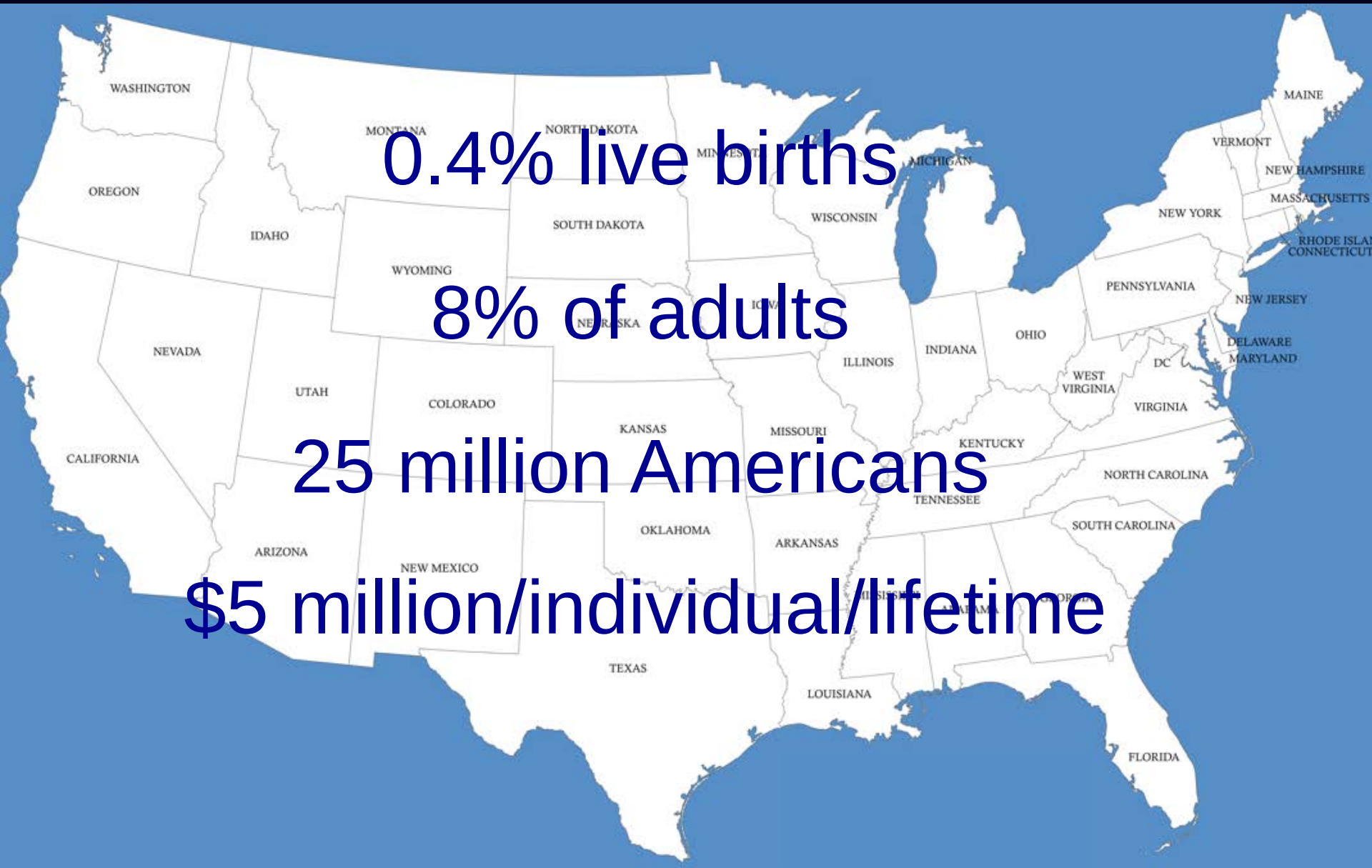
Alva Chair in Human Genetics,
Director, Lady Davis Institute
McGill University

- *What is the value of Mendelian genomic research to medicine & society?*

- *Are the Centres for Mendelian Genomics making a substantial contribution?*

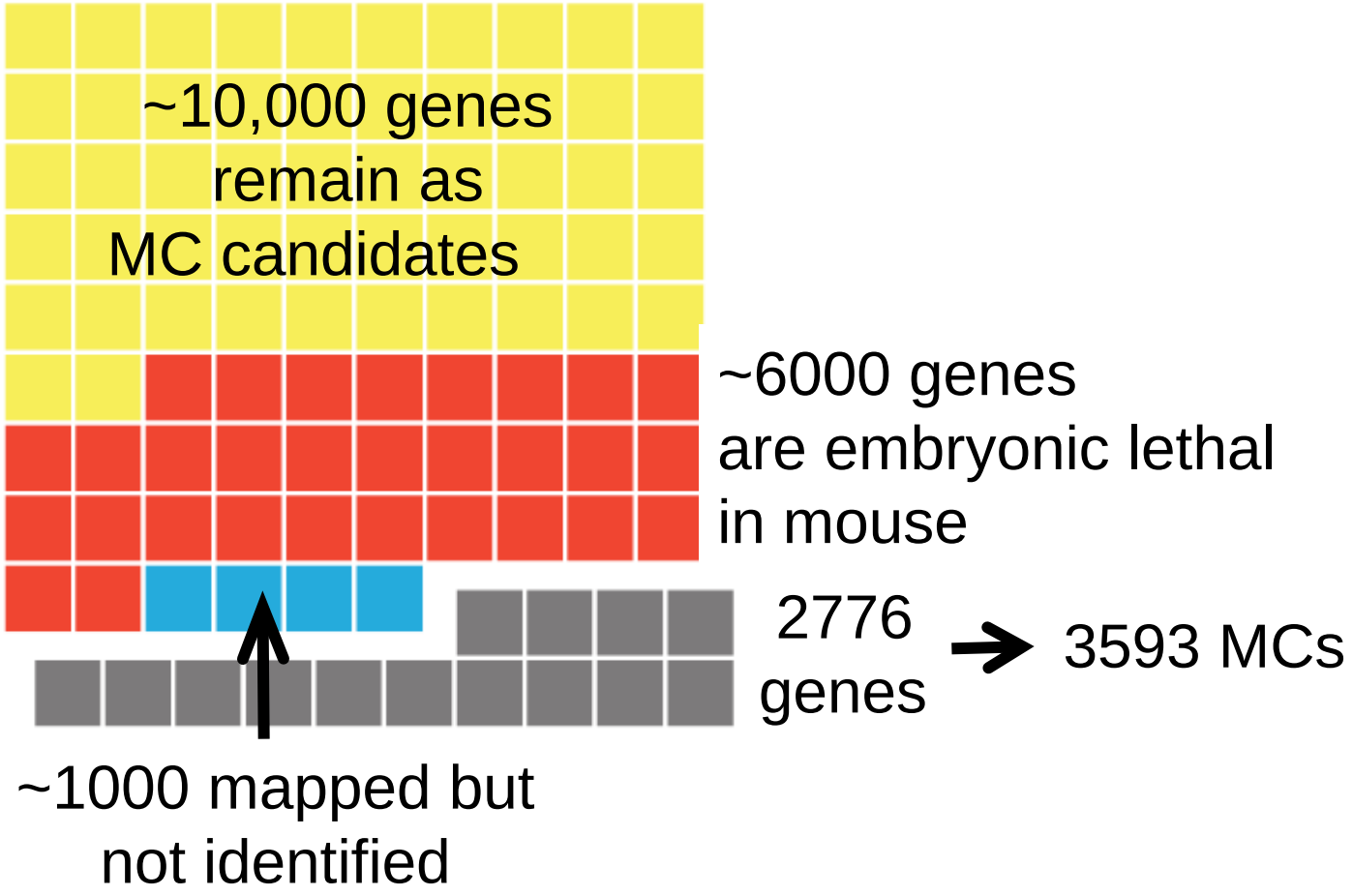
MCs are individually uncommon, but collectively



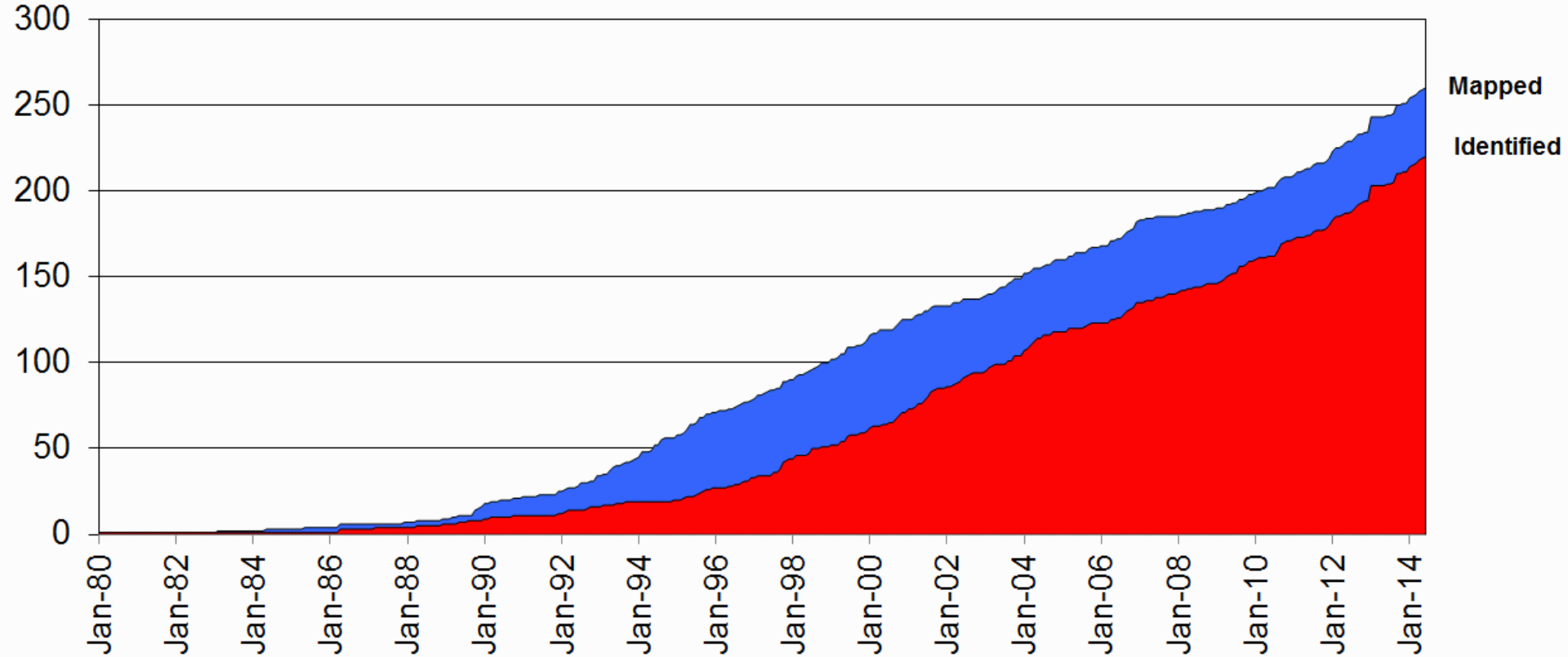
Mendelian Conditions: current scorecard

- Mendelian conditions ~7,300
- Disease genes ~2,776
- Explained phenotypes ~3,593
- Unexplained phenotypes ~3,703
- New MCs per year ~300

~17,000 genes remain as MC candidates



No evidence of saturation for MCs



Mapped and Identified Retinal Disease Genes 1980 - June 2014

- RetNet

Coding vs. Non-coding genes

- ~20,000 coding genes *Ezkurdia et al. HMG '14*
- ~20,000 non-coding genes *Makrythanasis, Clin Gen '13*
  - *long non-coding RNAs*
  - *lincRNAs*
  - *short non-coding RNAs*
  - *miRNAs*
- BUT only 8.2% of genome may be functional

Rands, PLoS Gen '14

Non-coding genes & 20 Mendelian conditions

Table 2. Representative examples of non-protein-coding pathogenic variants in genetic disorders

Genomic Element	Name	Disorder
MIR	MIR96	DFNA50 (Autosomal Dominant deafness 50)
	MIR184	EDICT syndrome
	MIR17HG	Feingold syndrome 2
Long ncRNA	TERC	AD dyskeratosis congenita; susceptibility to aplastic anemia
	RMRP	CHH (cartilage hair hypoplasia) syndrome; anauxetic dysplasia; metaphyseal dysplasia without hypotrichosis
	CISTR-ACT lncRNA	Type E polydactyly
	HELLP lincRNA	HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome
	ATXN8/ATXN8OS	Spinocerebellar ataxia 8 (SCA8)
Small ncRNA	snRNA RNU4ATAC	Microcephalic Osteodysplastic Primordial Dwarfism, type I (MOPD I)
Enhancer CNC	1 Mb from SHH	Postaxial polydactyly
	460 kb from SHH	Holoprocencephaly
	50 kb from SOST	Van Buchem disease
	Enhancer of IRF6	Cleft lip
	Up to 1.5 Mb 5′ or 3′ from SOX9	Pierre Robin sequence
	280 kb from FOXL2	BPES
	110 kb from BMP2	Brachydactyly type A2
	Intron of RET	Hirschprung disease (20× risk)

- *Makrythanasis, Antonarakis Clin Gen '13*

Why identifying the genes
for MCs matters
enormously to patients & their families

Unmet Medical Need

When there is NO diagnosis…

No prognosis

No best practice guidelines

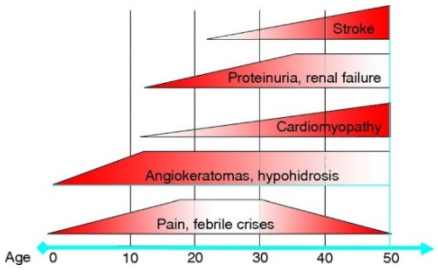
No accurate reproductive counseling

No available therapy

- K Boycott, Univ Ottawa

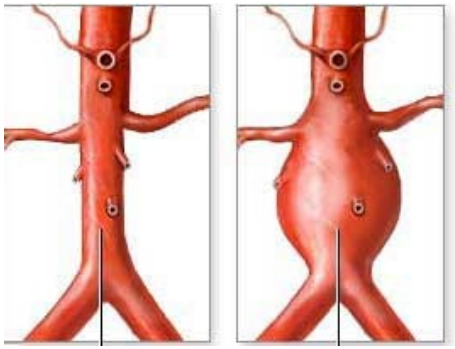
When there is a diagnosis…

Natural history

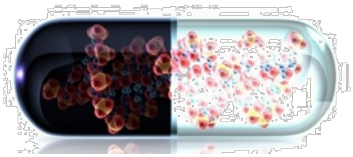


Accurate genetic counselling

Prevention of complications



Tailored therapy



- K Boycott, Univ Ottawa

Does Mendelian variation contribute to our understanding of complex diseases?

A Nondegenerate Code of Deleterious Variants in Mendelian Loci Contributes to Complex Disease Risk

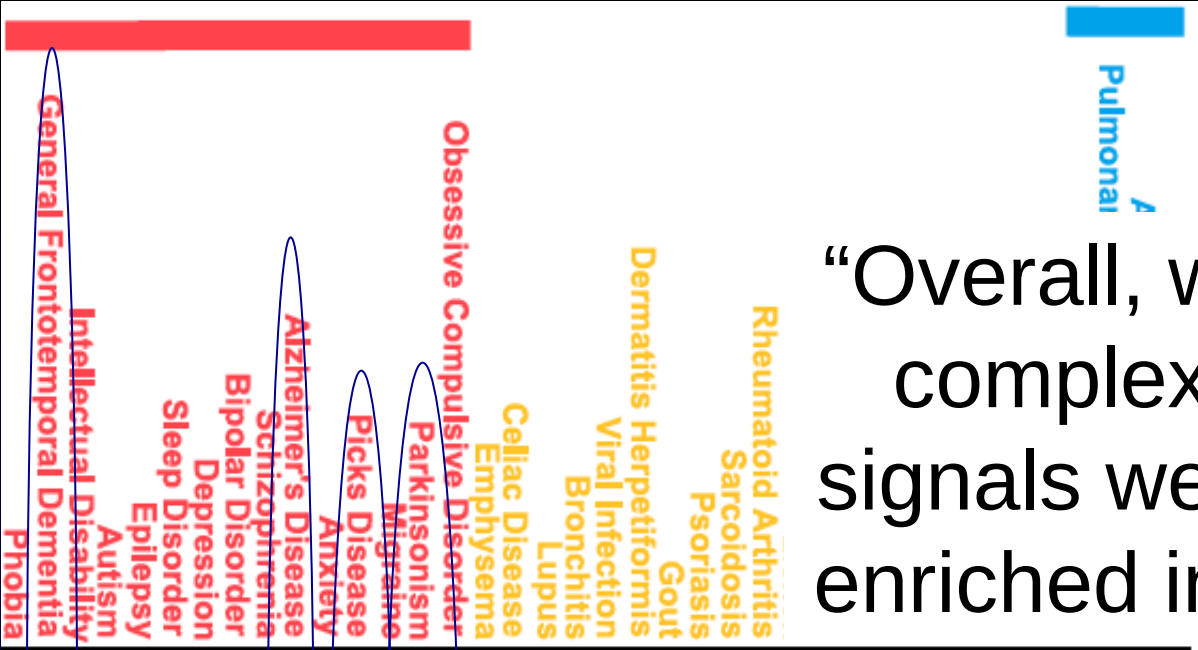
Blair et al. CELL 155, 70, 2013

The question:

Are common variants for complex diseases enriched within loci implicated by Mendelian comorbidities?

- Each Mendelian variant highlights a subset of genes that also play a role in common complex traits
- Each complex disease has a *unique* Mendelian disease allelic architecture, a “nondegenerate code” that identifies each illness by its associated Mendelian loci

Blair et al. CELL 155, 70, 2013



"Overall, we observed that complex disease GWA signals were globally (~2x) enriched in Mendelian loci"

Achromatopsia
Androgen Insensitivity Syndrome
Anophthalmos/Micropthalmos
Anterior Eye Anomalies
Autoimmune Lymphoproliferative Syndrome
Autoimmune Polyglandular Syndrome
Bartter Syndrome
Cerebral Degeneration Due to Generalized Li
Cerebral Lipidoses
Chondrodystrophy
Chronic Granulomatous Disease
Chronic Progressive External Ophthalmopleg
Circulating Enzyme Deficiencies
Combined Heart and Skeletal Defects
Congenital Disorders of Purine/Pyrimidine M
Congenital Ectodermal Dysplasia
Congenital Fistula of the Lip
Congenital Hirschsprung Disease
Congenital Hydrocephalus
Congenital Hypogammaglobulinemia
Congenital Ichthyosis
Congenital Pigmentary Anomalies
Cri-Du-Chat Syndrome
Cystic Fibrosis
Degenerative Diseases of the Basal Ganglia

NHGRI Centers for Mendelian Genomics (CMGs)

University of Washington Center for Mendelian Genomics *(coordinating center)*

Yale Center for Mendelian Disorders

Johns Hopkins Medicine | Baylor College of Medicine

Baylor-Johns Hopkins Center for Mendelian Genetics

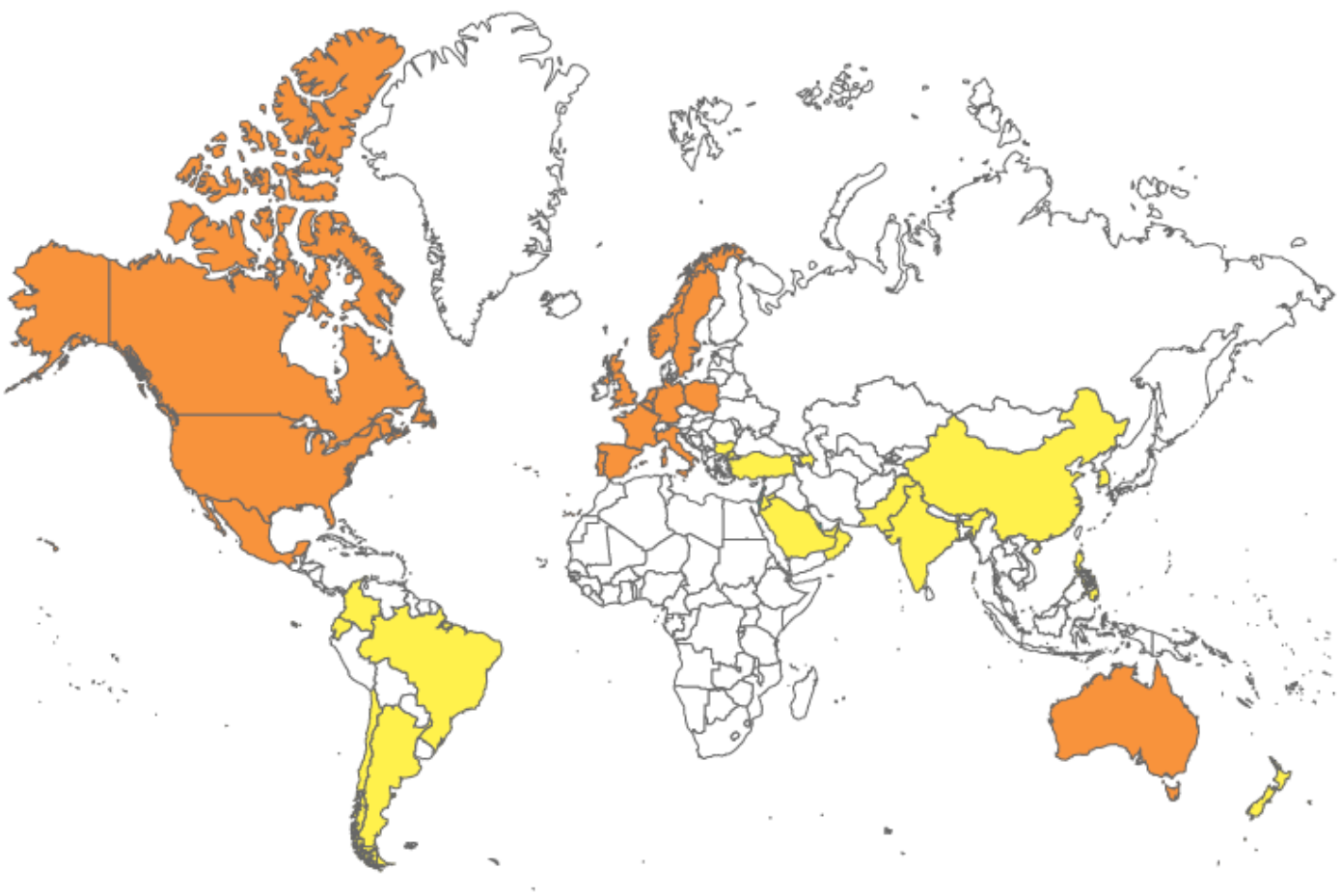
www.mendelian.org

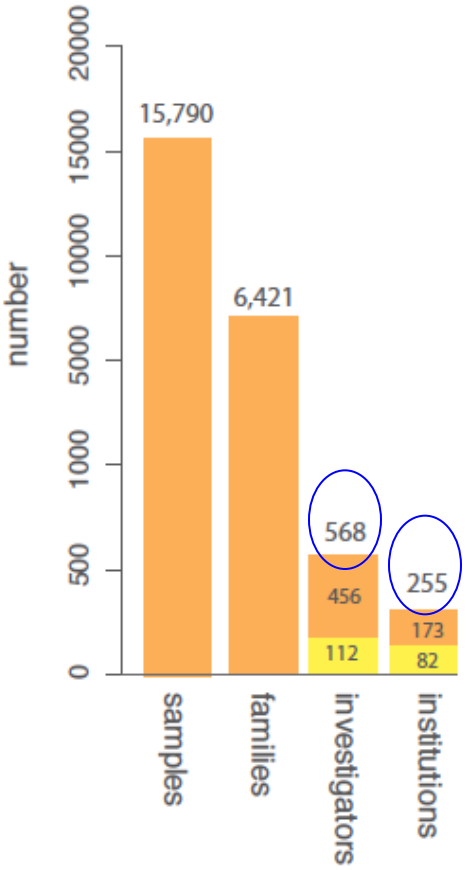
gmendel@mendelian.org

AGTC Centers for Mendelian Genomics

Goal: Identify and define the causes of all human monogenic diseases

The CMGs are an international research platform





The goal of solving most/all MCs requires unprecedented cooperation & coordination among clinicians & scientists worldwide

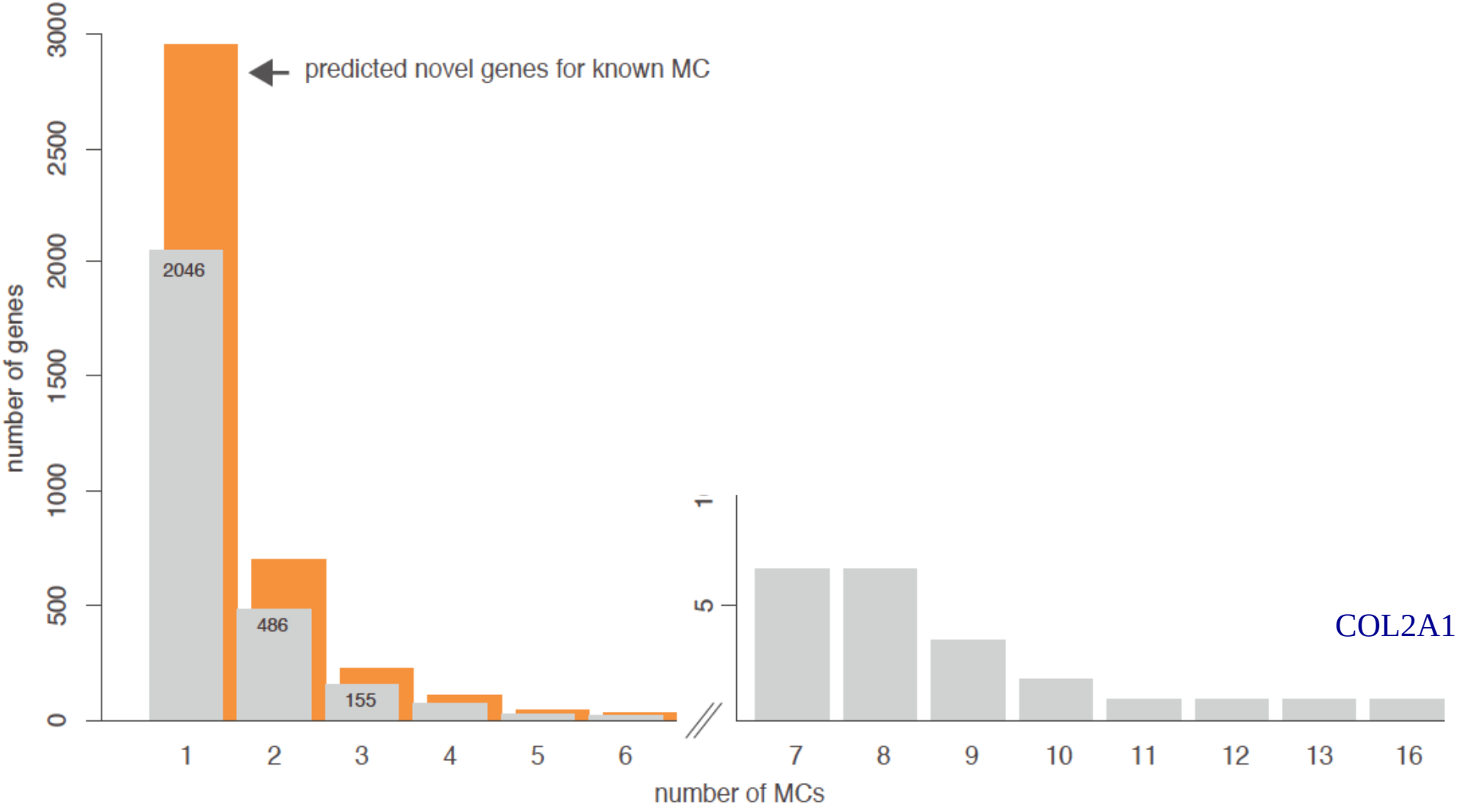
Biomedical & Clinical Impact of the CMGs

*Progress to date**

- 15,790 samples
- 6421 families studied: 673 known, 760 novel MCs
- 11,801 Wes, 60 WGs ⟶ 1/2 to dbGaP
- 286 novel MC genes discovered
- 229 known genes for MCs identified
- The clinical features of 139 known MCs were expanded

** provided by the CMGs*

Phenotropy: spectrum of phenotypes caused by variants in a gene



- provided by the CMGs

Identifying MC genes
greatly enhances our understanding of
human biology & pathophysiology

*CMG Publications**

- 98 papers, including 60 new disease loci & genetic disorders
- Nature (1), Science (1), Cell (2), Nature Genetics (6), NEJM (2), AJHG (17), Hum Mol Gen (4)

** provided by the CMGs*

The NEW ENGLAND JOURNAL of MEDICINE

A Form of the Metabolic Syndrome Associated with Mutations in *DYRK1B*

Keramati *et al*. NEJM 369, 621, 2013

Mutations in *DSTYK* and Dominant Urinary Tract Malformations

Sanna-Cherchi *et al*. NEJM 369, 621, 2013

4.5 % of the 423 original articles over the past 24 months
in the NEJM
were reports of new Mendelian disease genes

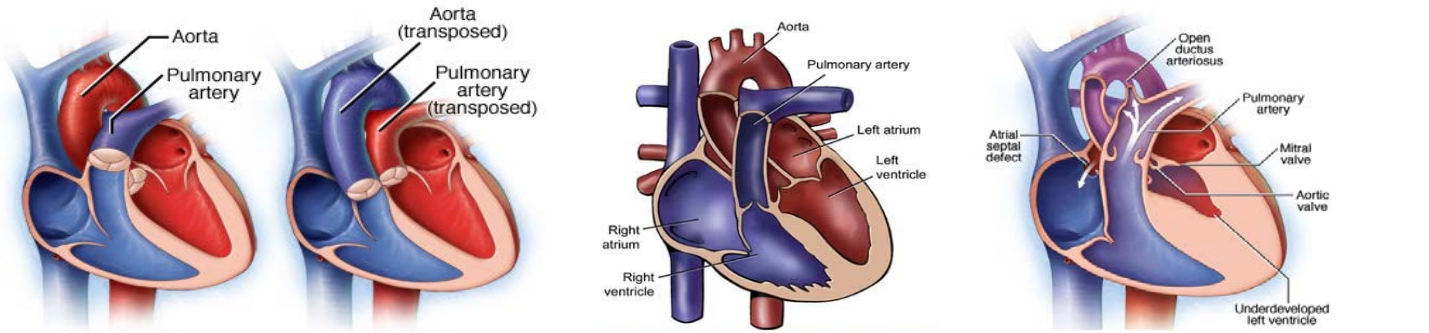
- E. Phimister

De novo mutations in histone-modifying genes in congenital heart disease

Saidi + 49 others

Nature **498**, 220–223 (13 June 2013)

AGTC
Centers for Mendelian Genomics

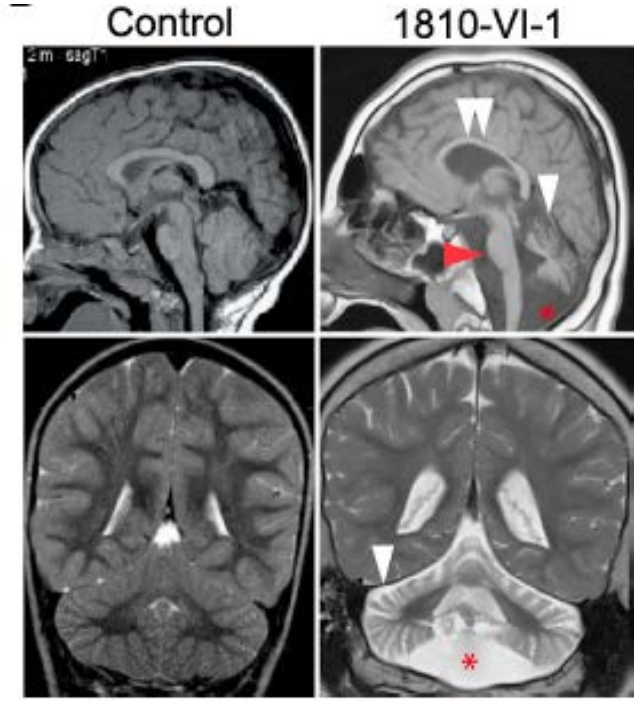


Normal heart **Transposition** **Tetralogy of Fallot** **Hypoplastic left heart syndrome**

- The most frequent birth defect, 0.8% of live births,
- Many cases are sporadic -> a role for *de novo* mutations?
- 362 severe CHD cases, parents: WES
- Enrichment of mutations in proteins that modulate H3K4 methylation
- *De novo* point mutations in several hundreds of genes that together → 10% of severe CHD

Human *CLP1* Mutations Alter tRNA Biogenesis, Affecting Both Peripheral and Central Nervous System Function

Ender Karaca,[1,21] Stefan Weitzer,[2,21] Davut Pehlivan,[1,21] Hiroshi Shiraishi,[2,21] Tasos Gogakos,[3] Toshikatsu Hanada,[2,3]
and 38 others



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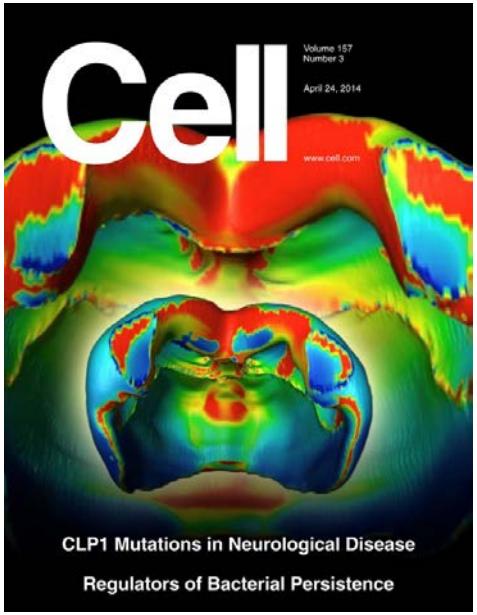


Mutation in *CLP1*, a kinase required for tRNA splicing,
⟶ abnormal neurodevelopment, & neurodegeneration

Finding families with new MCs

PhenoDB: A New Web-Based Tool for the Collection, Storage, and Analysis of Phenotypic Features

Ada Hamosh,[1]* Nara Sobreira,[1] Julie Hoover-Fong,[1] V. Reid Sutton,[2] Corinne Boehm,[1] François Schiettecatte,[3] and David Valle[1]

[1]McKusick-Nathans Institute of Genetic Medicine Johns Hopkins University, Baltimore, Maryland; [2]Department of Molecular & Human Genetics Baylor College of Medicine, Houston, Texas; [3]FS Consulting, Salem, Massachusetts

Hum Mut 34:561, 2013

- Rapid & efficient entry of families or cohorts
- Provides unique identifiers
- Clinical features based on OMIM Clinical Synopses
- Searchable

Identifying the genes for MCs is of major importance to the development of Rx for common diseases, as well as MCs

Mendelian genes identify drug targets applicable to the general population

Of 348 proteins linked to a human gene and specifically targeted by current therapeutics:

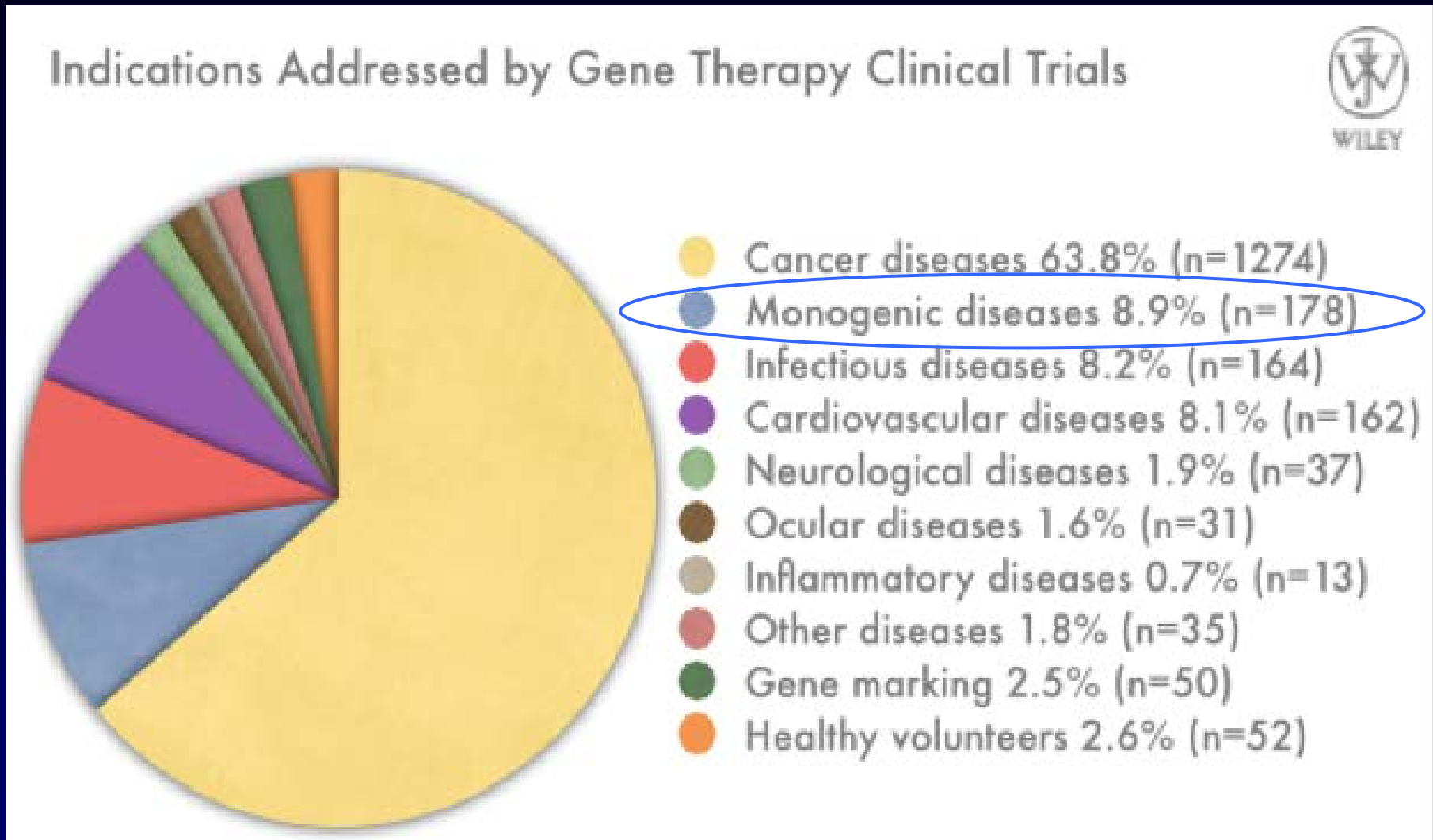
- 42.5% encode a gene underlying a MC
- vs. 28.2% of proteins targeted by current therapeutics are found within GWAS signals

Mendelian genes identify drug targets applicable to the general population

Mutations in

- Nav1.7 Na^+ channel channel = loss of pain
- ROMK K^+ channel, Bartter syndrome = low blood pressure
- PCSK9 protease = low LDL cholesterol
- Orexin receptor, narcolepsy = sleeping pill
- SOST; LRP5 = high bone mass
- APP and γ–secretase = Alzheimer's disease targets

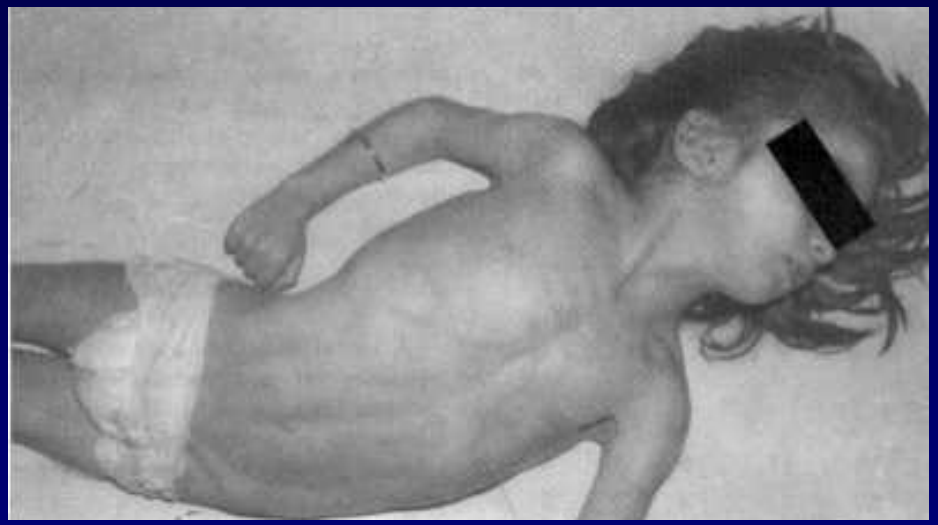
Gene Therapy: 1966 Human Trials in 2014



Gene Therapy Benefits Metachromatic Leukodystrophy

Alessandra Biffi,* Eugenio Montini, Laura Lorioli, Martina Cesani, Francesca Fumagalli,

Science, 341, 864, 2013



age 5 yr.

- A lysosomal enzyme defect: Aryl sulfatase A deficiency
- Progressive neurological deterioration, death 3-10 yr,

MCs are the epitome of Personalized Medicine

The application of knowledge of an individual's genome to their health care

Orphan Drugs

~ 200 companies are now conducting orphan drug clinical trials

a $50 billion industry, growing at rate of 25% per year

Some amazing successes:

http://www.phrma.org/sites/default/files/pdf/Rare_Diseases_2013.pdf

http://thomsonreuters.com/business-unit/science/subsector/pdf/the-economic-power-of-orphan-drugs.pdf

The Mouse Knockout Project

Phase I: 2011 –2016

- 18 centres around the world
- 5000 genes
- ~ $250 million committed, multiple funders

    + NIH $ for embryo phenotyping

    + NIH $3M for a Cas9-RGN mouse production tech development

Phase I: 2017 –2021

The remaining 15, 000 genes

Many human MCs have no mouse equivalent

IMMUNOLOGY REPORTS

Mycobacterium szulgai Chronic Multifocal Osteomyelitis in an Adolescent With Inherited STAT1 Deficiency

Oded Shamriz, MD, Dan Engelhard, MD,†‡ Andrea Psorn Rajs, MD,§ Hasia Kaidar-Shwartz, PhD,¶ Jean-Laurent Casanova, MD, PhD,‖ and Diana Averbuch, MD*†*

The Pediatric Infectious Disease Journal • Volume 32, Number 12, December 2013

Some general principles likely to be exposed by a larger collection disease genes

- Relationship of genes and variants to phenotype
- Phenotypic “expansion”
- Informing systems biology
- Relationship of Mendelian genes and variants to those contributing risk for complex traits
- A library of drug targets

Advantages of CMGs

- Deep experience in study design, sequencing and data analysis
  - Cost-effective, rigorous & productive access to cutting edge technology for experienced and naïve investigators with useful families/patient cohorts

Advantages of CMGs (cont'd)

- CMGs are immersed in broad issues re. Mendelian genomics, issues applicable to diverse projects

- CMGs are agnostic to clinical area, focused on solving all Mendelian traits

Summary: What has been the impact of CMG discoveries?

- CMGs have made relatively inexpensive, high-throughput gene discovery for MCs available worldwide
- Enormous amount of information about the biological function of each gene is provided by each MC “solved”
- Changing the thinking about extent of pleiotropy and genetic heterogeneity
- Enabled diagnostic and predictive testing for hundreds of MCs that that were undiagnosable
- Added 100s of starting points for the development and testing of targeted therapies
  - Key - only ~300 proteins targeted by current therapeutics

Summary: What differences have the CMGs made?

- Catalyzed the discovery of genes underlying Mendelian Conditions conditions
- 100s of new phenotypes and novel genes for Mendelian Conditions delineated
- 100s of “novel” genes for Mendelian Conditions
- Found new biological mechanisms for Mendelian Conditions
- Fostered development of statistical framework for assessing causality of variants for Mendelian Conditions
- Equipped PIs in the human genetics community with tools and skills to interpret and in many cases complete their own analysis

Thank you