The Path to Precision Medicine: From Discovery to Patient Care

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Vice President
Regeneron Genetics Center &
Professor (part-time), University of Maryland School of Medicine
The Reality of Therapeutic Development in 2018

- Despite increased investment in R+D in the pharmaceutical industry, the number of new molecular entities is not increasing.
- >90% of molecules that enter Phase I clinical trials fail to demonstrate sufficient safety and efficacy to gain regulatory approval.
- Most failures occur in Phase II clinical trials:
  - 50% due to lack of efficacy
  - 25% due to toxicity
- Pre-clinical models may be poor predictors of clinical benefit.
- *Compounds supported by human genetics evidence are substantially more likely to succeed.*
The Potential for Human Genetics to Accelerate Target Identification, Validation and Drug Development

2003
- Family studies identify PCSK9 GOF as a causal FH gene

2006
- Population studies identify PCSK9 LOF variants conferring ~88% reduction in CHD

2008
- Null APOC3 mutation enriched in Amish points to cardio-protective effects

2012
- Clinical proof of concept

2014
- Two population studies identify variants conferring ~40% reduction in CHD

2015
- Clinical proof of concept
Application of Human Genetics to Accelerate Novel Target Identification and Clinical Development

The RGC applies large-scale, fully-integrated human genetics approaches to advance science, guide the development of therapeutics, and improve patient outcomes.

“Do Well by Doing Good”

**Indication Discovery**
- Identify new indications for drug targets and programs

**Target Discovery**
- Identify new drug targets and pathways

**Biomarker**
- Develop pharmacogenetic markers to predict drug response

**Derisking**
- Confirm lack of “on-target adverse side effects” in drug target LoF carriers

**Genetic Classifier**
- Responders
- Non-Responders

**Mouse Genetics**

**Human Genetics**

*Image credits: Regeneron Genetics Center*
Ultra High-Throughput Sequencing and Analysis at the Regeneron Genetics Center

Automated Biobank (1.4M Samples)  Library Prep Automation (>200,000 Samples/Yr)  Illumina Fleet (>200,000 Exomes/Yr)  Cloud Based Informatics & Analysis

Technologies and Capabilities

- Automated biobank with 1.4M+ sample capacity
- Custom fully-automated exome and targeted sequencing sample preparation workflows
- Currently exome sequencing >4,000 exomes per week
  - >250,000 exomes completed
- Among the first “genome center in the cloud” with fully automated analysis pipelines
Maximizing Discovery Opportunities by Leveraging Human Genetics Resources Across Genetic Trait Architecture and Phenotypes

50+ Academic collaborators – Over 250,000 exomes sequenced

Integrated approaches across genetic trait architectures . . .
Geisinger-Regeneron DiscovEHR Collaboration

Two organizations focused on making genomic data medically actionable

Goal: Build comprehensive genotype-phenotype resource combining de-identified genomic and clinical data from >250,000 people to aid drug development and implementation of genomic medicine into patient care

- Geisinger: Integrated health care system
  - 1.6M participants (predominantly European Caucasian)
  - Amongst earliest adopters of EHRs (1996) and leaders in clinical informatics
    - Longitudinal EHR data: Median of ~18 outpatient visits per patient over 13.4 years
- Recruitment ongoing
  - 120,000 patients consented into MyCode-DiscovEHR cohort
  - >90,000 sequenced at the Regeneron Genetics Center
  - Large unselected populations as well as targeted efforts in diseases of interest and deeply phenotyped patients
    - Cardiac catheterization lab (~8,000)
    - Bariatric surgery (~4,000) - one of the largest in the world
Distribution and clinical impact of functional variants in 50,726 whole-exome sequences from the DiscovEHR study

Frederick E. Dewey,1* Michael F. Murray,2 John D. Overton,1 Lukas Habegger,1 Joseph B. Leader,3 Samantha N. Fetterolf,1 Colm O'Dushlaine,1 Cristopher V. Van Hout,1 Jeffrey Staples,1 Claudia Gonzaga-Jauregui,1 Raghu Metpally,2 Sarah A. Pendergrass,2 Monica A. Giovanni,2 H. Lester Kirchner,2 Suguanthi Balasubramanian,1 Noura S. Abul-Husn,1 Dustin N. Hartzel,2 Daniel R. Lavage,2 Korey A. Kost,1 Jonathan S. Packer,1 Alexander E. Lopez,1 John Penn,3 Semanti Mukherjee,1 Nehal Gosalia,1 Manoj Kanagaraj,1 Alexander H. Li,1 Lyndon J. Milnau,1 Lance J. Adams,2 Thomas N. Person,1 Kavita Praveen,1 Anthony Marchetta,1 Matthew S. Lebo,3 Christina A. Austin-Tse,1 Heather M. Mason-Sauers,3 Shannon Bruse,1 Scott Mellis,4 Robert Phillips,4 Neil Stahl,4 Andrew Murphy,4 Aris Economides,1 Kimberly A. Skelding,2 Christopher D. Still,2 James R. Elmore,2 Ingrid B. Borecki,1 George D. Yancopoulos,4 F. Daniel Davis,1 William A. Faucett,2 Omri Gottesman,1 Marylyn D. Ritchie,2 Alan R. Shuldiner,1 Jeffrey G. Reid,1 David H. Ledbetter,2 Aris Baras,1 David J. Carey2*

The DiscovEHR collaboration between the Regeneron Genetics Center and Geisinger Health System couples high-throughput sequencing to an integrated health care system using longitudinal electronic health records (EHRs). We sequenced the exomes of 50,726 adult participants in the DiscovEHR study to identify ~4.2 million rare single-nucleotide variants and insertion/deletion events, of which ~176,000 are predicted to result in a loss of gene function. Linking these data to EHR-derived clinical phenotypes, we find clinical associations supporting therapeutic targets, including genes encoding drug targets for lipid lowering, and identify previously unidentified rare alleles associated with lipid levels and other blood level traits. About 3.5% of individuals harbor deleterious variants in 76 clinically actionable genes. The DiscovEHR data set provides a blueprint for large-scale precision medicine initiatives and genomics-guided therapeutic discovery.
In-Depth, Longitudinal Health Records Enriched for Age-Related Diseases and Phenotypes

Patients by Years of Clinical Data

Most Prevalent Labs in GHS EHR

Most Prevalent Office Visit Dx in GHS EHR

In-Depth, Longitudinal Health Records Enriched for Age-Related Diseases and Phenotypes

Patients by Years of Clinical Data

Most Prevalent Labs in GHS EHR

Most Prevalent Office Visit Dx in GHS EHR
The RGC and GHS Have Developed A Large Number of High-quality, EHR-derived Phenotypes For Genetic Analyses

A constantly growing library of more than 8,000 quantitative and binary traits are available for high-throughput and in-depth genotype-first and phenotype-first analyses:

**Binary and Quantitative Trait Matrices:**
- Include PheWAS, Immune, Lab Traits, DEXA, Echo, EKG, Ocular Measures, PFT’s, Vitals and Anthropometrics

**Deep Dive Datasets:**
- Examples include Coronary Artery Disease and Lipids, COPD and Asthma, Bariatric Traits and Liver Histology, Gout
Sequence Variants Identified Using Whole Exome Sequencing of 50,726 DiscovEHR Participants (*Dewey et al, Science 2016*)

<table>
<thead>
<tr>
<th>Variant type</th>
<th>All variants</th>
<th>Allele frequency ≤ 1%</th>
</tr>
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<tbody>
<tr>
<td>Single nucleotide variants</td>
<td>4,028,206</td>
<td>3,947,488</td>
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<tr>
<td>Insertion/deletion variants</td>
<td>224,100</td>
<td>218,785</td>
</tr>
<tr>
<td>Predicted loss of function variants</td>
<td>176,365</td>
<td>175,393</td>
</tr>
<tr>
<td>Nonsynonymous variants</td>
<td>2,025,800</td>
<td>2,002,912</td>
</tr>
<tr>
<td>Total</td>
<td>4,252,306</td>
<td>4,166,273</td>
</tr>
</tbody>
</table>

*In 50K Exomes:*
- 92% (n=17,409) of genes with at least 1 heterozygous pLOF
- 7% (n=1,313) of genes with at least 1 homozygous pLOF

*Each individual:*
- Heterozygous pLOF for ~21 genes
- Homozygous pLOF for ~1 gene

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Action</th>
<th>Phase</th>
<th>Clinical effect</th>
<th>LOF carriers</th>
<th>LDL-c</th>
<th>HDL-c</th>
<th>Triglycerides</th>
<th>Total cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPARA</td>
<td>Fenofibrate</td>
<td>Agonist</td>
<td>Approved</td>
<td>Decreased triglycerides, increased HDL</td>
<td>2</td>
<td>0.8</td>
<td>9 mg/dl</td>
<td>0.2 -28%</td>
<td>0.09 113%</td>
</tr>
<tr>
<td>HMGCR</td>
<td>Atorvastatin, rosuvastatin, pravastatin, simvastatin</td>
<td>Antagonist</td>
<td>Approved</td>
<td>Decreased LDL, total cholesterol, increased HDL</td>
<td>12</td>
<td>0.7</td>
<td>-4 mg/dl</td>
<td>0.3 9%</td>
<td>0.6 -8% 0.7 -4 mg/dl</td>
</tr>
<tr>
<td>NPC1L1</td>
<td>Ezetemibe</td>
<td>Antagonist</td>
<td>Approved</td>
<td>Decreased LDL</td>
<td>121</td>
<td>0.03</td>
<td>-7 mg/dl</td>
<td>0.07 -4%</td>
<td>0.5 -3% 0.0004 -12 mg/dl</td>
</tr>
<tr>
<td>APOB</td>
<td>Mipomersen</td>
<td>Antagonist</td>
<td>Approved</td>
<td>Decreased LDL</td>
<td>80</td>
<td>0.0003</td>
<td>-15 mg/dl</td>
<td>0.06 6%</td>
<td>0.002 -15% 8.10^-7 -21 mg/dl</td>
</tr>
<tr>
<td>MTP</td>
<td>Lomitapide</td>
<td>Antagonist</td>
<td>Approved</td>
<td>Decreased LDL</td>
<td>24</td>
<td>0.9</td>
<td>1 mg/dl</td>
<td>0.4 4%</td>
<td>0.7 3% 1.0 0.2 mg/dl</td>
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<tr>
<td>HCAR3</td>
<td>Niacin</td>
<td>Agonist</td>
<td>Approved</td>
<td>Increased HDL, decreased triglycerides, LDL</td>
<td>107</td>
<td>0.4</td>
<td>-3 mg/dl</td>
<td>0.4 -2%</td>
<td>0.5 4% 0.3 -4 mg/dl</td>
</tr>
<tr>
<td>CETP</td>
<td>Anacetrapib, evacetrapib</td>
<td>Antagonist</td>
<td>Phase 3</td>
<td>Increased HDL</td>
<td>37</td>
<td>0.3</td>
<td>-6 mg/dl</td>
<td>2.0x10^-6 23%</td>
<td>0.6 5% 0.1 9 mg/dl</td>
</tr>
<tr>
<td>PCSK9</td>
<td>Alirocumab, evolocumab, bococizumab</td>
<td>Antagonist</td>
<td>Phase 3</td>
<td>Decreased LDL</td>
<td>52</td>
<td>8.8x10^-9 -25 mg/dl</td>
<td>0.3</td>
<td>3% 0.03 -12% 6.4x10^-6 -21 mg/dl</td>
<td></td>
</tr>
<tr>
<td>APOC3</td>
<td>APOC3 inhibitors</td>
<td>Antagonist</td>
<td>Phase 2</td>
<td>Decreased triglycerides, increase HDL</td>
<td>226</td>
<td>0.3</td>
<td>-3 mg/dl</td>
<td>1.5x10^-4 28%</td>
<td>1.5x10^-47 -48% 0.2 -4 mg/dl</td>
</tr>
<tr>
<td>ACLY</td>
<td>ATP citrate lyase inhibitors</td>
<td>Antagonist</td>
<td>Phase 2</td>
<td>Decreased LDL</td>
<td>13</td>
<td>0.2</td>
<td>-14 mg/dl</td>
<td>1.0 0%</td>
<td>0.3 -13% 0.4 -10 mg/dl</td>
</tr>
<tr>
<td>ANGPTL3</td>
<td>ANGPTL3 inhibitors</td>
<td>Antagonist</td>
<td>Phase 2</td>
<td>Decreased triglycerides, LDL, HDL</td>
<td>150</td>
<td>0.0004</td>
<td>-10 mg/dl</td>
<td>0.0002 -8%</td>
<td>6.4x10^-15 -27% 1.6x10^-10 -19 mg/dl</td>
</tr>
</tbody>
</table>

8/11 Lipid therapy targets harbor LOFs with nominally significant or directionally consistent clinical associations that recapitulate drug effects.
DiscovEHRy of New Drug Targets

The NEW ENGLAND JOURNAL OF MEDICINE

Inactivating Variants in ANGPTL4 and Risk of Coronary Artery Disease

Frederick E. Dewey, M.D., Viktoria Gusarova, Ph.D., Colm O'Dushlaine, Ph.D., Omri Gottesman, M.D., Jesus Trejos, M.S., Charleen Hunt, Ph.D., Cristopher V. Van Hout, Ph.D., Lukas Habegger, Ph.D., David Buckler, Ph.D., Ka-Man V. Lai, Ph.D., Joseph B. Leader, Ph.D., Michael F. Murray, M.D., Marylyn D. Ritchie, Ph.D., H. Lester Kirchner, Ph.D., David H. Ledbetter, Ph.D., John Penn, M.S., Alexander Lopez, M.S., Ingrid B. Borecki, Ph.D., John D. Overton, Ph.D., Jeffrey G. Reid, Ph.D., David J. Carey, Ph.D., Andrew J. Murphy, Ph.D., George D. Yancopoulos, M.D., Ph.D., Aris Baras, M.D., Jesper Gromada, Ph.D., D.M.Sc., and Alan R. Shuldiner, M.D.

March 3, 2016
Loss-of-Function Carriers in a ANGPTL4 Have Favorable Lipid Phenotypes and Are Protected From CAD (Dewey et al, NEJM 2016)
Hypolipidemic Effects of Anti-ANGPTL4 Antibody in Mice and Monkeys (Dewey et al, NEJM 2016)

AE: Some mice and one monkey developed abdominal lymphadenopathy and chylos ascites.
**ANGPTL4 p.E40K Human Homozygotes do not Exhibit Increased Rates of Lymphatic Abdominal Pathology in DiscovEHR**

In chart review of 17 p.E40K homozygotes, 5 had CT abdominal imaging, and 4/5 had explicit mention of normal abdominal lymphatics, 1/5 had no mention of lymphatic abnormalities.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Non-carriers (n=41,777)</th>
<th>E40/K40 heterozygotes (n=1,661)</th>
<th>K40 homozygotes (n=17)</th>
<th>pLOF carriers (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>P*</td>
<td>N (%)</td>
</tr>
<tr>
<td>Disorders of lymphoid system</td>
<td>3,831 (9.2)</td>
<td>154 (9.3)</td>
<td>0.9</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Disorder of lymph node</td>
<td>1,661 (4.0)</td>
<td>70 (4.2)</td>
<td>0.7</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Lymphadenitis</td>
<td>295 (7.1)</td>
<td>12 (7.2)</td>
<td>0.9</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Mesenteric lymphadenitis</td>
<td>12 (0.03)</td>
<td>0 (0.0)</td>
<td>0.5</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Granulomatous lymphadenitis</td>
<td>5 (0.01)</td>
<td>0 (0.0)</td>
<td>0.7</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Ascites</td>
<td>308 (0.7)</td>
<td>11 (0.7)</td>
<td>0.8</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>282 (0.7)</td>
<td>17 (1.0)</td>
<td>0.1</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>3,291 (7.9)</td>
<td>142 (8.6)</td>
<td>0.3</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>15,183 (36.3)</td>
<td>612 (37.0)</td>
<td>0.2</td>
<td>4 (35.2)</td>
</tr>
<tr>
<td>Diarrhea symptom</td>
<td>6,099 (14.6)</td>
<td>222 (13.4)</td>
<td>0.2</td>
<td>2 (10.2)</td>
</tr>
</tbody>
</table>

*Versus sequenced non-carriers

Frederick Dewey and Peter Benotti
**ANGPTL4 p.E40K and Loss of Function Variants are Associated with Reduced Odds of Type 2 Diabetes: A new indication for ANGPTL4 inhibition?**

The p.E40K variant was associated with ~15% reduced odds of diabetes per allele. Loss of function variant carriers had 58% reduced odds of diabetes.

### Take home points:
- The p.E40K variant was associated with ~15% reduced odds of diabetes per allele.
- Loss of function variant carriers had 58% reduced odds of diabetes.

### Table: Allele Frequency and Odds Ratio

<table>
<thead>
<tr>
<th>Disease</th>
<th>Allele Frequency: Cases</th>
<th>Allele Frequency: Controls</th>
<th>Odds Ratio* (95% CI)</th>
<th>P*</th>
<th>Allele Frequency: Cases</th>
<th>Allele Frequency: Controls</th>
<th>Odds Ratio* (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 2 diabetes</strong></td>
<td>1.84 (355 hets, 6 homs)</td>
<td>2.06 (1,053 hets, 14 homs)</td>
<td>0.86 (0.76-0.99)</td>
<td>0.03</td>
<td>0.05 (10 hets)</td>
<td>0.11 (58 hets)</td>
<td>0.42 (0.19-0.83)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Adjusted for age, age^2, sex, principal components of ancestry, and BMI.

**Abbreviations:** AF, allele frequency; hets, heterozygotes; homs, homozygotes; CAF, cumulative allele frequency; OR, odds ratio.

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**Legend:**
- SP: Soluble Protein
- Coiled-coil: Coiled-coil domain
- Fibrinogen-like domain

**Figure:**
- Diagram showing the ANGPTL4 protein structure with highlighted regions.
## Insights From Whole Exome Sequencing in Mendelian Diseases Collaborations

<table>
<thead>
<tr>
<th>Families/samples sequenced</th>
<th>756/5747</th>
</tr>
</thead>
<tbody>
<tr>
<td>Families/samples analyzed</td>
<td>395/2049</td>
</tr>
<tr>
<td>Families with known causative variants</td>
<td>23</td>
</tr>
<tr>
<td>Families with novel variants in known disease genes</td>
<td>92</td>
</tr>
<tr>
<td>Families with novel disease genes</td>
<td>126</td>
</tr>
<tr>
<td>Families with multiple candidate genes</td>
<td>153</td>
</tr>
</tbody>
</table>
Principle 1: Genetic Homogeneity:
- Gene pool of entire population derives from a small number of founders

Principle 2: Drift:
- Rare (single copy) founder LOF alleles can increase in frequency
  - Opportunity for novel large-effect gene discovery
  - Opportunities to identify modifier genes

Principle 3: Consanguinity and large families:
- Further opportunity to identify homozygotes for enriched LOF alleles

Principle 4: Homogeneous lifestyle
- Fewer confounding influences
- Geographically localized → Genotype-first call-back studies
Building the World’s Largest Founder Population Collection for Discovery of Novel Disease-associated Genetic Variants:
*Discovery Research Investigating Founder Population Traits (DRIFT) Program*

- Catalog population-specific allelic architecture
- Understand the biological and functional consequences of specific mutations identified
  - Genotype – Phenotype associations (especially of rare LoF/GoF mutations enriched in a given population)
  - Replication/extension in larger general population
  - “Genotype-first” call back studies
- Share and establish best practice approaches to relieve disease burden in these populations
Why Study Complex Diseases in the Amish?

- A cultural isolate – traditional dress, no electricity, phones, cars
- Genetically homogeneous closed founder population
  - Complex genetics less complex
  - Enrichment of rare large-effect mutations (founder effect)
- Western/Central European in origin
- Very large extended pedigrees (mean sibship size = 7)
  - Extensive genealogical records (Fisher Book, AGD)
  - Geographically localized
  - Homogeneous lifestyle (e.g., diet, minimal use of medications)
- Generalizability of findings
UNIVERSITY OF MARYLAND AMISH COMPLEX DISEASES RESEARCH PROGRAM:
HUNDREDS OF PHENOTYPES IN >7,000 SUBJECTS SINCE 1995 (4,725 SEQUENCED TO DATE)

- Diabetes/Obesity
- Osteoporosis
- OI/OPPG
- Longevity
- CVD
  - Coronary artery calcification
  - Hypertension/salt sensitivity
  - Hyperlipidemia
- Thyroid Disease
- Celiac Disease
- Breast density/cancer
- Pharmacogenomics (CVD, HTN, T2D)
- Nutrigenomics
- Gut microbiome/Metabolic syndrome
- Amish Wellness Program
- Mental Health/Bipolar disease & Depression
- Pain

Broad consent for “genetic studies”
Rich phenotyping (PheWAS)
Permission to recontact for “call back”
Studies are ongoing
Some Cool Findings in the Amish: Many drifted alleles that inform biology and precision medicine

- ~1 in 8 Amish carry R3527Q APOB, a cause of autosomal dominant familial hypercholesterolemia (Shen et al. Arch Int Med 2010)
- ~1 in 25 Amish carry R19X APOC3 and have low triglycerides levels and are protected from CAD (Pollin et al. Science 2008)
- First GWAS for clopidogrel pharmacogenomics; identification of common LOFs in CYP2C19 as a major determinant of response (Shuldiner, JAMA 2009)
- ~1 in 20 Amish carry a 19 bp frame-shift mutation in LIPE that increases risk for T2D by 2-fold and causes partial lipodystrophy in homozygotes (Albert et al. NEJM 2014)
- Novel genes for monogenic diseases that inform biology and therapeutic development (Strauss, Genetics in Medicine 2017)
- Two new stories:
  - A novel gene associated with serum lipids and new biology
  - KCNQ1 and long QT syndrome in the Amish
CHARACTERISTICS OF 4,725 SEQUENCED AMISH SUBJECTS

- **Clinical characteristics of UMD Amish Research Clinic participants**
  - Nominally healthy adults
  - Population-based
  - 210 traits available and analyzed
- **Relationship estimation**
  - 3,913 P/O pairs, 5,901 sib pairs
  - 17 twin/duplicate pairs (omitted)
  - 1,120 unrelated by 2nd° relationships or closer
  - 773 unrelated by 3rd° relationships or closer

<table>
<thead>
<tr>
<th>Trait</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>2617 (56%)</td>
</tr>
<tr>
<td>Age, yrs median (IQR)</td>
<td>41 (30-55)</td>
</tr>
<tr>
<td>BMI, kg/m² median (IQR)</td>
<td>26 (23.1-29.5)</td>
</tr>
</tbody>
</table>
RGC EXOME SEQUENCING IDENTIFIES *B4GALT1* AS A NOVEL GENE ASSOCIATED WITH LDL-C IN THE AMISH

- In exome sequence data, variant in highest LD with Asn352Ser *B4GALT1* is 2.8Mb distant, $R^2$ 0.78; P-value with LDL in Amish $\sim 10^{-5}$
- Whole genome sequence data in the Amish (TOPMED) failed to identify a variant more highly associated with LDL-C in this region
- Association not present in published meta-GWAS or other studies
- MAF of 352Ser in Amish = 0.061
  - MAF = 0.0004 (7/93K) in GHS
  - 7E-06 (2/277K) in gnomAD
B4GALT1 ASN352SER IS ASSOCIATED WITH SERUM LIPID AND OTHER TRAITS

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotypic Means*</th>
<th>Genotypic Means No Covars</th>
<th>Counts(Ref/Het/Alt)</th>
<th>Effect (95% CI)</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum lipids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>210.6 / 190.9 / 172.7</td>
<td>210.4 / 192.3 / 176.2</td>
<td>3995/527/12</td>
<td>-17.18 (-22.4, -11.95)</td>
<td>1.3E-10</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>134.7 / 117.4 / 103.5</td>
<td>134.6 / 118.3 / 103.5</td>
<td>3991/526/12</td>
<td>-14.61 (-19.37, -9.86)</td>
<td>1.8E-09</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>61.4 / 59.4 / 58.6</td>
<td>61.3 / 59.6 / 61.6</td>
<td>3995/527/12</td>
<td>-2.14 (-3.88, -0.41)</td>
<td>0.0155</td>
</tr>
<tr>
<td>Triglycerides (log10), mg/dL</td>
<td>62.7 / 61.2 / 49.8</td>
<td>62.5 / 62.5 / 51.8</td>
<td>3995/527/12</td>
<td>-0.015 (-0.037, 0.007)%</td>
<td>0.1760</td>
</tr>
<tr>
<td>Chol/HDL</td>
<td>3.39 / 3.15 / 2.94</td>
<td>3.39 / 3.16 / 2.87</td>
<td>3318/450/11</td>
<td>-0.03 (-0.04, -0.01)%</td>
<td>0.0003</td>
</tr>
<tr>
<td>NonHDL Cholesterol ,mg/dL</td>
<td>161.5 / 144.5 / 91.1</td>
<td>161.0 / 149.0 / 99.0</td>
<td>727/87/1</td>
<td>-14.33 (-23.57, -5.08)%</td>
<td>0.0025</td>
</tr>
<tr>
<td>CAD-related traits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Calcification (log10)</td>
<td>0.301 / 0.201 / NA</td>
<td>0.298 / 0.220 / NA</td>
<td>202/42/0</td>
<td>-0.11 (-0.21, 0)%</td>
<td>0.0433</td>
</tr>
<tr>
<td>Pericardial Fat</td>
<td>69.5 / 82.7 / NA</td>
<td>71.5 / 71.4 / NA</td>
<td>148/27/0</td>
<td>12.76 (1.06, 24.46)</td>
<td>0.0339</td>
</tr>
<tr>
<td>Liver traits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST (log10), U/L</td>
<td>18.0 / 18.6 / 35.2</td>
<td>18.0 / 18.7 / 34.3</td>
<td>3910/517/12</td>
<td>0.03 (0.02 - 0.05)%</td>
<td>6.0E-08**</td>
</tr>
<tr>
<td>ALT (log10), U/L</td>
<td>17.2 / 16.9 / 20.3</td>
<td>17.2 / 16.9 / 19.7</td>
<td>3978/530/13</td>
<td>-0.001 (-0.02 - 0.02)%</td>
<td>0.8920</td>
</tr>
<tr>
<td>AlkPhos (log10), U/L</td>
<td>53.8 / 52.9 / 62.9</td>
<td>53.8 / 53.1 / 61.8</td>
<td>3987/531/13</td>
<td>0.004 (-0.02 - 0.01)%</td>
<td>0.5391</td>
</tr>
<tr>
<td>Liver fat (by EBCT)</td>
<td>1.27 / 1.33 / NA</td>
<td>1.27 / 1.32 / NA</td>
<td>166/38/0</td>
<td>0.05 (-0.005,0.110)</td>
<td>0.0774</td>
</tr>
<tr>
<td>Coagulation traits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>280.8 / 255 / 253.8</td>
<td>280.5 / 257.1 / 273.3</td>
<td>564/54/3</td>
<td>-23.97 (-38.35, -9.59)</td>
<td>1.15E-03</td>
</tr>
</tbody>
</table>

* Genotypic Means are on the clinical scale, removing the effects of Age, Age^2, Sex, and Study

** Recessive model P value = 9x10^{-23}, recessive models for other traits were substantially less significant than for additive model
GLYCAN SYNTHESIS PATHWAY

β4GalT-1 Asn352Ser may impact transferring galactose to an acceptor sugar molecule
**B4GALT1 HOMOZYGOUS LOSS OF FUNCTION IN HUMANS**

*B4GALT1*-Congenital Disorders of Glycosylation (CDG2D) presents as a non-neurologic glycosylation disorder with hepatointestinal involvement (Guillard, et al., The Journal of Pediatrics, 2011. PMID: 21920538)

<table>
<thead>
<tr>
<th>Table 1. Clinical features and laboratory findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features</strong></td>
</tr>
<tr>
<td>Perinatal bleeding diathesis</td>
</tr>
<tr>
<td>Axial hypotonia</td>
</tr>
<tr>
<td>Dandy-Walker malformation</td>
</tr>
<tr>
<td>Dysmorphic facial features</td>
</tr>
<tr>
<td>Hepatomegaly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activated partial thromboplastin time, seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin III (%)</td>
</tr>
<tr>
<td>Protein C (%)</td>
</tr>
<tr>
<td>Protein S (%)</td>
</tr>
<tr>
<td>Platelets (× 10^9/L)</td>
</tr>
<tr>
<td>Creatine kinase (IU/L)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (IU/L)</td>
</tr>
</tbody>
</table>

13 Amish *B4GALT1* 352Ser Homozygotes – adults with no overt phenotype

?Hypomorph or neomorph?

- Two children homozygous for (1031-1032insC) leading to premature stop and loss of C-terminal 50 amino acids
- Galactosyltransferase activity was reduced to 5% that of controls.
- Presented with coagulation disturbances with hepatopathy, mild hypotonia, and dysmorphic facial features and a variable presentation of diarrhea, and myopia.

Transfer of UDP[3H]-Gal to Para-nitrophenyl-N-acetyl-b-D-glucosamine in fibroblasts from control subjects (1-4), patient 1 (5), and patient 2 (6).
ASN352SER IS IN THE LONG FLEXIBLE LOOP CLOSE TO THE ACTIVE SITE OF B4GalT-1

• Contain residues necessary for interacting with Mn^{2+} and substrate
• Covers the sugar-nucleotide-binding pocket creating the acceptor binding site
• Communicates flexibility to the long loop
• Holds the UDP-Gal in place then interacts with the GlcNAc-acceptor residue (closed conformation)

Asn352Ser mutation is in the most flexible region of the long loop, close to the hydrophobic pocket which facilitates binding of the GlcNAc-containing acceptor carbohydrate chain

Binding of Mn^{2+} with N254, M344 and H347 – first step of the β4GalT1-catalyzed reaction

## Analysis of Global Glycans Released from All Glycoproteins in Plasma

Plasma from 5 matched pairs discordant for Asn352Ser *B4GALT1* Genotype

<table>
<thead>
<tr>
<th>ID</th>
<th>N352S</th>
<th>age</th>
<th>sex</th>
<th>LDL</th>
<th>Lipid meds</th>
<th>APOB</th>
<th>dateOfVisit</th>
</tr>
</thead>
<tbody>
<tr>
<td>W01856*</td>
<td>2</td>
<td>56</td>
<td>2</td>
<td>98</td>
<td>0</td>
<td>0</td>
<td>7/30/2013</td>
</tr>
<tr>
<td>W02011*</td>
<td>0</td>
<td>63</td>
<td>2</td>
<td>123</td>
<td>0</td>
<td>0</td>
<td>10/3/2013</td>
</tr>
<tr>
<td>W02817</td>
<td>2</td>
<td>30</td>
<td>2</td>
<td>69</td>
<td>0</td>
<td>0</td>
<td>11/4/2014</td>
</tr>
<tr>
<td>W02634</td>
<td>0</td>
<td>30</td>
<td>2</td>
<td>129</td>
<td>0</td>
<td>0</td>
<td>9/2/2014</td>
</tr>
<tr>
<td>W03967</td>
<td>2</td>
<td>29</td>
<td>2</td>
<td>76</td>
<td>0</td>
<td>0</td>
<td>5/23/2016</td>
</tr>
<tr>
<td>W03852</td>
<td>0</td>
<td>29</td>
<td>2</td>
<td>122</td>
<td>0</td>
<td>0</td>
<td>4/4/2016</td>
</tr>
<tr>
<td>W01944</td>
<td>2</td>
<td>71</td>
<td>1</td>
<td>117</td>
<td>0</td>
<td>0</td>
<td>9/6/2013</td>
</tr>
<tr>
<td>W01548</td>
<td>0</td>
<td>71</td>
<td>1</td>
<td>148</td>
<td>0</td>
<td>0</td>
<td>3/18/2013</td>
</tr>
<tr>
<td>W01305</td>
<td>2</td>
<td>31</td>
<td>2</td>
<td>52</td>
<td>0</td>
<td>0</td>
<td>12/7/2012</td>
</tr>
<tr>
<td>W01263</td>
<td>0</td>
<td>31</td>
<td>2</td>
<td>130</td>
<td>0</td>
<td>0</td>
<td>11/5/2012</td>
</tr>
</tbody>
</table>

*Sibling pair
APOB (1) R3527Q mutation
APOB (0) no mutation
Differences in Abundance Between 352Ser Homozygote and Wildtype Plasma Proteins in Global N-Linked Glycan Profiling

- Major difference in four glycoforms (G0F, bG0, G1S1 and G2S2) between each pair was observed.
- Most notably, significant difference in the glycan G1S1 was observed in each pair.

<table>
<thead>
<tr>
<th>Peak No.</th>
<th>Abbreviation</th>
<th>Glycan Structure</th>
<th>% Peak Area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>W02817</td>
</tr>
<tr>
<td>1</td>
<td>G0F</td>
<td></td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>bG0</td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>2</td>
<td>G1S1</td>
<td></td>
<td>4.32</td>
</tr>
<tr>
<td>3</td>
<td>G2S2</td>
<td></td>
<td>29.08</td>
</tr>
</tbody>
</table>

Monosaccharide symbols: ■ N-acetyl glucosamine (GlcNAc); ● Mannose (Man); ● Galactose (Gal, G); ♦ N-acetyl neuraminic acid (NeuAc, sialic acid, S)
Galactosylation and Sialylation or Plasma Proteins is Decreased in 352Ser Homozygotes Compared to WT Homozygotes

<table>
<thead>
<tr>
<th>Paired Samples</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6 (Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>W02817</td>
<td>W02634</td>
<td>W03967</td>
<td>W03852</td>
<td>W01944</td>
<td>W01548</td>
</tr>
<tr>
<td>% Fucosylation</td>
<td>22.4%</td>
<td>17.0%</td>
<td>20.5%</td>
<td>19.0%</td>
<td>21.9%</td>
<td>26.2%</td>
</tr>
<tr>
<td>% Galactosylation</td>
<td>88.7%</td>
<td>95.9%</td>
<td>89.1%</td>
<td>94.2%</td>
<td>86.2%</td>
<td>92.9%</td>
</tr>
<tr>
<td>% Sialylation</td>
<td>73.5%</td>
<td>82.6%</td>
<td>73.3%</td>
<td>78.4%</td>
<td>72.2%</td>
<td>78.9%</td>
</tr>
</tbody>
</table>

Total Percentage Fucosylation

Total Percentage Galactosylation

Total Percentage Sialylation

- Red: 352Ser Homozygotes
- Blue: Wildtype
- Green: Duplicate Control
Fibrinogen N-linked Glycans Differ between 352Ser Homozygote and Wildtype Homozygotes

Significant difference in four glycoforms (G0F, G1S1, G2S1 and G2S2) between each pair was observed.

<table>
<thead>
<tr>
<th>Peak No.</th>
<th>Abbreviation</th>
<th>Glycan Structure</th>
<th>% Peak Area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>W02817</td>
</tr>
<tr>
<td>2</td>
<td>G0F</td>
<td><img src="image" alt="G0F Structure" /></td>
<td>2.26</td>
</tr>
<tr>
<td>9</td>
<td>G1S1</td>
<td><img src="image" alt="G1S1 Structure" /></td>
<td>19.45</td>
</tr>
<tr>
<td>12</td>
<td>G2S1</td>
<td><img src="image" alt="G2S1 Structure" /></td>
<td>31.86</td>
</tr>
<tr>
<td>18</td>
<td>G2S2</td>
<td><img src="image" alt="G2S2 Structure" /></td>
<td>15.75</td>
</tr>
</tbody>
</table>

Monosaccharide symbols: ▼ Fucose (Fuc, F); ■ N-acetyl glucosamine (GlcNAc); ● Mannose (Man); ● Galactose (Gal, G); ♦ N-acetyl neuraminic acid (NeuAc, sialic acid, S)
Significant difference in four glycoforms (G0F, G1F, G2F and G2FS1) between each pair was observed.
Decreased Galactosylation of Major Plasma Proteins in 352Ser B4GALT1 Homozygotes Compared to Wild Type Homozygotes

**Total Glycoproteins**

- 352Ser Homozygote: 87.7%
- WT: 94.4%
- Percent change: -6.7%

**Enriched Fibrinogen**

- 352Ser Homozygote: 77.9%
- WT: 93.0%
- Percent change: -15.1%

**Enriched Total IgG**

- 352Ser Homozygote: 31.4%
- WT: 57.1%
- Percent change: -25.7%

P-values:

- Total Glycoproteins: 0.000008
- Enriched Fibrinogen: 3.6E-9
- Enriched Total IgG: 0.0002
B4galT1 Knockdown in Zebrafish Results in Decrease in LDL-C which is Rescued by Overexpression of B4GalT1 mRNA

May Montasser and Norann Zaghloul
1 IN 40 (2.5%) OF AMISH HAVE A PATHOGENIC MUTATION IN KCNQ1 PREDISPOSING THEM TO LONG QT SYNDROME AND SUDDEN DEATH

- **KCNQ1** variants known to be associated with Long QT Syndrome (rare LOFs; estimated at 1:2500 in the general population
- People with Long QT Syndrome are at increased risk of syncope and sudden cardiac death from birth to old age
  - Highest risk in prepubertal boys and women of childbearing age
  -Estimated to cause 1/10 crib deaths
  -Treatment = beta-blocker; avoid potential provocations (QT prolonging drugs, strenuous exercise, other stressors)
- Thr224Met KCNQ1 highly associated with EKG QTc in the Amish (SIFT : deleterious; Polyphen: probably damaging)

<table>
<thead>
<tr>
<th>Phenotype name</th>
<th>Variant increases QTc by 23 ms</th>
<th>Variant</th>
<th>rsID</th>
<th>Gene</th>
<th>HGVS</th>
<th>P-value</th>
<th>Effect (ms)</th>
<th>Met224</th>
<th>Homo (n)</th>
<th>Het (n)</th>
<th>Met224 Hom (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc value</td>
<td>11:2571391:C:T</td>
<td>rs199472706</td>
<td>KCNQ1</td>
<td>p.Thr224Met:</td>
<td>p.Thr97Met</td>
<td>2.5806E-18</td>
<td>23</td>
<td>0.0126</td>
<td>4294</td>
<td>111</td>
<td>0</td>
</tr>
</tbody>
</table>

- Same mutation reported in 1 patient of 2500 patients from the FAMILION long QT syndrome study (Kapplinger et al Heart Rhythm 2009); ClinVar = VUS
- In initial chart review, 38 of 112 carriers have prolonged QT interval on EKG (men >440 ms; women>460 ms)
- Implications to Amish research participants and the community
Thr224Met KCNQ1 Return of Results: Improving the health of the Amish community

More information needed:
- What is absolute risk of syncope and sudden death to individuals?
- How many can be diagnosed with LQTS without genetic information?
- In the Amish, would treatment with β-blocker be accepted?
- Would Amish follow cascade testing recommendations (1st degree relatives)?

Intervention:
- IRB approved, letter to inform 124 participants about potential health risk
- 1st Visit - Home visit by medical geneticist (EAS) and Amish liaison to:
  - Draw blood for CLIA confirmation, lying and standing EKG, Schwartz score
  - Complete medical history including cardiac questions
  - 3-4 generation pedigree, including sudden deaths
- 2nd Visit:
  - Discuss CLIA confirmation
  - β-blocker (nadolol) based on American Rhythm Society guidelines (QTc>470 or<470 with symptoms)
  - Recommendation to test 1st degree relatives

LQTS = QTc ≥ 500 msec or Schwartz score ≥ 3.5
EKG upon immediate standing improves sensitivity

L. Streeten, V. See, L. Jeng, K. Maloney, T Pollin, B Mitchell

Table 1: Diagnostic Criteria for LQTS (Schwartz Score)

<table>
<thead>
<tr>
<th>Points</th>
<th>A. QTc(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>≥480 ms</td>
</tr>
<tr>
<td>2</td>
<td>460-479 ms</td>
</tr>
<tr>
<td>1</td>
<td>450-459 ms (in males)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>B. QTc(^a) 4th minute of recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>from exercise stress test ≥480 ms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>C. Torsade de pointes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>D. T wave alternans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>E. Notched T wave in 3 leads</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>F. Low heart rate for age@</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

Clinical History

<table>
<thead>
<tr>
<th>Points</th>
<th>A. Syncope*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>With stress</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>B. Without stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>A. Congenital deafness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

Family History

<table>
<thead>
<tr>
<th>Points</th>
<th>A. Family members with definite LQTS$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>B. Unexplained sudden cardiac death age 30 among immediate family members$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>
Thr224Met KCNQ1 Return of Results:

Response to date
- 80/124 (65%) responses to initial letter; 72 yes, 8 no
- 65 seen for first visit (since 9/17), 7 seen for 2nd visit

Treatment to date
- Nadalol started on 3 individuals
  - 14 yo with QTc 610 ms
  - 16 yo with QTc 620 ms
  - 62 yo with syncopal episode & incontinence of stool
- One started by PMD
- 3 Declined treatment

Ongoing implementation work
- Cascade screening/evaluation
- Clinical outcomes
- ELSI evaluation

<table>
<thead>
<tr>
<th>Response to date</th>
<th>Total</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>47</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Age</td>
<td>47 ± 18</td>
<td>45 ± 18</td>
<td>50 ± 16</td>
</tr>
<tr>
<td>Syncope</td>
<td>14 (30%)</td>
<td>9 (32%)</td>
<td>4 (21%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>14 (30%)</td>
<td>9 (32%)</td>
<td>4 (21%)</td>
</tr>
<tr>
<td>FH Sudden death &lt;30 yrs in 1st degree relative*</td>
<td>6 (13%)</td>
<td>4 (14%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Normal QTc (supine)</td>
<td>6 (15%)</td>
<td>4 (&lt;460)</td>
<td>2 (&lt;440)</td>
</tr>
<tr>
<td>Supine Max QTc</td>
<td>486 ± 31</td>
<td>490 ± 30</td>
<td>479 ± 31</td>
</tr>
<tr>
<td>Standing Max QTc</td>
<td>501 ± 22</td>
<td>500 ± 22</td>
<td>502 ± 23</td>
</tr>
<tr>
<td>Clinical diagnosis of LQTS</td>
<td>25 (53%)</td>
<td>18 (64%)</td>
<td>7 (38%)</td>
</tr>
</tbody>
</table>

*2 crib deaths, 6 year-old male walking to school, 12 year old while swimming
The Future of Precision Medicine is Here Today

The GHS Genome-First Return of Results Program
Geisinger GenomeFirst Program

- Informed consent specifies intent to return results that are medically actionable after CLIA confirmation
- Geisinger will NOT return results that are NOT medically actionable
- Geisinger experts will decide what to return
  - Geisinger “76” (56 ACMG + 20) genes causative of 27 diseases that are medically actionable
  - e.g., hereditary breast and ovarian cancer; Lynch syndrome; familial hypercholesterolemia; hypertrophic cardiomyopathy

Initial analyses indicate that ~3.5% of study participants will test positive for an actionable variant
# Geisinger 76: 1 in 25 Patients Have an Actionable Result

<table>
<thead>
<tr>
<th>GENOMIC CONDITION</th>
<th>Number or patients diagnosed</th>
<th>CLINICAL RISK</th>
<th>DISEASE-ALTERING INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Hypercholesterolemia (FH)</td>
<td>1 in 250</td>
<td>Early-onset Coronary Artery Disease and Stroke</td>
<td>Targeted screening and aggressive medical management</td>
</tr>
<tr>
<td>Hereditary Breast and Ovarian Cancer Syndrome</td>
<td>1 in 400</td>
<td>Early-onset Breast, Ovarian, and Prostate Cancers</td>
<td>Targeted screening with prophylactic medical and surgical intervention</td>
</tr>
<tr>
<td>Lynch Syndrome</td>
<td>1 in 440</td>
<td>Early-onset Colon and Uterine Cancers</td>
<td>Targeted screening and management of pre-cancerous changes</td>
</tr>
<tr>
<td>TOTAL</td>
<td>&gt; 1 in 100</td>
<td>Multiple Cancers and Cardiovascular Diseases</td>
<td>Life-saving screening and intervention before development of disease</td>
</tr>
</tbody>
</table>

Other conditions: cardiomyopathy, long QT syndrome, malignant hyperthermia, arrhythmogenic right ventricular cardiomyopathy, MEN2, tuberous sclerosis, hereditary pheochromocytomas and paragangliomas
Barbara Barnes’ MyCode Story

• 57 Year old grandmother bringing up three grandchildren ages 3, 5, and 14
• Found to have a pathogenic BRCA1 mutation
  – “Okay, so what do we do next? I have 15 more years to go until they’re raised.”
• Genetic counseling and workup
  – Negative mammogram
  – Elected to have preventive bilateral salpingo-oophorectomy
  – Stage 1 cancer found in one fallopian tube
  – Completing chemotherapy with expected excellent outcome
  – Daughter tested for BRCA1
Kim Mummert’s MyCode Story

- 66 year old GHS employee
- Tested positive for a Lynch Syndrome mutation
- Obtained genetic counseling
  - More frequent colonoscopy
  - Two children in their 20’s will be screened
Genetic identification of familial hypercholesterolemia within a single U.S. health care system

Prevalence and Clinical Impact of FH Variants in DiscovEHR

A
Distribution of 229 heterozygous carriers by FH gene
- LDLR (29 variants; 19 pLOF)
- PCSK9 (4 variants)
- APOB (2 variants)

B
Population characteristics
<table>
<thead>
<tr>
<th></th>
<th>FH variant positive/total</th>
<th>Estimated prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>All DiscovEHR participants</td>
<td>229/50,726</td>
<td>1:222</td>
</tr>
<tr>
<td>Participants recruited from cardiac catheterization lab</td>
<td>57/6,747</td>
<td>1:118</td>
</tr>
<tr>
<td>Participants recruited from other sites</td>
<td>172/43,979</td>
<td>1:256</td>
</tr>
</tbody>
</table>

C
Participants with severe hypercholesterolemia (LDL-C > 190 mg/dl)
N = 4,435 of 42,696 individuals with LDL-C data available (10.4%)

D

FH variant positive: 112 of 4,435 (1:40)

Currently on statin
- FH variant negative: 38%
- FH variant positive: 58%

Statin-treated with LDL-C < 100 mg/dl
- FH variant negative: 46%
- FH variant positive: 77%
Why GenomeFirst Is Important:
Most patients with FH are not diagnosed and treated inadequately

A. FH Gene

<table>
<thead>
<tr>
<th>Gene</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>2.6 (2.0-3.5)</td>
<td>4.3x10^{-11}</td>
</tr>
<tr>
<td>LDLR - all</td>
<td>3.8 (2.5-5.6)</td>
<td>8.0x10^{-11}</td>
</tr>
<tr>
<td>LDLR - pLOF</td>
<td>5.5 (3.4-8.7)</td>
<td>7.7x10^{-13}</td>
</tr>
<tr>
<td>APOB</td>
<td>1.9 (1.2-3.1)</td>
<td>7.6x10^{-3}</td>
</tr>
<tr>
<td>PCSK9</td>
<td>2.1 (0.8-6.0)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

B. FH Gene

<table>
<thead>
<tr>
<th>Gene</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>3.7 (2.6-5.2)</td>
<td>5.5x10^{-14}</td>
</tr>
<tr>
<td>LDLR - all</td>
<td>7.0 (4.5-10.9)</td>
<td>1.2x10^{-17}</td>
</tr>
<tr>
<td>LDLR - pLOF</td>
<td>10.3 (6.1-17.3)</td>
<td>9.8x10^{-19}</td>
</tr>
<tr>
<td>APOB</td>
<td>1.7 (0.9-3.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>PCSK9</td>
<td>3.9 (1.1-14.1)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

- Only 35 (15.7%) of the 229 FH variant carriers had EHR evidence of a “Pure Hypercholesterolemia” diagnosis or at least one encounter at Lipid Clinic
- Criteria supporting a clinical diagnosis of FH were found using EHR data in only 55% of variant carriers
- Active statin use was identified in 58% and high-intensity statin use in 37% of carriers
- Only 46% of statin-treated carriers had a LDL cholesterol level below 100 mg/dl.
- Genomic screening can prompt the diagnosis of FH patients, the majority of whom are receiving inadequate lipid-lowering therapy

Summary and Conclusions

- The future of drug discovery and precision medicine will be fueled by human genomic discovery.
- Genetic “experiments of nature” can inform therapeutic target discovery and provide insight into mechanism.
- Return of medically actionable genetic results will require significant health care system resources to realize downstream health and economic benefits.
- Partnerships between industry, academia and health care systems can accelerate genomic discovery and implementation of precision medicine.
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