

The Path to Precision Medicine: From Discovery to Patient Care



Alan R. Shuldiner, MD

Vice President

Regeneron Genetics Center &

Professor (part-time), University of Maryland School of Medicine



The Reality of Therapeutic Development in 2017

- 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 Power of Human Genetics to Accelerate Target Identification, Validation and Drug Development

2003

Mutations in PCSK9 cause autosomal dominant hypercholesterolemia

[illegible]

Analysis of the distribution of *Aspergillus nidulans* (AN100) and *Aspergillus fumigatus* (AF100) in a risk factor for the university hospital atmosphere is characterized by an increase in the density of the distribution of environmental levels that is associated with an increase in the space. The *Aspergillus fumigatus* population is associated with AF100. In studying the distribution of *Aspergillus nidulans* in the hospital environment, it was found that the distribution of the density of the distribution of environmental levels that is associated with an increase in the space. The *Aspergillus fumigatus* population is associated with AF100. In studying the distribution of *Aspergillus nidulans* in the hospital environment, it was found that the distribution of the density of the distribution of environmental levels that is associated with an increase in the space. The *Aspergillus fumigatus* population is associated with AF100.

Family studies
identify PCSK9
GOF as a causal
FH gene

2006

Sequence Variations in *POU3F1*, *Low LDL*,
and Association against Coronary Artery Disease

1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 2266, 2267, 2268, 2269, 2270, 2271, 2272, 2273, 2274, 2275, 2276, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2291, 2292, 2293, 2294, 2295, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2303, 2304, 2305, 2306, 2307, 2308, 2309, 2310, 2311, 2312, 2313, 2314, 2315, 2316, 2317, 2318, 2319, 2320, 2321, 2322, 2323, 2324, 2325, 2326, 2327, 2328, 2329, 2330, 2331, 2332, 2333, 2334, 2335, 2336, 2337, 2338, 2339, 2340, 2341, 2342, 2343, 2344, 2345, 2346, 2347, 2348, 2349, 2350, 2351, 2352, 2353, 2354, 2355, 2356, 2357, 2358, 2359, 2360, 2361, 2362, 2363, 2364, 2365, 2366, 2367, 2368, 2369, 2370, 2371, 2372, 2373, 2374, 2375, 2376, 2377, 2378, 2379, 2380, 2381, 2382, 2383, 2384, 2385, 2386, 2387, 2388, 2389, 2390, 2391, 2392, 2393, 2394, 2395, 2396, 2397, 2398, 2399, 2400, 2401, 2402, 2403, 2404, 2405, 2406, 2407, 2408, 2409, 2410, 2411, 2412, 2413, 2414, 2415, 2416, 2417, 2418, 2419, 2420, 2421, 2422, 2423, 2424, 2425, 2426, 2427, 2428, 2429, 2430, 2431, 2432, 2433, 2434, 2435, 2436, 2437, 2438, 2439, 2440, 2441, 2442, 2443, 2444, 2445, 2446, 2447, 2448, 2449, 2450, 2451, 2452, 2453, 2454, 2455, 2456, 2457, 2458, 2459, 2460, 2461, 2462, 2463, 2464, 2465, 2466, 2467, 2468, 2469, 2470, 2471, 2472, 2473, 2474, 2475, 2476, 2477, 2478, 2479, 2480, 2481, 2482, 2483, 2484, 2485, 2486, 2487, 2488, 2489, 2490, 2491, 2492, 2493, 2494, 2495, 2496, 2497, 2498, 2499, 2500, 2501, 2502, 2503, 2504, 2505, 2506, 2507, 2508, 2509, 2510, 2511, 2512, 2513, 2514, 2515, 2516, 2517, 2518, 2519, 2520, 2521, 2522, 2523, 2524, 2525, 2526, 2527, 2528, 2529, 2530, 2531, 2532, 2533, 2534, 2535, 2536, 2537, 2538, 2539, 2540, 2541, 2542, 2543, 2544, 2545, 2546, 2547, 2548, 2549, 2550, 2551, 2552, 2553, 2554, 2555, 2556, 2557, 2558, 2559, 2560, 2561, 2562, 2563, 2564, 2565, 2566, 2567, 2568, 2569, 2570, 2571, 2572, 2573, 2574, 2575, 2576, 2577, 2578, 2579, 2580, 2581, 2582, 2583, 2584, 2585, 2586, 2587, 2588, 2589, 2590, 2591, 2592, 2593, 2594, 2595, 2596, 2597, 2598, 2599, 2600, 2601, 2602, 2603, 2604, 2605, 2606, 2607, 2608, 2609, 2610, 2611, 2612, 2613, 2614, 2615, 2616, 2617, 2618, 2619, 2620, 2621, 2622, 2623, 2624, 2625, 2626, 2627, 2628, 2629, 2630, 2631, 2632, 2633, 2634, 2635, 2636, 2637, 2638, 2639, 2640, 2641, 2642, 2643, 2644, 2645, 2646, 2647, 2648, 2649, 2650, 2651, 2652, 2653, 2654, 2655, 2656, 2657, 2658, 2659, 2660, 2661, 2662, 2663, 2664, 2665, 2666, 2667, 2668, 2669, 2670, 2671, 2672, 2673, 2674, 2675, 2676, 2677, 2678, 26

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

2012

Effect of a Monoclonal Antibody to DC9K7 on LM, Cholesterol

Journal of Interpersonal Violence 26(12)
 © The Author(s) 2011
 Reprints and permissions: sagepub.com/journalsPermissions.nav
 DOI: 10.1177/0886260511421111
 http://jiv.sagepub.com
 Hosted at <http://online.sagepub.com>

Submit your manuscript to the SAGE Journals Online service at www.sagepub.com/journalsOnline.nav and benefit from:

- Convenient online submission
- Thorough peer review
- Immediate publication on acceptance
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► jiv.sagepub.com

Clinical proof of concept

2008

A Null Mutation in Human *APOL3* Confers a Favorable Plasma Lipid Profile and Apparent Cardioprotection

[illegible]

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

2014

[illegible]

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

2015

遊戲中的「量」與「質」

Targeting APOC in the Familial Chylomicronemia Syndrome

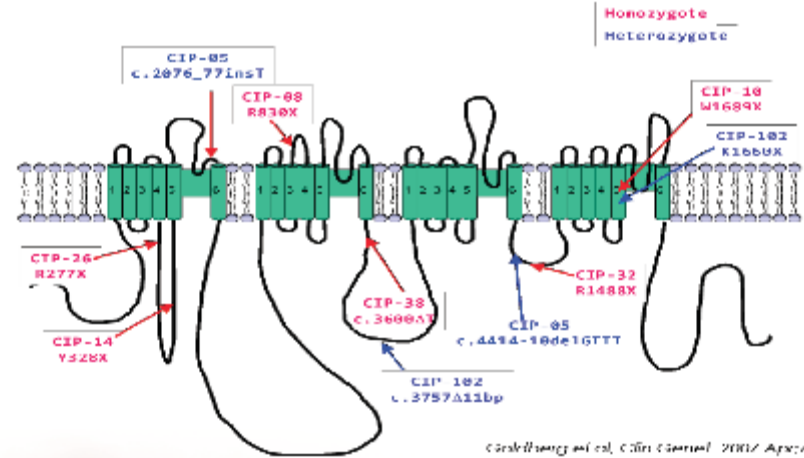
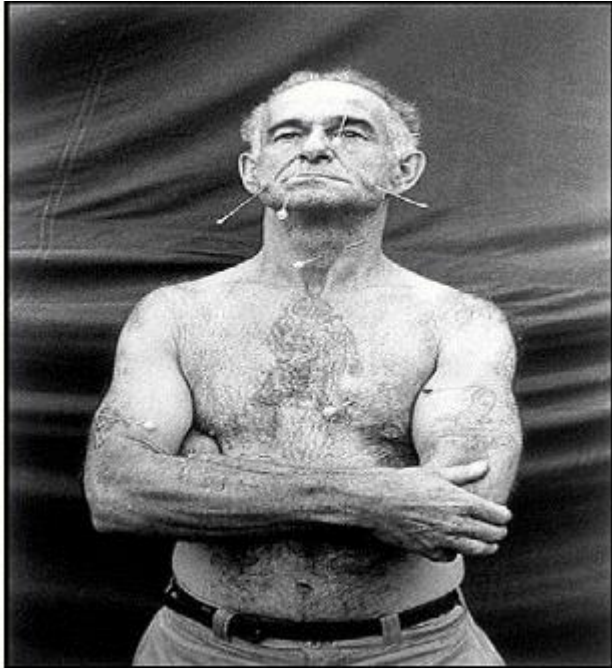
Daniel Gaudin, M.D., Ph.D., David Brice, Ph.D., Karim Feghali, Ph.D.,
Christopher Almers, Ph.D., David S. Glick, M.D., Steven H. Phillips, M.D.,
and Robert A. Heide, M.D., M.Sc., Joseph L. Witztum, M.D.

OBJECTIVE

The genetic chylomicronemia syndrome is a severe disorder characterized by very high plasma triglyceride levels and the presence of chylomicrons in the plasma. While CD36, GPIIb/IIIa, and apoB-48 are well established targets, this mutation is not in the causal gene of the ApoB48 gene. CD36 is located on chromosome 10p12 and is a member of the LDL receptor family. We have used a mouse model of the human disease to study the role of CD36 in the pathogenesis of the disease. We have found that mice lacking CD36 have normal plasma triglyceride levels and normal plasma chylomicron levels. These results suggest that CD36 is not a major target for the treatment of the disease. We have also found that mice lacking CD36 have normal plasma triglyceride levels and normal plasma chylomicron levels. These results suggest that CD36 is not a major target for the treatment of the disease.

Clinical proof of concept

Congenital Insensitivity to Pain (CIP) and the SCN9A Gene: Human Genetics Provides Insights Into New Pain Drug Targets

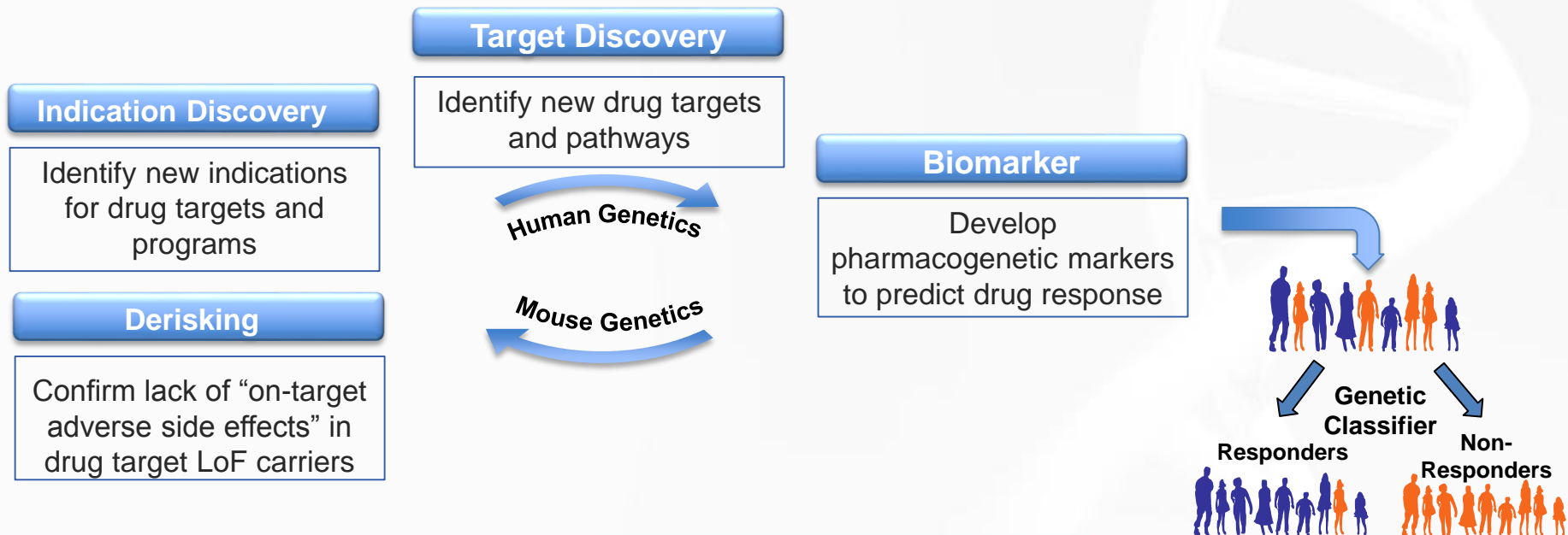


- CIP → pain free burns, fractures, childbirth, etc
- Extremely rare: <1/1,000,000 prevalence
- Mutations in SCN9A cause insensitivity to pain
- Efforts to mimic the effects of pain insensitivity through therapeutics blocking the corresponding protein are being pursued

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”



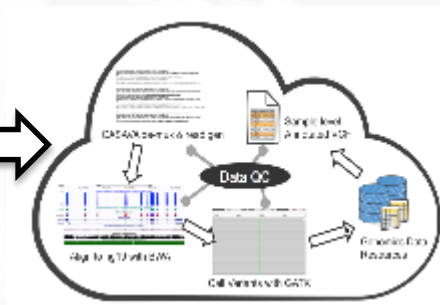
Engine Driving Identification of Rare Loss of Function Mutations that Inform Human Biology and Drug Development: Ultra High-Throughput Sequencing and Analysis at the Regeneron Genetics Center

**Automated Biobank
(1.4M Samples)**

**Library Prep Automation
(>200,000 Samples/Yr)**

**Illumina Fleet
(>150,000 Exomes/Yr)**

**Cloud Based Informatics
& Analysis**



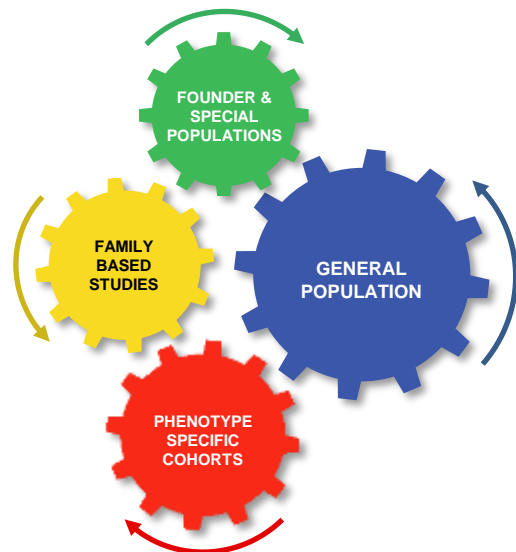
Technologies and Capabilities

- Automated biobank with 1.4M+ sample capacity
- Custom fully-automated exome and targeted sequencing sample preparation workflows
- Currently exome sequencing >2,500 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 . . .



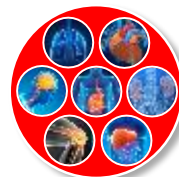
. . . will power genomic discovery



General Population

Geisinger

biobank^{uk}
improving the health of future generations



Phenotype Specific Cohorts

Feinstein Institute
for Medical Research
Northwell Health



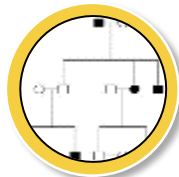
UNIVERSITY OF UTAH
HEALTH CARE



UConn
Health Center



Penn



Family Studies



COLUMBIA UNIVERSITY
MEDICAL CENTER

BCM
Baylor College of Medicine

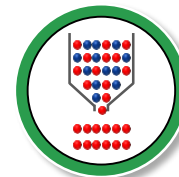


MARIO NEGRI
ISTITUTO DI RICERCA
FARMACOLOGICHE

SickKids



NIH
National Institutes of Health



Founder & Special Populations



UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE



NIH
National Institutes of Health



Global Gene Corp



EINSTEIN
Albert Einstein College of Medicine



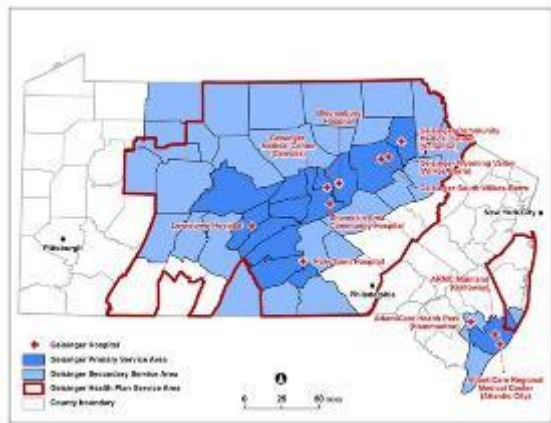
Geisinger-Regeneron DiscovEHR Collaboration

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
 - 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
 - 119,000 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

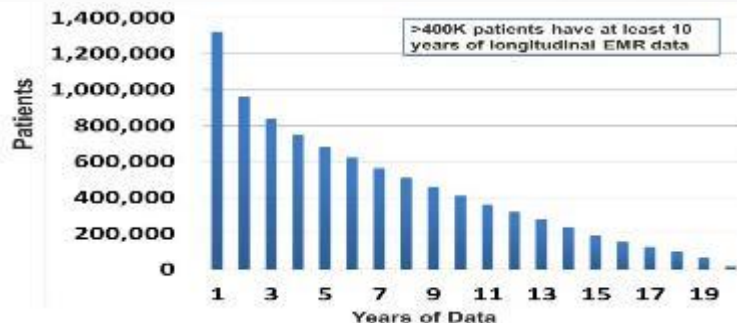
Frederick E. Dewey,^{1*} Michael F. Murray,² John D. Overton,¹ Lukas Habegger,¹ Joseph B. Leader,² Samantha N. Fetterolf,² Colm O'Dushlaine,¹ Cristopher V. Van Hout,¹ Jeffrey Staples,¹ Claudia Gonzaga-Jauregui,¹ Raghu Metpally,² Sarah A. Pendergrass,² Monica A. Giovanni,² H. Lester Kirchner,² Suganthi Balasubramanian,¹ Noura S. Abul-Husn,¹ Dustin N. Hartzel,² Daniel R. Lavage,² Korey A. Kost,² Jonathan S. Packer,¹ Alexander E. Lopez,¹ John Penn,¹ Semanti Mukherjee,¹ Nehal Gosalia,¹ Manoj Kanagaraj,¹ Alexander H. Li,¹ Lyndon J. Mitnaul,¹ Lance J. Adams,² Thomas N. Person,² Kavita Praveen,¹ Anthony Marcketta,¹ Matthew S. Lebo,³ Christina A. Austin-Tse,³ Heather M. Mason-Suares,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,² 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. Carey^{2*}

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.

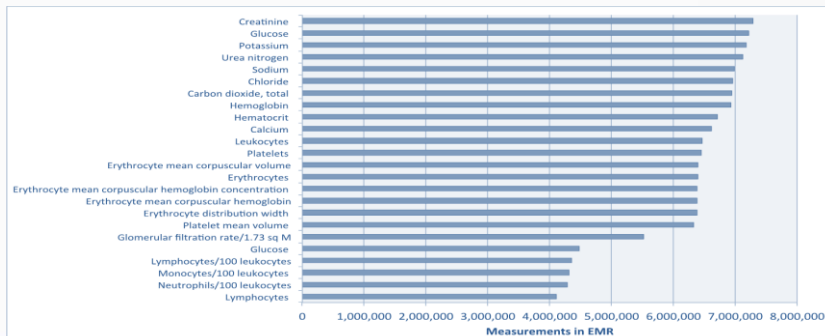
23 DECEMBER 2016 • VOL 354 ISSUE 6319

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

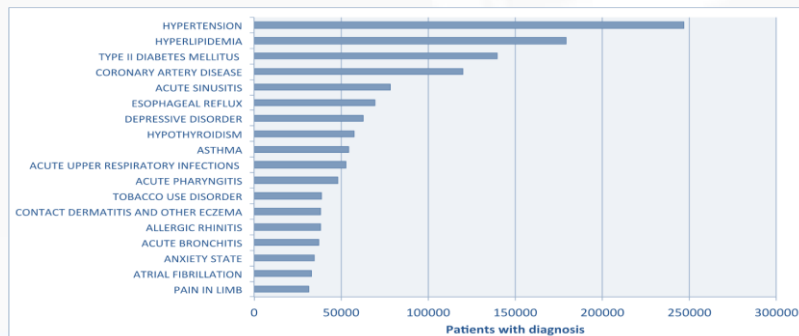
Patients by Years of Clinical Data



Most Prevalent Labs in GHS EHR

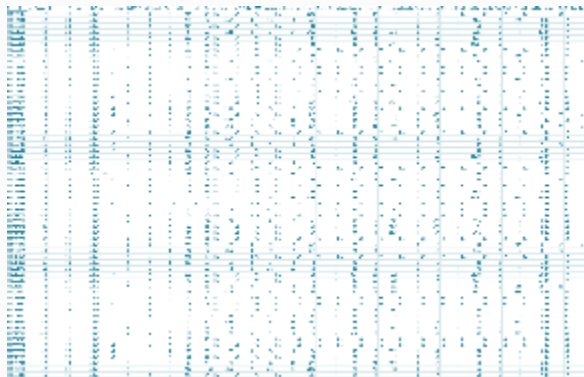


Most Prevalent Office Visit Dx in GHS EHR



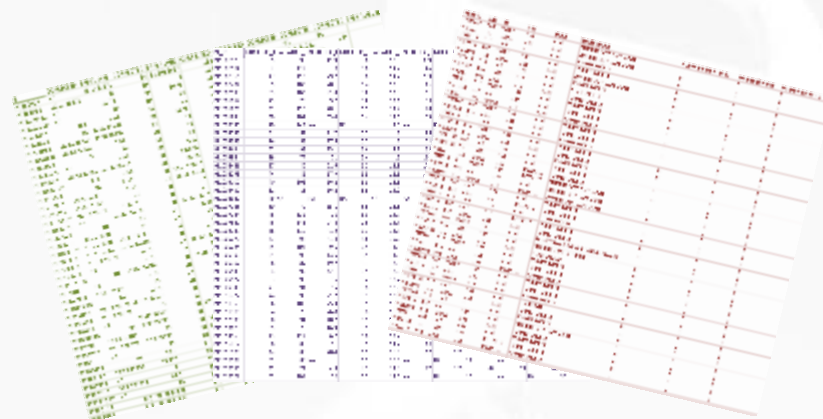
The RGC and GHS Have Developed A Large Number of High-quality, EHR-derived Phenotypes For Genetic Analyses

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:

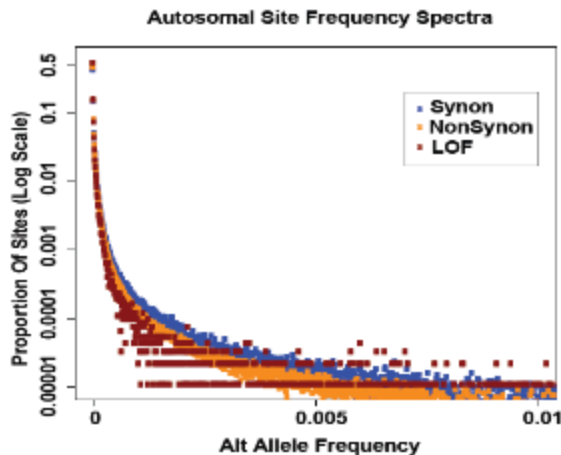
Include PheWAS, Immune, Lab Traits, DEXA, Echo, EKG, Ocular Measures, PFT's, Vitals and Anthropometrics



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*)



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

Variant type	All variants	Allele frequency $\leq 1\%$
Single nucleotide variants	4,028,206	3,947,488
Insertion/deletion variants	224,100	218,785
Predicted loss of function variants	176,365	175,393
Nonsynonymous variants	2,025,800	2,002,912
Total	4,252,306	4,166,273

Proof-of-principle: DiscovEHR Genetics Predict Efficacy of Established Targets for Hyperlipidemia *(Dewey et al, Science 2016)*

						LDL-c		HDL-c		Triglycerides		Total cholesterol	
Target	Agent	Action	Phase	Clinical effect	LOF carriers	p	effect	p	effect	p	Effect	p	effect
PPARA	Fenofibrate	Agonist	Approved	Decreased triglycerides, increased HDL	2	0.8	9 mg/dl	0.2	-28%	0.09	113%	0.4	27 mg/dl
HMGCR	Atorvastatin, rosuvastatin, pravastatin, simvastatin	Antagonist	Approved	Decreased LDL, total cholesterol, increased HDL	12	0.7	-4 mg/dl	0.3	9%	0.6	-8%	0.7	-4 mg/dl
NPC1L1	Ezetemibe	Antagonist	Approved	Decreased LDL	121	0.03	-7 mg/dl	0.07	-4%	0.5	-3%	0.0004	-12 mg/dl
APOB	Mipomersen	Antagonist	Approved	Decreased LDL	80	0.0003	-15 mg/dl	0.06	6%	0.002	-15%	8.x10 ⁻⁷	-21 mg/dl
MTTP	Lomitapide	Antagonist	Approved	Decreased LDL	24	0.9	1 mg/dl	0.4	4%	0.7	3%	1.0	0.2 mg/dl
HCAR3	Niacin	Agonist	Approved	Increased HDL, decreased triglycerides, LDL	107	0.4	-3 mg/dl	0.4	-2%	0.5	4%	0.3	-4 mg/d;
CETP	Anacetrapib, evacetrapib	Antagonist	Phase 3	Increased HDL	37	0.3	-6 mg/dl	2.0x10 ⁻⁶	23%	0.6	5%	0.1	9 mg/dl
PCSK9	Alirocumab, evolocumab, bococizumab	Antagonist	Phase 3	Decreased LDL	52	8.8x10 ⁻⁹	-25 mg/dl	0.3	3%	0.03	-12%	6.4x10 ⁻⁶	-21 mg/dl
APOC3	APOC3 inhibitors	Antagonist	Phase 2	Decreased triglycerides, increase HDL	226	0.3	-3 mg/dl	1.5x10 ⁻⁴³	28%	1.5x10 ⁻⁸⁷	-48%	0.2	-4 mg/dl
ACLY	ATP citrate lyase inhibitors	Antagonist	Phase 2	Decreased LDL	13	0.2	-14 mg/dl	1.0	0%	0.3	-13%	0.4	-10 mg/dl
ANGPTL3	ANGPTL3 inhibitors	Antagonist	Phase 2	Decreased triglycerides, LDL, HDL	150	0.0004	-10 mg/dl	0.0002	-8%	6.4x10 ⁻¹⁵	-27%	1.6x10 ⁻¹⁰	-19 mg/dl

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

ORIGINAL ARTICLE

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*)

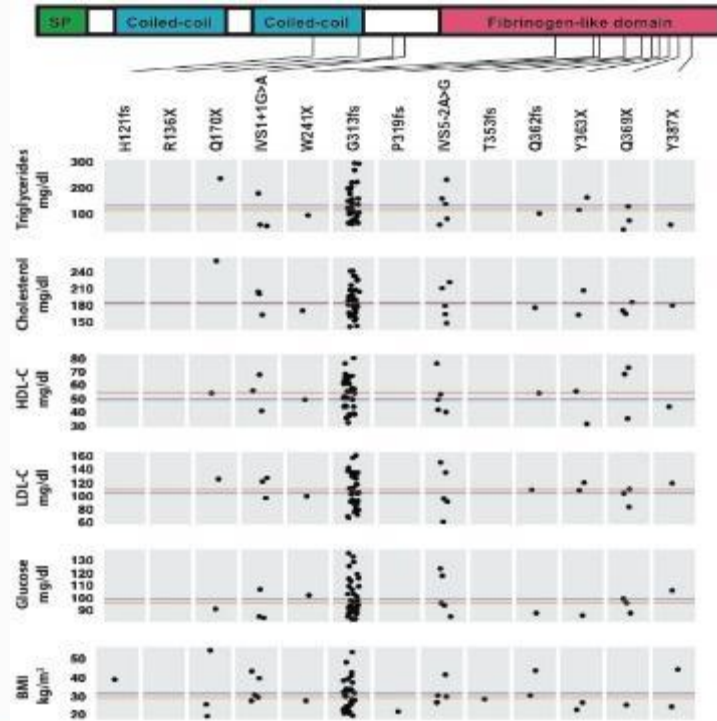


Table 2. Association between *ANGPTL4* E40K or Other Inactivating Mutations and Lipid Levels.^a

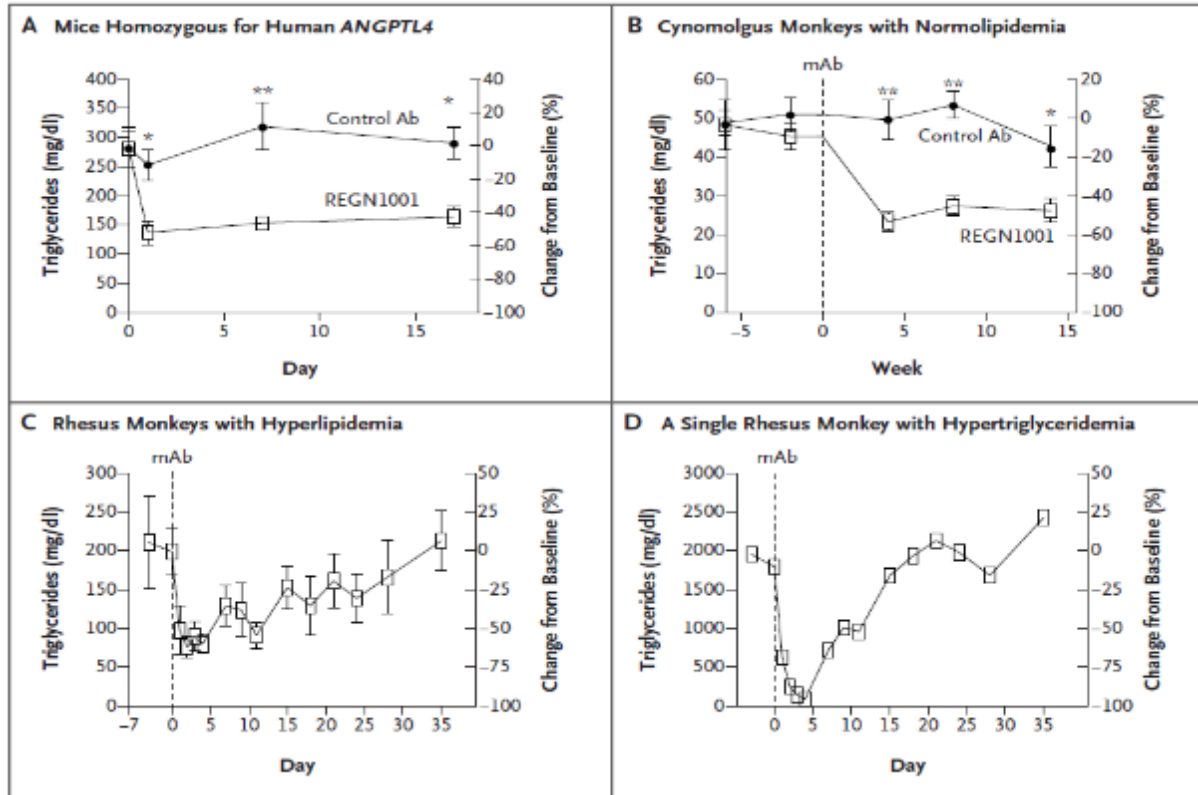
Lipid	Noncarriers (N=41,177)	E40K Heterozygotes (N=1661)	E40K Homozygotes (N=17)	P Value [†]	Heterozygotes with Other Inactivating Mutation (N=75)	P Value [‡]
		median (IQR)			median (IQR)	
Triglycerides — mg/dl	132 (95–182)	115 (85–157)	81 (61–122)	2.0×10 ^{−23}	115 (78–162)	0.02
HDL cholesterol — mg/dl	48 (40–59)	52 (43–63)	67 (54–72)	1.6×10 ^{−17}	54 (44–62)	0.009
LDL cholesterol — mg/dl	114 (94–135)	116 (96–138)	107 (89–132)	0.20	119 (101–136)	0.60
Total cholesterol — mg/dl	195 (172–218)	196 (173–219)	182 (168–209)	0.90	193 (179–208)	0.80

Table 3. Association between *ANGPTL4* E40K or Other Inactivating Mutations and Coronary Artery Disease.^a

Variants	Allele Frequency		Odds Ratio (95% CI)	P Value
	CAD Cases	CAD Controls		
E40K mutation in 1661 heterozygotes and 17 homozygotes	1.71	2.10	0.81 (0.70–0.92)	0.002
Heterozygous inactivating mutations in 75 participants	0.06	0.10	0.56 (0.32–1.00)	0.05

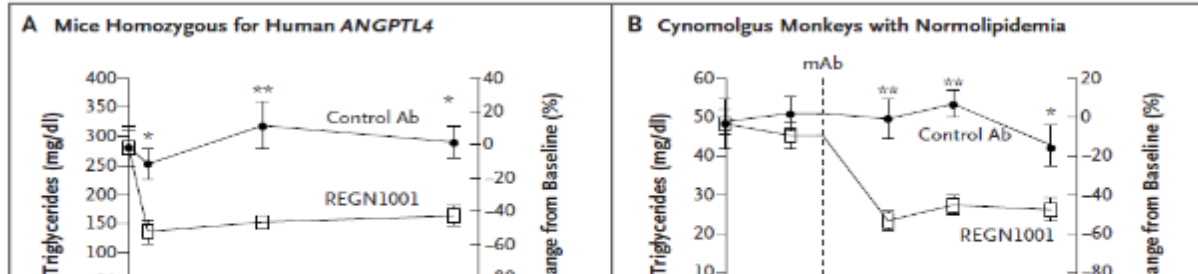
Hypolipidemic Effects of Anti-ANGPTL4 Antibody in Mice and Monkeys

(Dewey et al, NEJM 2016)

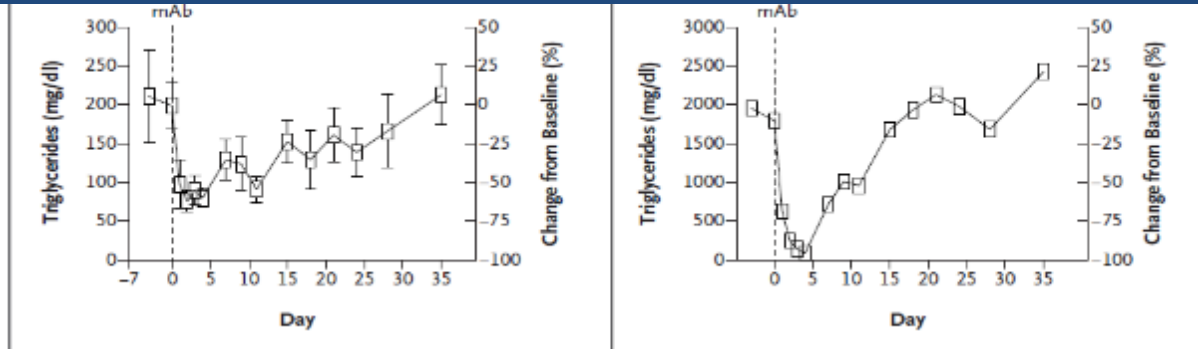


Hypolipidemic Effects of Anti-ANGPTL4 Antibody in Mice and Monkeys

(Dewey et al, NEJM 2016)



AE: Some mice and one monkey developed abdominal lymphadenopathy and chylous ascities



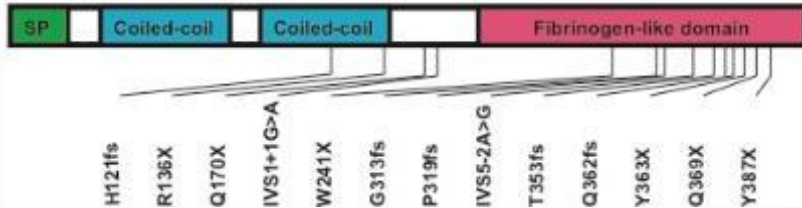
ANGPTL4 p.E40K Human Homozygotes do not Exhibit Increased Rates of Lymphatic Abdominal Pathology in DiscovEHR

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

Phenotype	Non-carriers (n=41,777)	E40/K40 heterozygotes (n=1,661)		K40 homozygotes (n=17)		pLOF carriers (n=75)	
	N (%)	N (%)	P*	N (%)	P*	N (%)	P*
Disorders of lymphoid system	3,831 (9.2)	154 (9.3)	0.9	1 (5.9)	0.7	5 (6.7)	0.6
Disorder of lymph node	1,661 (4.0)	70 (4.2)	0.7	0 (0.0)	0.7	1 (1.3)	0.4
Lymphadenitis	295 (7.1)	12 (7.2)	0.9	0 (0.0)	0.7	0 (0.0)	1.0
Mesenteric lymphadenitis	12 (0.03)	0 (0.0)	0.5	0 (0.0)	0.9	0 (0.0)	0.9
Granulomatous lymphadenitis	5 (0.01)	0 (0.0)	0.7	0 (0.0)	1.0	0 (0.0)	0.9
Ascites	308 (0.7)	11 (0.7)	0.8	1 (5.9)	0.1	2 (2.7)	0.2
Peritonitis	282 (0.7)	17 (1.0)	0.1	0 (0.0)	0.7	2 (2.7)	0.2
Malabsorption	3,291 (7.9)	142 (8.6)	0.3	0 (0.0)	0.3	8 (10.7)	0.5
Abdominal discomfort	15,183 (36.3)	612 (37.0)	0.2	4 (35.2)	0.6	17 (22.7)	0.03
Diarrhea symptom	6,099 (14.6)	222 (13.4)	0.2	2 (10.2)	0.7	11 (14.7)	1.0

*Versus sequenced non-carriers

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



Diabetes													Total
Cases	0	0	0	1	0	6	0	2	0	0	0	0	10/9,948
Controls	1	1	3	3	1	33	1	4	1	2	2	3	55/26,198

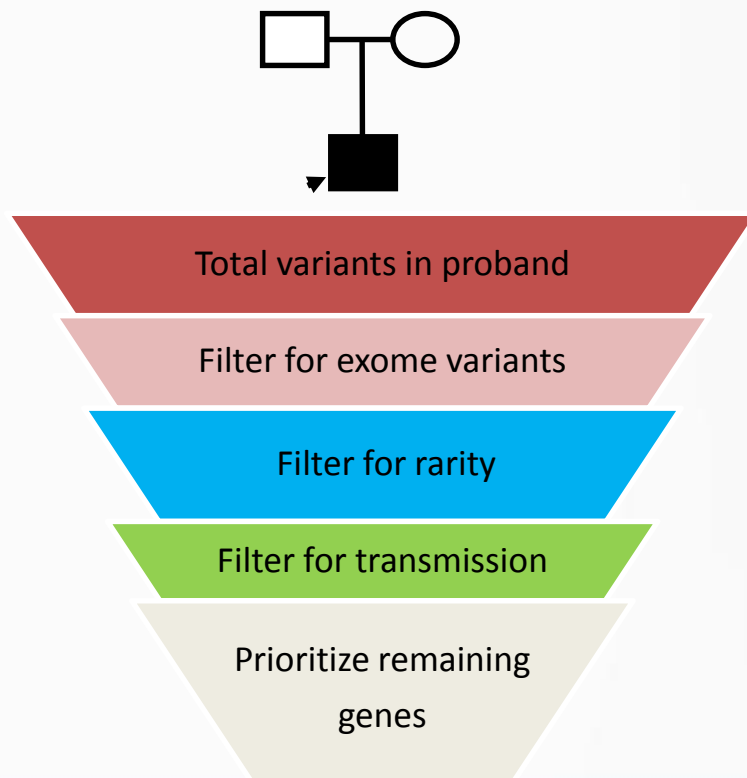
- **Take home points:**
 - The p.E40K variant was associated with ~15% reduced odds of diabetes per allele
 - Loss of function variant carriers had 58% reduced odds of diabetes

the	p.E40K (n = 1,661 heterozygotes and 17 homozygotes)				Heterozygous loss-of-function variants (n = 75)			
Disease	Allele Frequency: Cases	Allele Frequency: Controls	Odds Ratio* (95% CI)	P*	Allele Frequency: Cases	Allele Frequency: Controls	Odds Ratio* (95% CI)	P*
Type 2 diabetes	1.84 (355 hets, 6 homs)	2.06 (1,053 hets, 14 homs)	0.86 (0.76-0.99)	0.03	0.05 (10 hets)	0.11 (58 hets)	0.42 (0.19-0.83)	0.01

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

*Adjusted for age, age², sex, principal components of ancestry, and BMI.

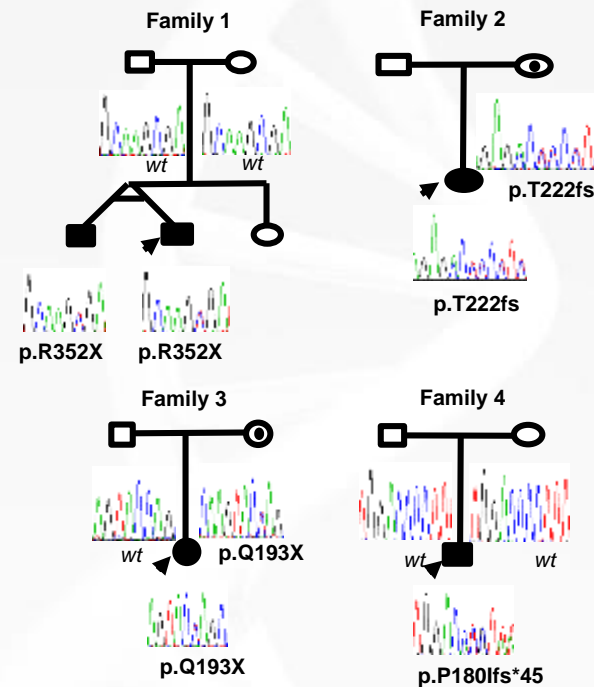
Insights From Whole Exome Sequencing in Mendelian Diseases Collaborations (CUMC, CSC & TSK)



Families/samples sequenced	756/5747
Families/samples analyzed	395/2049
Families with known causative variants	23 (15)
Families with novel variants in known disease genes	92 (32)
Families with novel disease genes	126
Families with multiple candidate genes	153

Gene Discovery in Familial Pediatric Onset Pulmonary Arterial Hypertension: *TBX4* Implicated in Multiple PAH Families

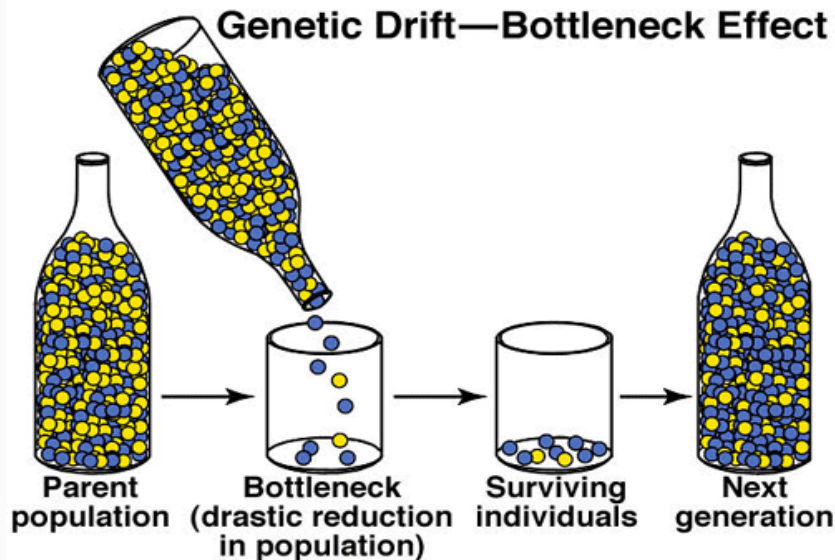
Family/Proband ID	VARIANT	INHERITANCE	DELETERIOUS PREDICTION	GHS ALLELE FREQUENCY
Family 1	c.C1054T; p.R352X	<i>de novo</i>	damaging	0
Family 2	c.664delA; p.T222fs	maternal	damaging	0
Family 3	c.C577T; p.Q193X	maternal	damaging	0
Family 4	c.537_546del; p.P180Ifs*45	<i>de novo</i>	damaging	0
Family 5	c.1070_1070 delC; p.S359Lfs*20	<i>de novo</i>	damaging	0
Family 6	c.C293G; p.P98R	<i>de novo</i>	damaging	0
Family 7	c.1115dupC; p.Pro372fs	paternal	damaging	0
Family 8	c.498_500delCTC; p.166_167delS	paternal	damaging	0
Singleton 1	c.702+1G>A (splicing)	unknown	damaging	0
Singleton 2	25.9kb deletion	unknown	damaging	0



- ~71 families and 192 singletons recruited through CUMC; enriched for pediatric onset PAH
- Rare, deleterious variants in *TBX4* identified in 16 different cases (10 families & 6 singletons)

Founder Populations: Stacking the Deck for Discovery of Novel Genes for Aging and Age-Related Phenotypes

Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.



- **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





Why Study Complex Diseases in the Amish?

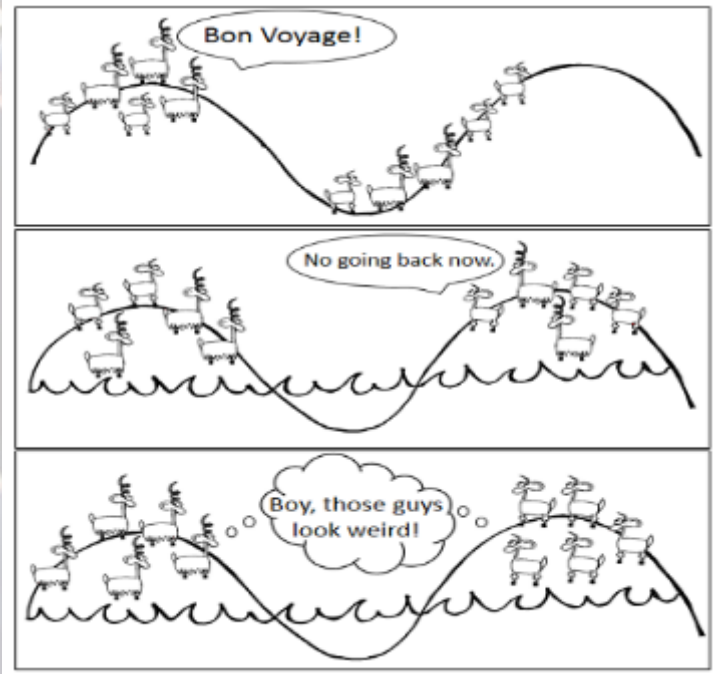


Why Study Complex Diseases in the Amish?

- A cultural isolate – traditional dress, no electricity, phones, cars
- Genetically homogeneous closed founder population



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

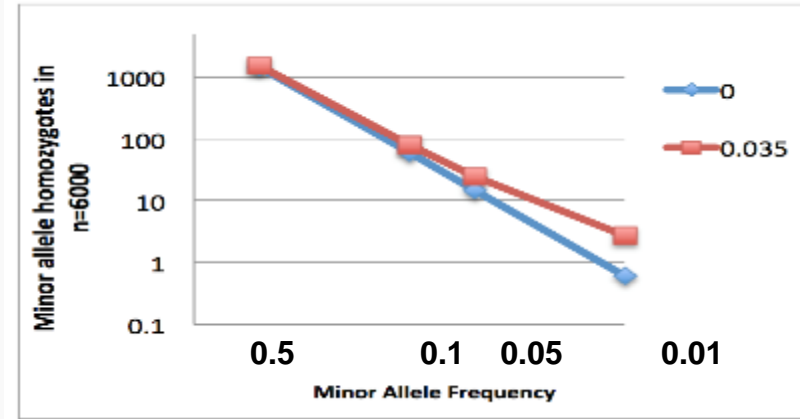
Why Study Complex Diseases in the Amish?



- 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

Old Order Amish Demography has Increased the Number of Some Minor Allele Homozygotes

- Alleles have drifted to higher frequency in the Amish, R3527Q *APOB*; R19X *APOC3*, L28P *DRK1B*, etc.
- Finite population size results in consanguinity, ~3.5% of each Amish genome is autozygous
- Example: allele drifts from 1% to 5% in the Amish, ~40 fold increase in minor allele homozygotes



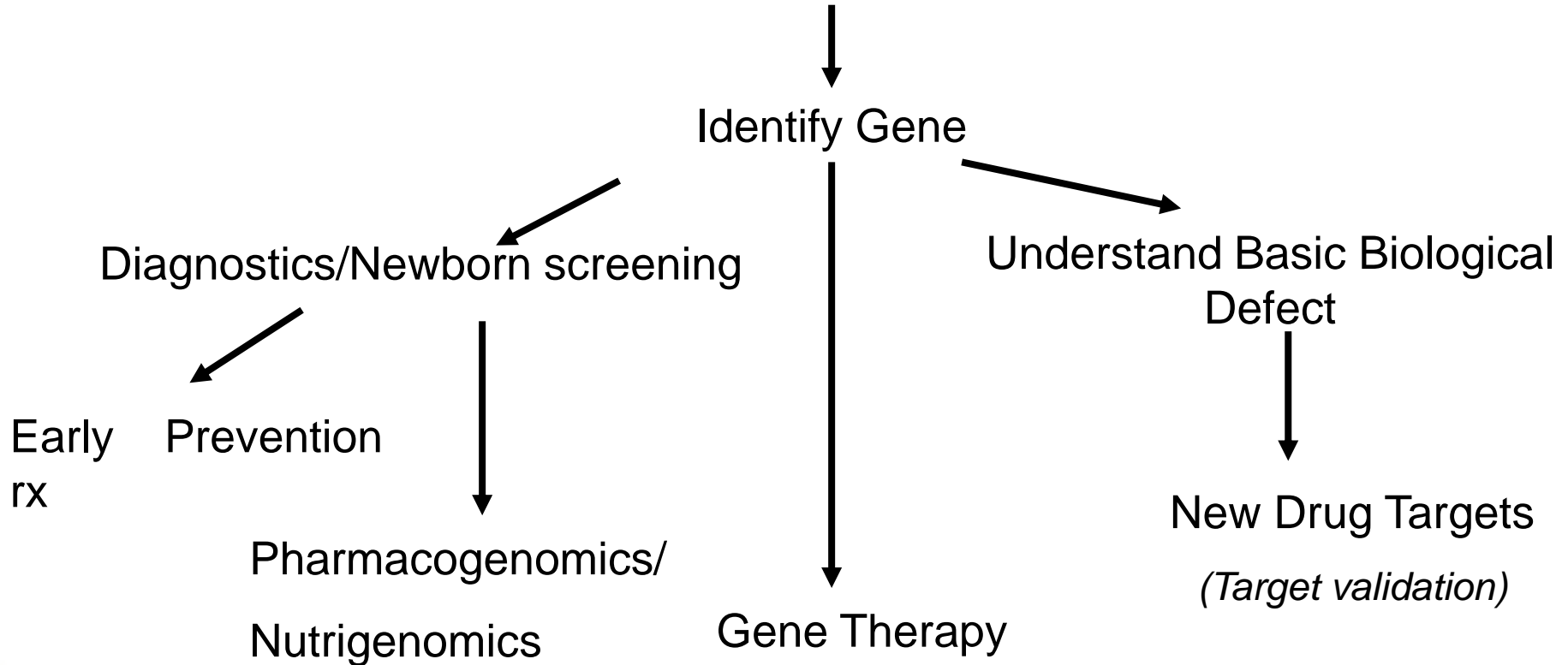
Expected minor allele homozygotes in n=6000

		Inbreeding Coefficient	
		0	0.035
MAF	0.5	1500	1553
	0.1	60	79
	0.05	15	25
	0.01	0.6	3



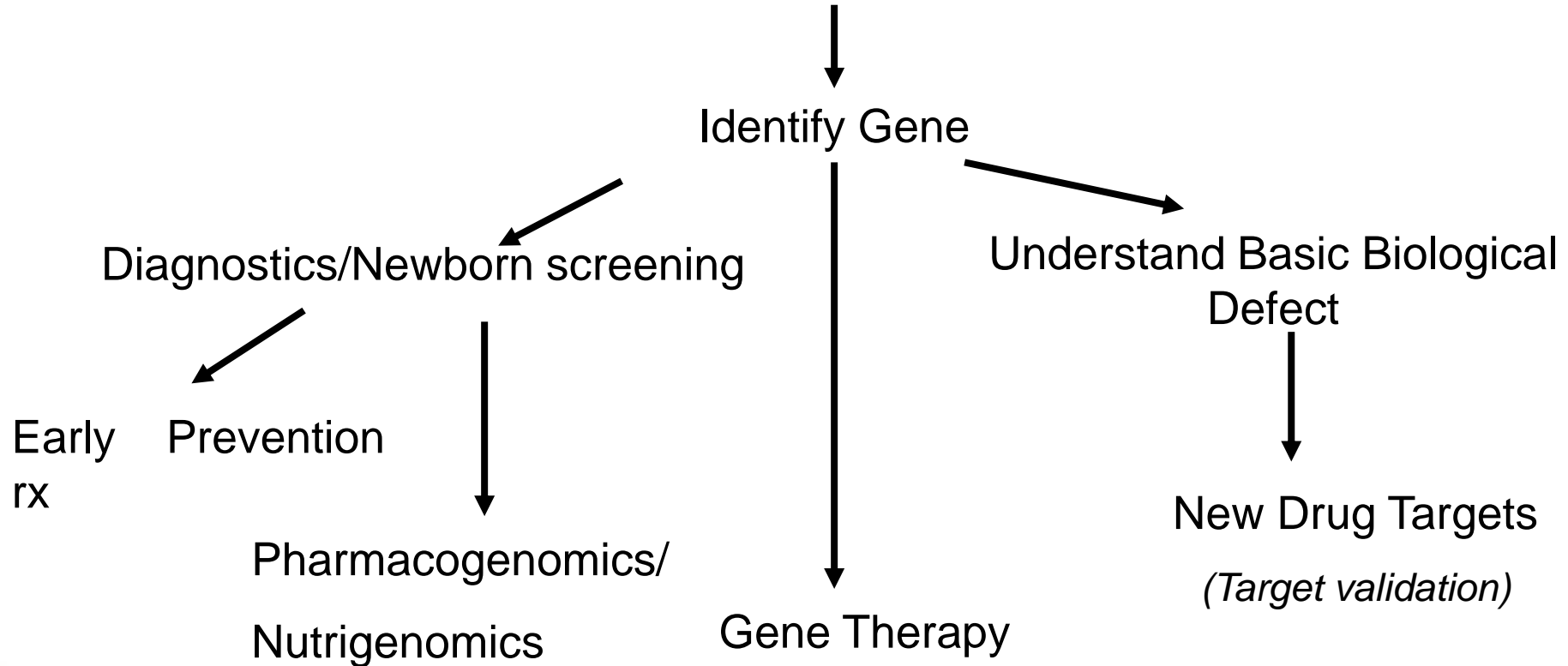
The Path to Personalized Medicine

Disease/Trait With Genetic Component



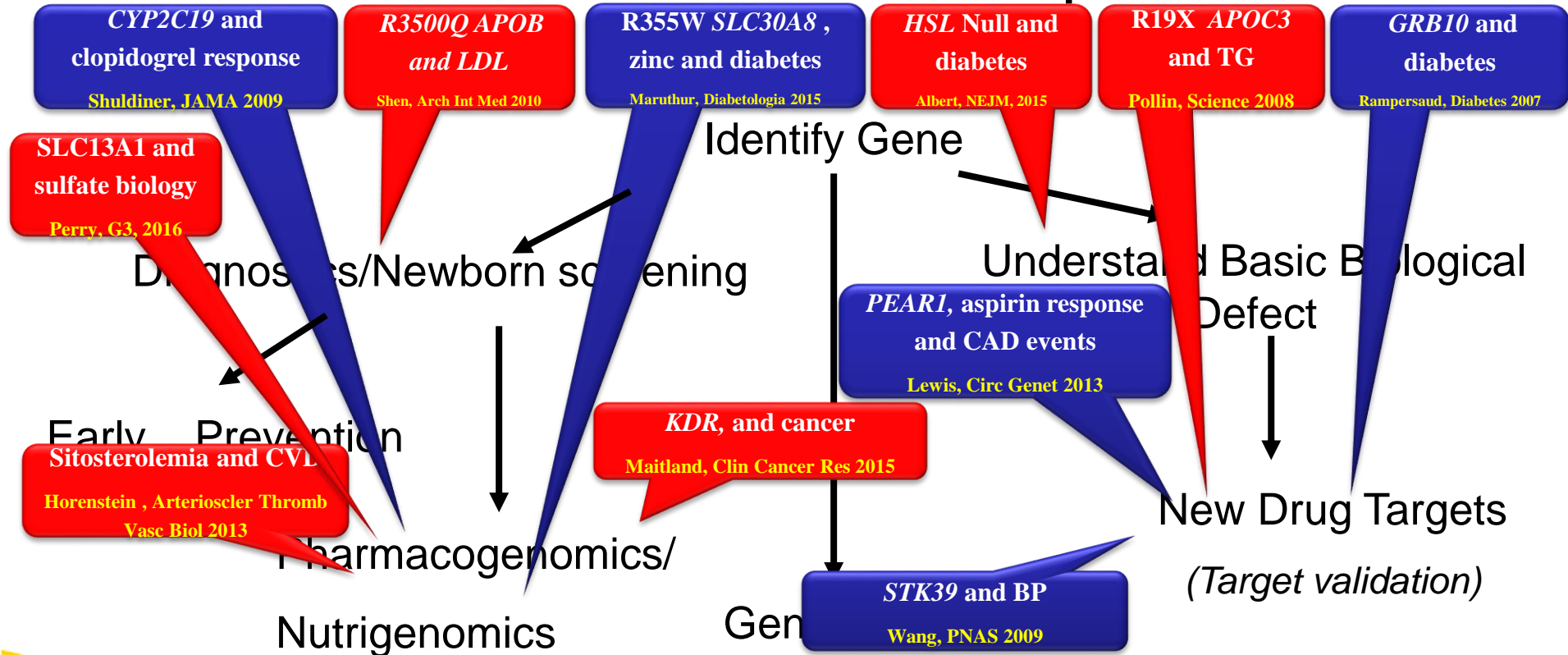
The Path to Personalized Medicine

Disease/Trait With Genetic Component



The Path to Personalized Medicine

Disease/Trait With Genetic Component



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)
- ~ 1 in 40 Amish carry T224M *KCNQ1*, which is highly associated with longer QT interval, a risk factor for syncope and sudden death

Novel genes for monogenic diseases that inform biology and therapeutic development (Strauss, Genetics in Medicine 2017)

- ~ 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)

Arch Intern Med. 2010; November 9; 130(22):1830-1838. doi:10.1001/archinternmed.2010.1681

Familial Defective Apolipoprotein B-100 and Increased Low-Density Lipoprotein Cholesterol and Coronary Artery Calcification in the Old Order Amish

Haining Shen, MD, PhD, G. L. Pollin, MS, PhD, Richard F. Lowrance, F. DiBiase, Kathleen A. Ryan, MPH, M. Shady, L. MD, John S. Bunker, D. Mitchell, PhD, Division of Endocrinology, Hematology, Metabolic, Clinical, and Cardiology (Dr. Pollin), Research and Education (Dr. Bunker), Baltimore, Maryland; Department of Health, Arts and Sciences (Dr. Ryan), School of Medicine, Johns Hopkins University (Dr. Mitchell); Darden, Princeton, New Jersey (Dr. Shen); and Department of Human Genetics (Dr. Shen), Johns Hopkins University (Dr. Shen).

Abstract

Background—Elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for coronary artery disease (CAD).

Methods—To identify the genetic basis of the elevated LDL-C in the Old Order Amish, we performed a genome-wide association study (GWAS) in a cohort of 1,000 Amish individuals.

Results—We identified a novel locus on chromosome 2p24.3 that is highly associated with LDL-C levels (P < 10⁻¹⁰).

A Null Mutation in Human *APOC3* Confers a Favorable Plasma Lipid Profile and Apparent Cardioprotection

Paul L. Pollin, Coleen M. Jones, Richard F. Lowrance, Kathleen A. Ryan, M. Shady, L. MD, John S. Bunker, D. Mitchell, PhD, Division of Endocrinology, Hematology, Metabolic, Clinical, and Cardiology (Dr. Pollin), Research and Education (Dr. Bunker), Baltimore, Maryland; Department of Health, Arts and Sciences (Dr. Ryan), School of Medicine, Johns Hopkins University (Dr. Mitchell); Darden, Princeton, New Jersey (Dr. Shen); and Department of Human Genetics (Dr. Shen), Johns Hopkins University (Dr. Shen).

Abstract—ApoC3 is a major component of low-density lipoprotein (LDL) particles and is a major determinant of plasma LDL levels. We have previously shown that a null mutation in the *APOC3* gene (R19X) is associated with a favorable plasma lipid profile and a reduced risk of coronary artery disease (CAD) in the Old Order Amish.

Methods—We performed a genome-wide association study (GWAS) in a cohort of 1,000 Amish individuals. We identified a novel locus on chromosome 2p24.3 that is highly associated with LDL-C levels (P < 10⁻¹⁰). We then performed a fine-mapping study and identified a null mutation in the *APOC3* gene (R19X) as the most likely causal variant.

Arch Intern Med. 2010; November 9; 130(22):1830-1838. doi:10.1001/archinternmed.2010.1681

ORIGINAL ARTICLE

Null Mutation in Hormone-Sensitive Lipase Gene and Risk of Type 2 Diabetes

Jessica S. Richard, B. Horenstein, Sambit Chai, M. Jeffrey R. O'Connell, Alice S. Ryan, Ph.D., and Carol A. Willer, Ph.D.

Division of Endocrinology and Metabolic Diseases

ORIGINAL RESEARCH ARTICLE

Genetics in Medicine

Genomic diagnostics within a medically underserved population: efficacy and implications

Kristin A. Springer, PhD, Claudia Gonzalez-Portugal, PhD, Kristin M. Springer, PhD, Kaitlin B. Horenstein, PhD, Anand K. Kishore, PhD, Christopher Van Hous, PhD, Doreen L. Robinson, PhD, M. L. Young, PhD, K. M. Pritchard, PhD, Adam D. Haines, PhD, Mandy Kulkarni, PhD, Amy Zerna, PhD, Jeffrey C. Hall, PhD, John D. Cawthon, PhD, Frederick T. Dewey, PhD, Robert M. Hines, PhD, Ian Hargreaves, PhD, Scott L. Meltz, MD, PhD, Alan R. Shuldiner, PhD, and Erik D. Poll-The, PhD

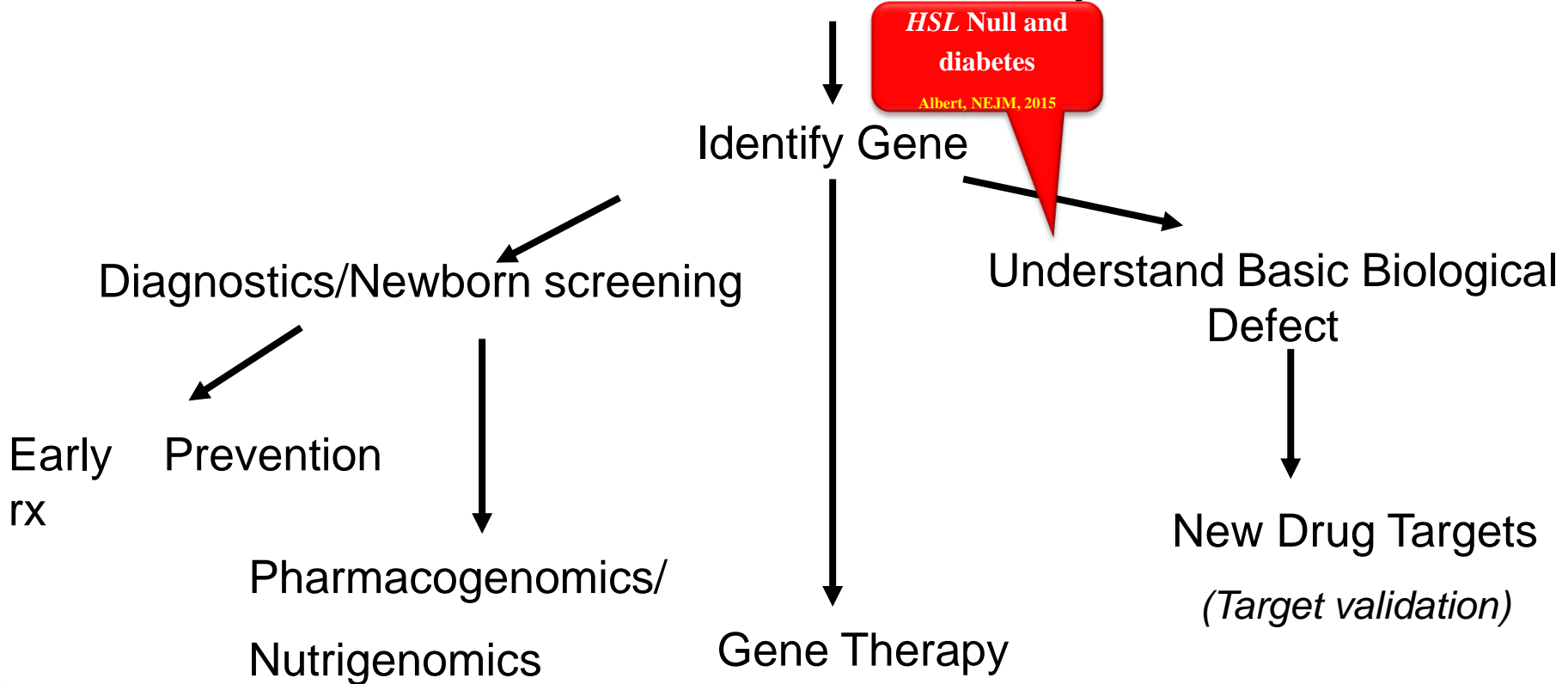
Purpose—We designed a genomic sequencing (NGS) and clinical genomics (CG) pipeline to identify monogenic and polygenic diseases in a medically underserved population. We performed a genome-wide association study (GWAS) in a cohort of 1,000 Amish individuals. We identified a novel locus on chromosome 2p24.3 that is highly associated with LDL-C levels (P < 10⁻¹⁰). We then performed a fine-mapping study and identified a null mutation in the *APOC3* gene (R19X) as the most likely causal variant.

Results—The null mutation in the *APOC3* gene (R19X) is associated with a favorable plasma lipid profile and a reduced risk of coronary artery disease (CAD) in the Old Order Amish. We performed a fine-mapping study and identified a null mutation in the *APOC3* gene (R19X) as the most likely causal variant.

Conclusion—We designed a genomic sequencing (NGS) and clinical genomics (CG) pipeline to identify monogenic and polygenic diseases in a medically underserved population. We performed a genome-wide association study (GWAS) in a cohort of 1,000 Amish individuals. We identified a novel locus on chromosome 2p24.3 that is highly associated with LDL-C levels (P < 10⁻¹⁰). We then performed a fine-mapping study and identified a null mutation in the *APOC3* gene (R19X) as the most likely causal variant.

The Path to Personalized Medicine

Disease/Trait With Genetic Component



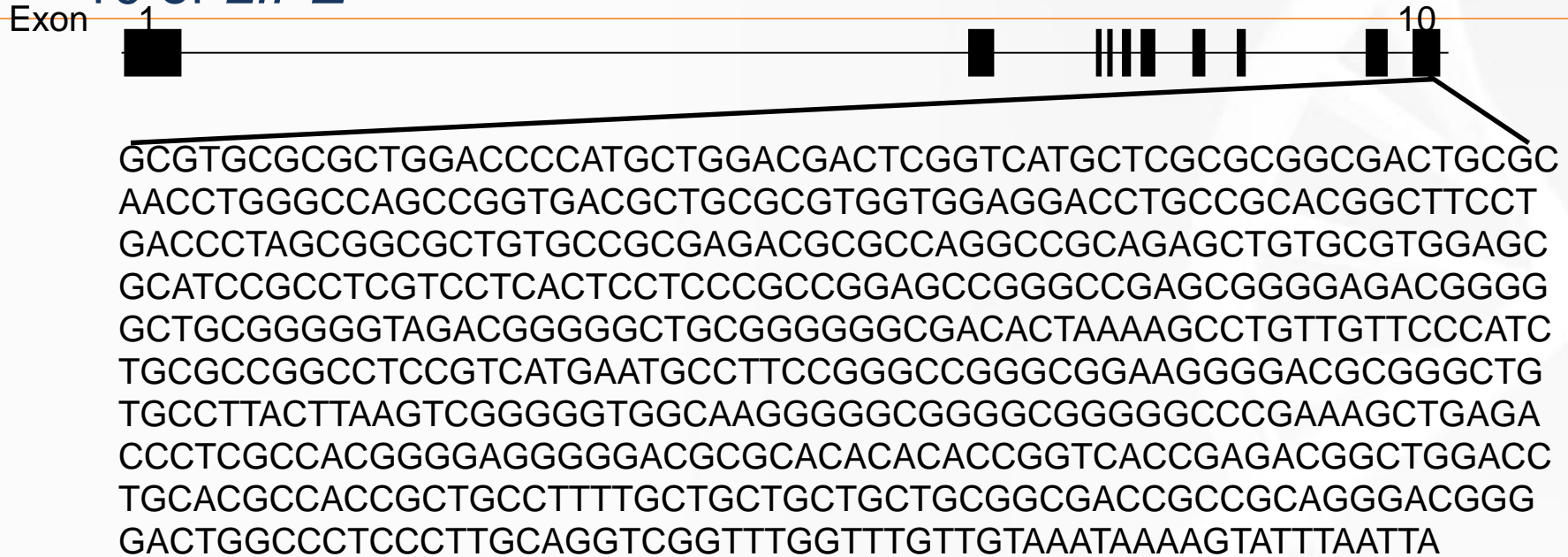
ORIGINAL ARTICLE

Null Mutation in Hormone-Sensitive Lipase Gene and Risk of Type 2 Diabetes

Jessica S. Albert, Ph.D., Laura M. Yerges-Armstrong, Ph.D.,
Richard B. Horenstein, M.D., Toni I. Pollin, Ph.D., Urmila T. Sreenivasan, M.S.,
Sumbul Chai, M.S., William S. Blaner, Ph.D., Soren Snitker, M.D., Ph.D.,
Jeffrey R. O'Connell, Ph.D., Da-Wei Gong, Ph.D., Richard J. Breyer III, M.D.,
Alice S. Ryan, Ph.D., John C. McLenithan, Ph.D., Alan R. Shuldiner, M.D.,
Carole Sztalryd, Ph.D., and Coleen M. Damcott, Ph.D.

June 2014

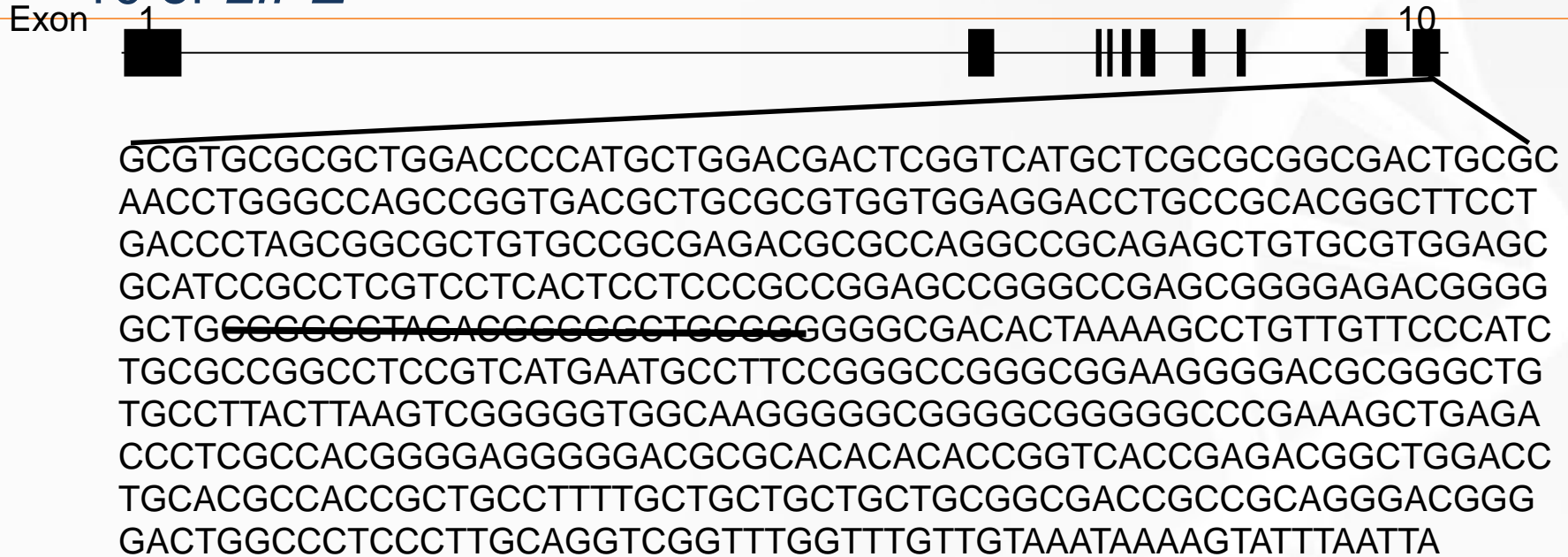
19 base pair deletion (p.V1068GfsX19) identified in exon 10 of *LIPE*



HSL



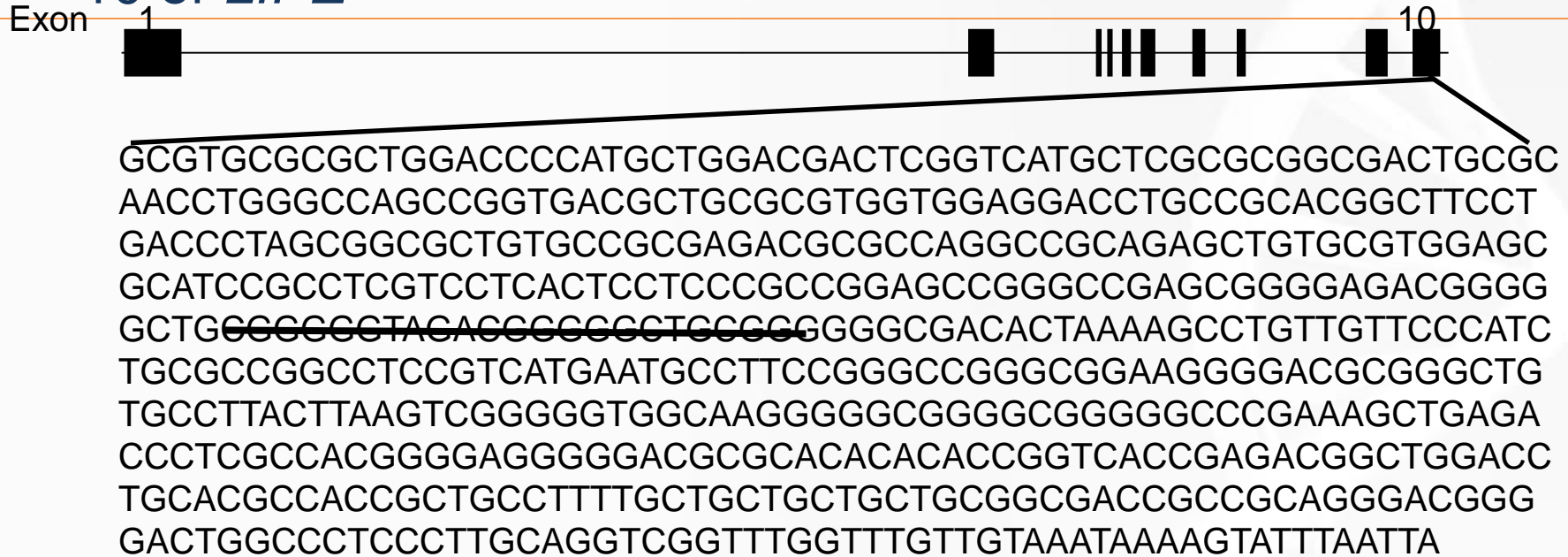
19 base pair deletion (p.V1068GfsX19) identified in exon 10 of *LIPE*



HSL



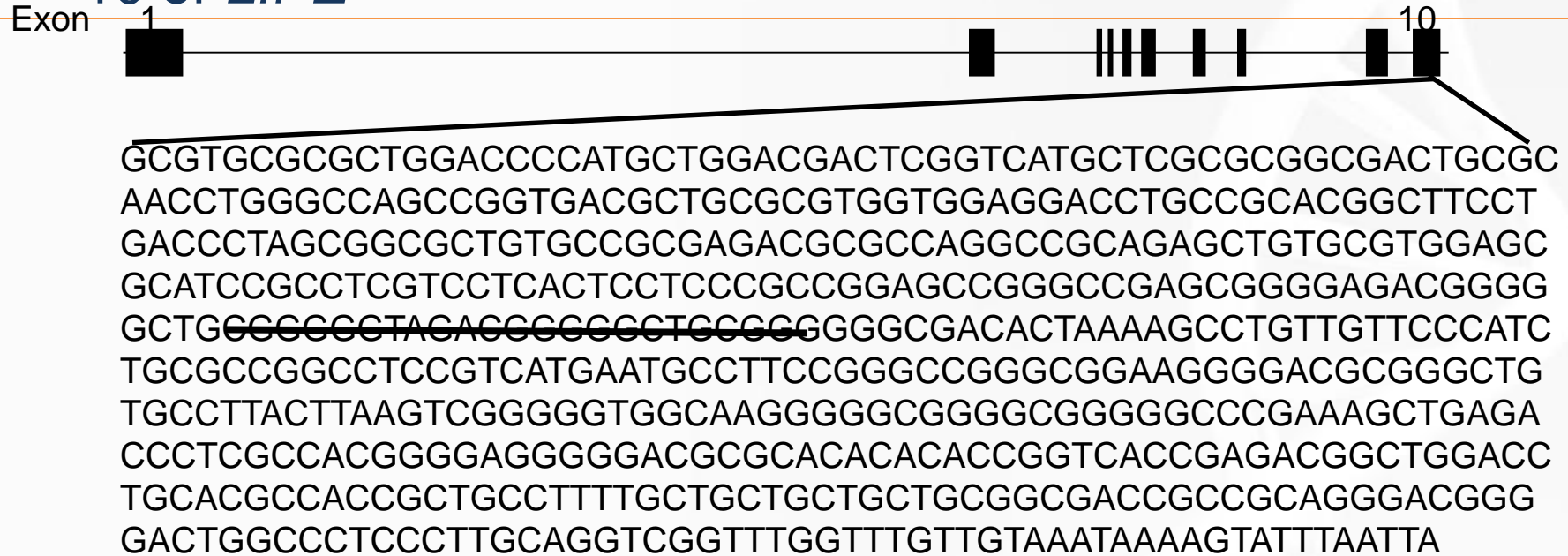
19 base pair deletion (p.V1068GfsX19) identified in exon 10 of *LIPE*



HSL ACALDPMLDDSVMLARRLRNLGQPVTLRVVEDLPHGFLTLAALCRETRQAAELCVERIR
LVLTPPAGAGPSGETGAAGVDGGCGGRH



19 base pair deletion (p.V1068GfsX19) identified in exon 10 of *LIPE*



HSL ACALDPMLDDSVMLARRLRNLGQPVTLRVVEDLPHGFLTLAALCRETRQAAELCVERIR
LVLTPPAGAGPSGETGAAGVDGGCGGRH



19 base pair deletion (p.V1068GfsX19) identified in exon 10 of *LIPE*



HSL ACALDPMLDDSVMLARRLRNLGQPVTLRVVEDLPHGFLTLAALCRETRQAAELCVERIR
LVLTPPAGAGPSGETGAAGVDGGCGGRH



GDTKSLLFPSAPASVMNAFRAGRKGTRAVPYLSRGWQGGGAGARKLRPSPRGGGRAHTPVT
ETAGPARHRCLLLLLRRPPQGRGLALPCRSVWFVNKSI

FABP4

19 base pair deletion (p.V1068GfsX19) identified in exon 10 of *LIPE*

Exon



GCGTGCGCGCTGGACCCCATGCTGGACGACTCGGTCATGCTCGCGCGGCGACTGCGC
AACCTGGGCCAGCCGGTGACGCTGCGCGTGGTGGAGGACCTGCCGCACGGCTTCCT
GACCCTA
GCATCC
GCTGCG
TGCGCC
TGCCTTA
CCCTCGC
TGCACGCCACCGCTGCCTTTTGCTGCTGCTGCTGCGGCGACCGCCGCAGGGACGGG
GACTGGCCCTCCCTTGCAGGTCGGTTTGGTTTGTGTAATAAAAGTATTTAATTA

Amish carrier frequency = 0.013

(4 homozygotes)

GHS carrier frequency 0.00073

(No homozygotes)

HSL ACALDPMLDDSVMLARRLRNLGQPVTLRVVEDLPHGFLTAAALCRETRQAAELCVERIR
LVLTPPAGAGPSGETGAAGVDGGCGGRH



GDTKSLLFPSAPASVMNAFRAGRKGTRAVPYLSRGWQGGGAGARKLRPSPRGGGRAHTPVT
ETAGPARHRCLLLLLRRPPQGRGLALPCRSVWFVNKSI

HSL knockout mouse

General

- Non-obese
- Male infertility

Adipose tissue

- Decreased lipolysis
- Increased DAG
- Decreased cholesterol esterase activity



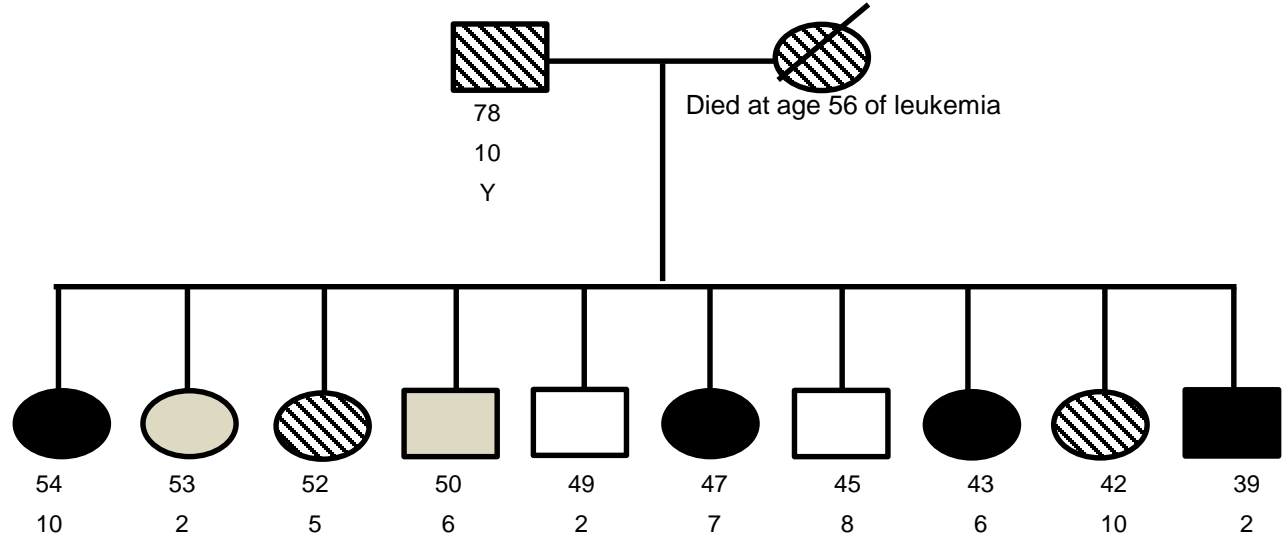
Systemic

- Normoglycemic
- Normoinsulinemic
- Decreased TAG
- Increased HDL

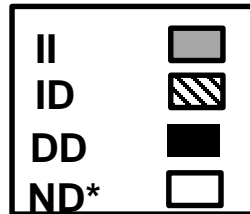


Mating of heterozygous HSL Homo Sapiens

Age (2009):
Number of Children:
Diagnosed diabetes:



Age (2009):
Number of Children:

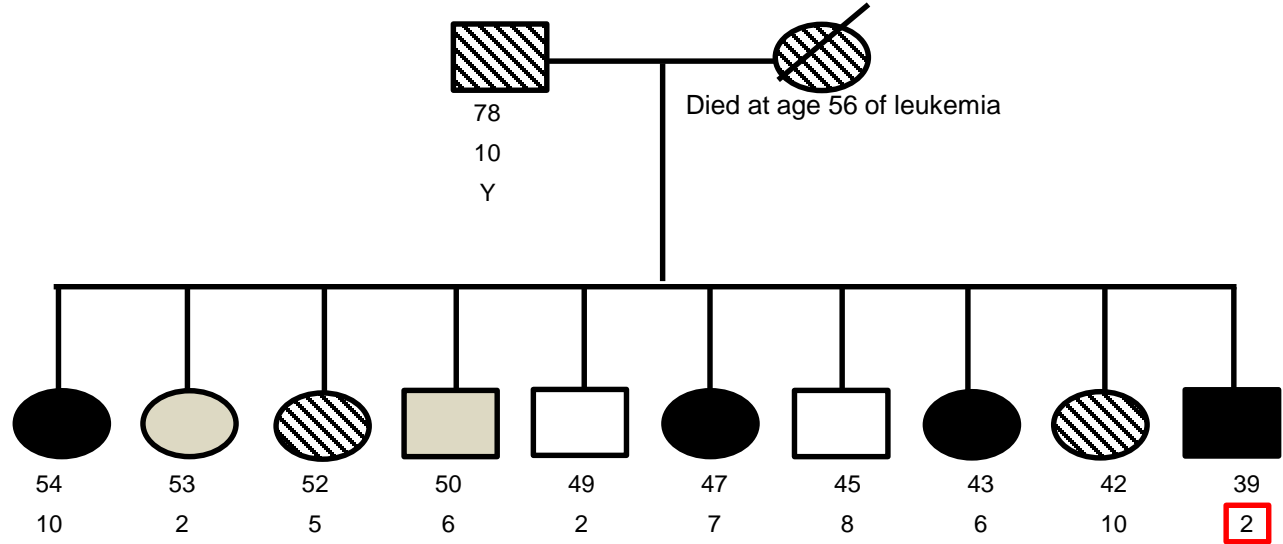


*not yet determined

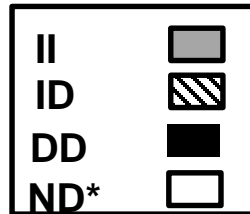


Mating of heterozygous HSL Homo Sapiens

Age (2009):
Number of Children:
Diagnosed diabetes:



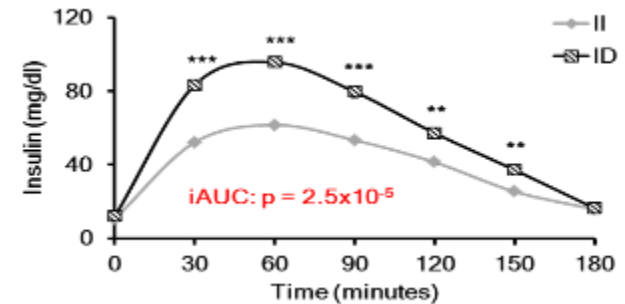
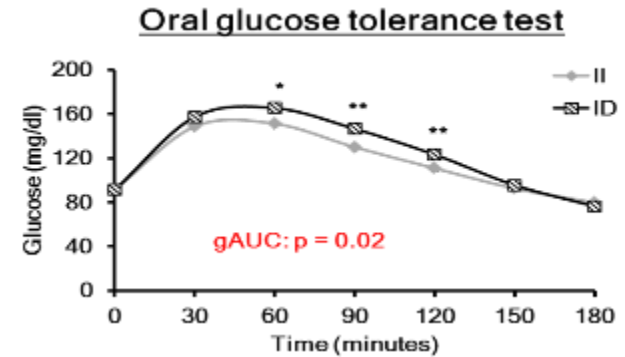
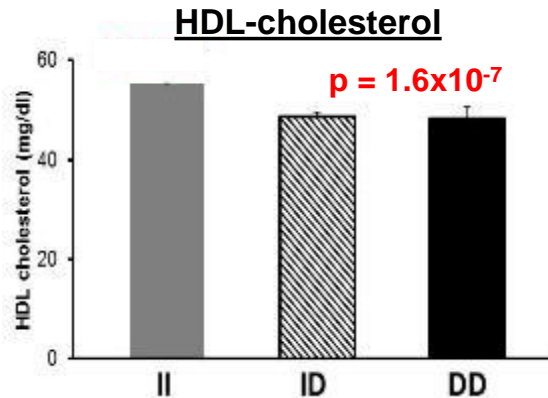
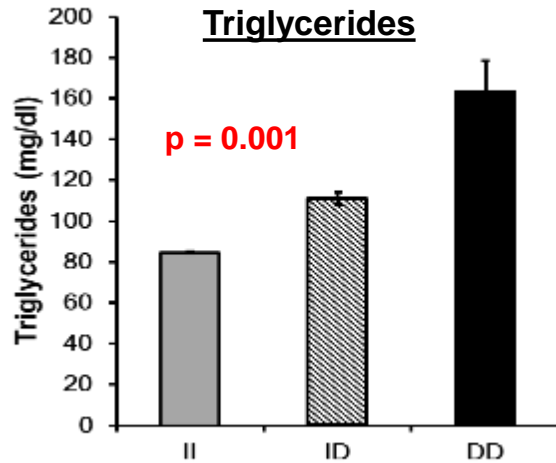
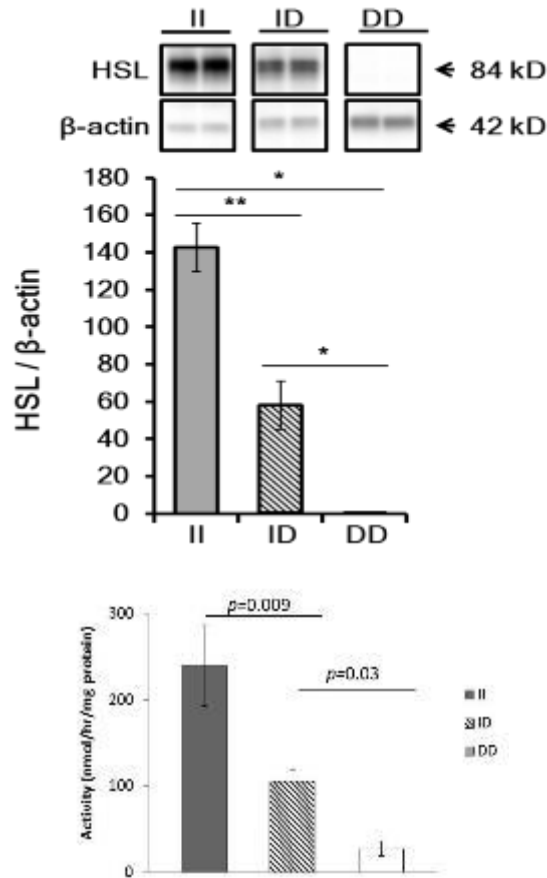
Age (2009):
Number of Children:



*not yet determined



p.V1068GfsX19 HSL is a Null Mutation



OR for DM = 2.0; p = 0.02

Albert et al, NEJM, 2014

Current age:
Number of children:
Diagnosed diabetes:

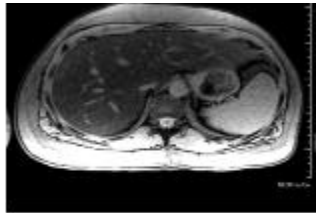


Subject number	1	2	3	4	5	6	7	8	9	10
Current age	46	49	56	44	53	55	42	51	47	52
BMI (kg/m ²)	27	28	27	31	23	23	29	22	24	29
Body Fat (%)	31.3	33.2	33.6	40.8	36.8	36.3	21.1	13.4	16.2	30.6
VAT (cm ²)	82.7	-	89	74.6	76.6	77.3	64.8	-	43.5	53.4
Abdominal SAT (cm ²)	276	-	318	316	205	212	193	-	79.9	222
Calf SAT (cm ²)	14.7	-	7.7	33.6	22.6	21.5	8.6	-	13.8	23.4
Abdominal SAT:Calf SAT	18.8	-	41.4	9.4	9.1	9.9	22.3	-	5.8	9.5
Liver Fat (%)	9.4	-	25.3	3.7	2.8	2.8	3.5	-	2.4	1.7
Adiponectin (μg/ml)	4.3	-	3.6	10.9	28	17.5	4.7	22.4	10.5	17.9
Leptin (ng/ml)	4.6	4.8	9.2	18.9	6.3	9	1.8	0.6	0.8	4.6
Fasting triglycerides (mg/dl)	148	152	256	81	140	109	193	53	73	146
HDL Cholesterol (mg/dl)	52	53	40	53	69	70	46	65	70	70
Fasting insulin (μU/ml)	7.9	20.3	15	7.6	2.6	9.1	5.6	3.3	4.6	-
Fasting glucose (mg/dl)	98	125	256	102	84	86	202	90	93	85
HOMA-IR	1.9	6.3	9.5	1.9	0.5	1.9	2.8	0.7	1.1	-
2-hr OGTT glucose (mg/dl)	204	-	-	140	119	101	470	112	150	107
Diagnosed diabetes (Age)	Y (46)	Y (46)	Y (48)	IGT	N	N	Y (40)	N	N	N
Number of offspring:	6	7	10	10	5	2	2	2	8	6

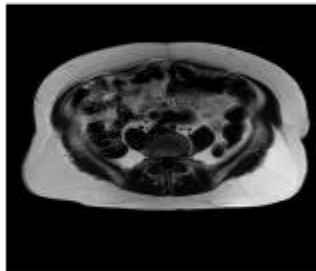
Increased liver and visceral fat; decreased LE fat in DD homozygotes

MRI

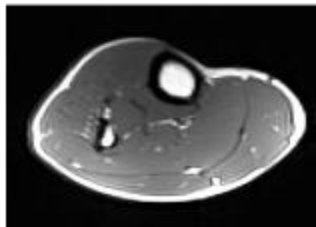
DD
Age 56
BMI 27 kg/m²



Liver
(25.3% vs 2.8% fat)

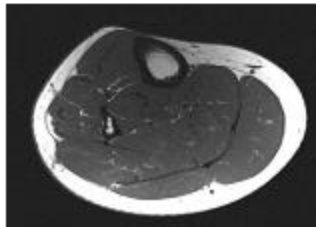
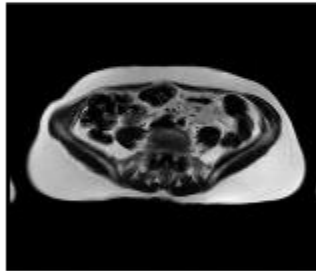
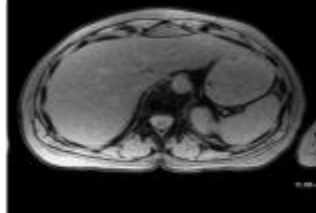


L4-L5/visceral fat
(89.0 cm² vs. 77.3 cm²)

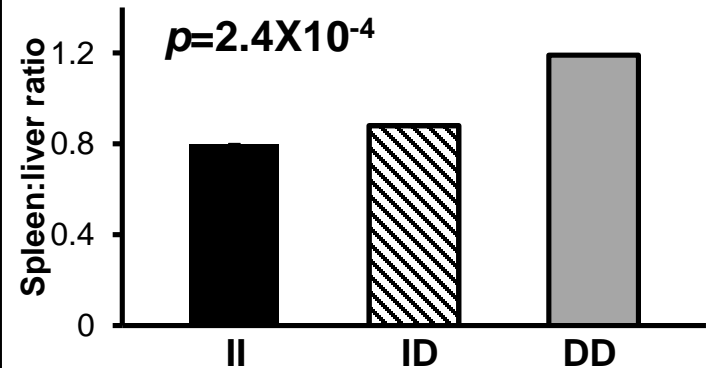
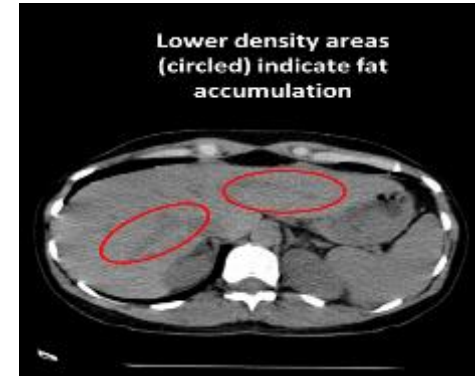


Calf
7.7 cm² vs 21.5 cm²

II
Age 55
BMI 23 kg/m²



CT

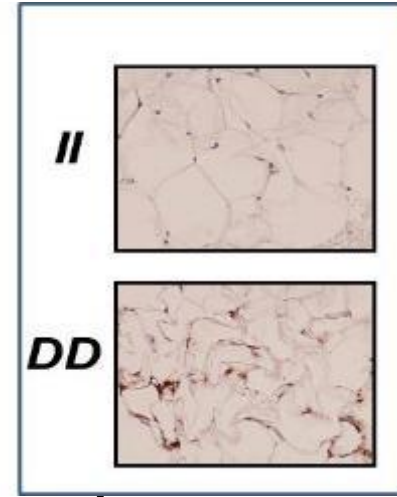


Albert et al, NEJM, 2014

Unexpected effect of HSL deficiency on adipocyte function



Liberase



↑ WAT
cytokine
release

↑ Infiltration by
macrophages

↓ Expression of
PPAR γ - regulated
genes

↓ Lipolysis

↓ Fat cell
size

↓ Adipocyte
insulin
sensitivity



Unexpected effect of HSL deficiency on adipocyte function

Implications:

In addition to its metabolic function, HSL may have an endocrine function to generate endogenous ligands for PPAR γ

Opportunity to identify endogenous ligand(s) for PPAR γ as next diabetes therapeutic

HSL KO (or deficient) humans with diabetes should respond well to PPAR γ agonists (thiazolidinediones)

HSL activators as therapeutic to decrease TG and increase insulin sensitivity and glucose tolerance in patients with diabetes

Building the World's Largest Founder Population Collection for Discovery of Novel Disease-associated Genetic Variants:

Discovery Research Investigating Founder Population Traits (DRIFT) Goals



- 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)
 - Replicate/extension in larger general population
 - “Genotype-first” call back studies
- Share and establish best practice approaches to relieve disease burden in these populations

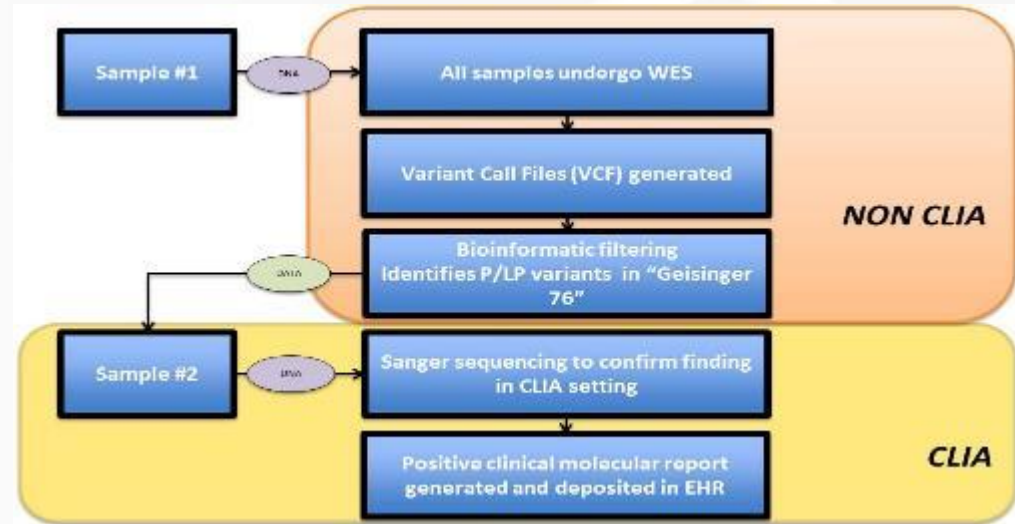
The Future of Precision Medicine is Here Today

The GHS
Genome-First
Return of Results
Program



Geisinger GenomeFirst Program

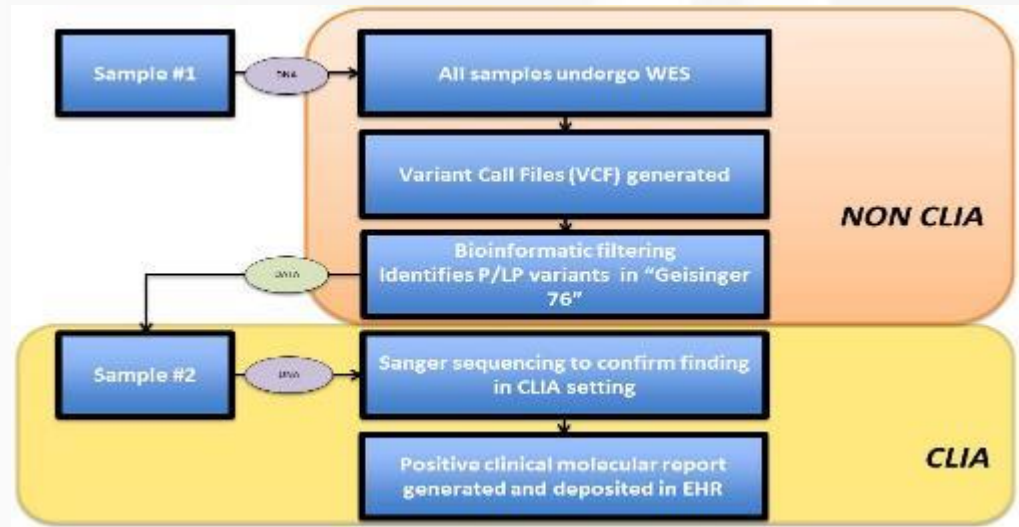
- Informed consent specifies intent to return results that are medically actionable after CLIA confirmation
- Geisinger will NOT return results that are NOT medically actionable
- Geisinger experts will decide what to return
 - Geisinger “76” (56 ACMG + 20) genes causative of 27 diseases that are medically 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 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



Geisinger 76: 1 in 25 Patients Have an Actionable Result

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

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



RESEARCH ARTICLE SUMMARY

Science



HUMAN GENETICS

Genetic identification of familial hypercholesterolemia within a single U.S. health care system

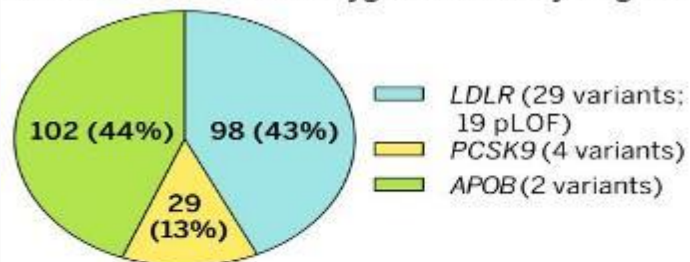
Noura S. Abul-Husn, Kandamurugu Manickam, Laney K. Jones, Eric A. Wright, Dustin N. Hartzel, Claudia Gonzaga-Jauregui, Colm O'Dushlaine, Joseph B. Leader, H. Lester Kirchner, D'Andra M. Lindbuchler, Marci L. Barr, Monica A. Giovanni, Marylyn D. Ritchie, John D. Overton, Jeffrey G. Reid, Raghu P. R. Metpally, Amr H. Wardeh, Ingrid B. Borecki, George D. Yancopoulos, Aris Baras, Alan R. Shuldiner, Omri Gottesman, David H. Ledbetter, David J. Carey, Frederick E. Dewey, Michael F. Murray*

Abul-Husn, et al, Science 2016

Prevalence and Clinical Impact of FH Variants in DiscovEHR

A

Distribution of 229 heterozygous carriers by FH gene

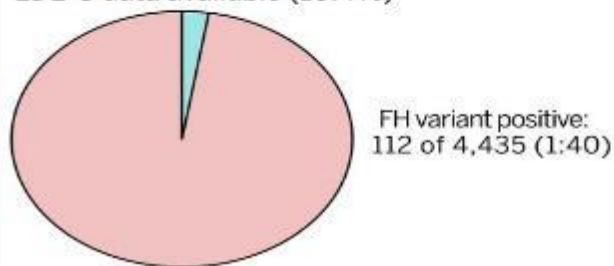


B

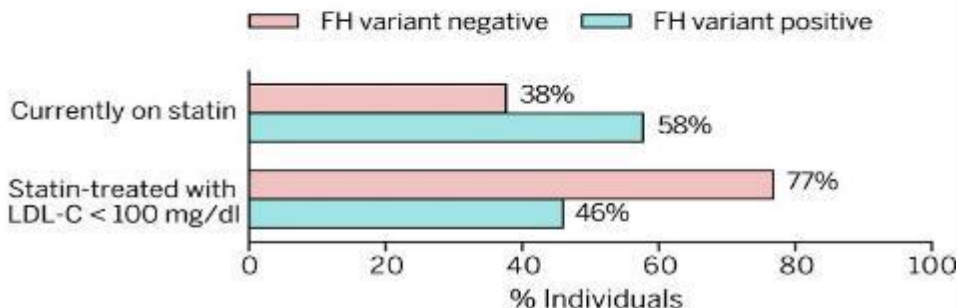
Population characteristics	FH variant positive/total	Estimated prevalence
All DiscovEHR participants	229/50,726	1:222
Participants recruited from cardiac catheterization lab	57/6,747	1:118
Participants recruited from other sites	172/43,979	1:256

C

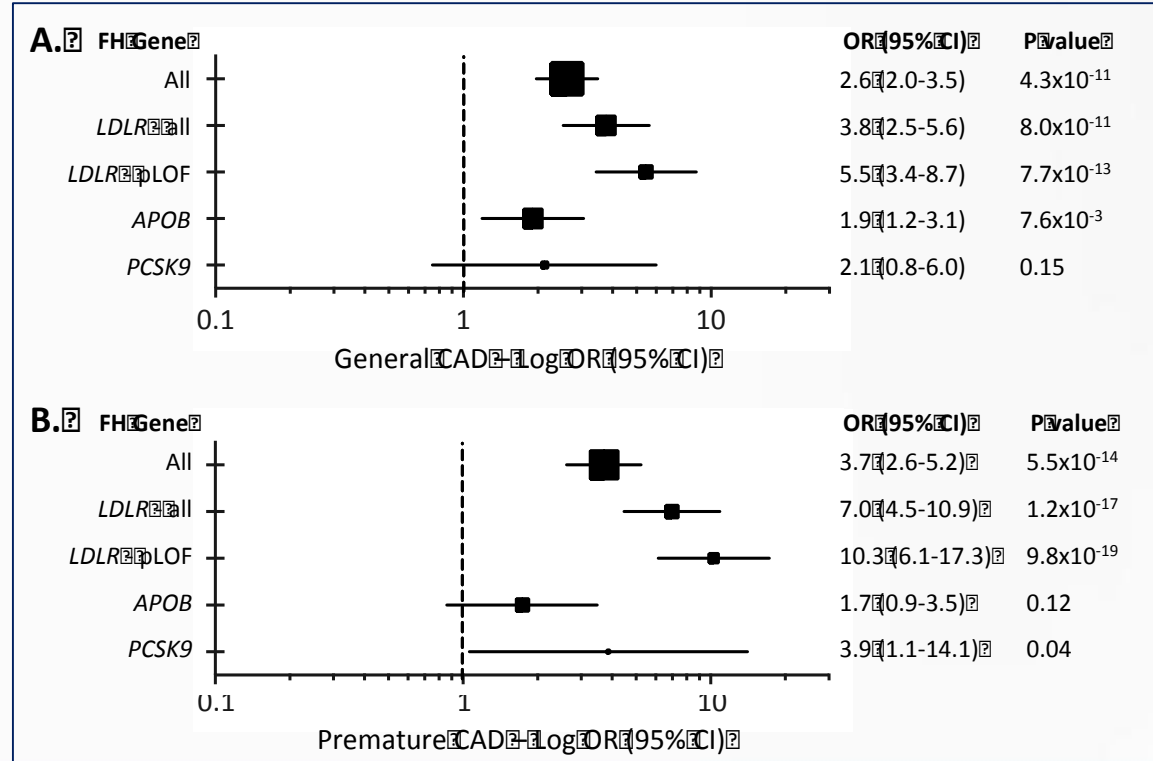
Participants with severe hypercholesterolemia (LDL-C > 190 mg/dl)
N = 4,435 of 42,696 individuals with LDL-C data available (10.4%)



D



Why GenomeFirst Is Important: Most patients with FH are not diagnosed and treated inadequately



- 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

Acknowledgements – Regeneron and Collaborators

Thank you to the thousands of patients, volunteers, collaborators, investigators, and scientists who make this work possible

➤ RGC Leadership

Aris Baras
Rick Dewey
Aris Economides
John Overton
Jeff Reid
Alan Shuldiner

➤ Regeneron Team (all but especially)

Noura Abul-Husn	Alejandra King
Xiadong Bai	Alexander Lopez
Suganthi Balasubramanian	Evan Maxwell
Shannon Bruse	Lyndon Mitnaul
Rostislav Chernomorsky	Semanti Mukherjee
Jonathan Chung	Colm O'Dushlaine
Jan Freudenberg	Chiatogu Onyewu
Jesper Gromada	Jonathan Packer
Claudia Gonzaga-Jauregui	John Penn
Nehal Gosalia	Christopher Sprangel
Viktoria Gusalova	Jeffrey Staples
Lukas Habegger	Tanya Teslovich
Julie Horowitz	Ricardo Ulloa
Marcus Jones	Cristopher Van Hout

➤ Geisinger Health System

David J. Carey
David H. Ledbetter
Michael Murray
Marylyn D. Ritchie
Marc Williams
W. Andrew Faucett
Sarah A. Pendergrass
Chris Still
Tooraj Mirshahi
H. Lester Kirchner
Joseph B. Leader
G. Craig Wood
Lance J. Adams
Peter Benotti
Vishal C. Mehra
Raghu Metpally
Uyenlinh L. Mirshahi
Cassandra M Hartle
F. Daniel Davis
Daniel R. Lavage
Dustin Hartzel
John Snyder
Neil Manus
Ryan D. Colonie

➤ Columbia University

Wendy Chung
Rudy Leibel

Acknowledgements – University of Maryland

**Jess Albert
Coleen Damcott
Julie Ducharme
Adam Fisch
Susan Fried
Mao Fu
Amish Gandhi
Da-Wei Gong
Kristen Hairston
Amanda Holmes
Nicole Hoppman
Richard Horenstein
Hong Hu
Yasmin Khan
Jie Liu**

**Patrick McArdle
Daniel McBride
John McLenithan
Cary McMahon
Braxton Mitchell
Karen Norton
Jeffrey O'Connell
Sandra Ott
Christina Perry
Toni Pollin
Evadnie Rampersaud
Laurie Reinhart
Kathy Ryan
Mona Sabra
Larry Sauder
Jack Shelton**

**Haiqing Shen
Julia Shi
Kristi Silver
John Sorkin
Soren Snitker
Nanette Steinle
Elizabeth Streeten
Carole Sztalryd
Keith Tanner
Magnda Tolea
Robert Vogel
Matthew Weir
Rongze Yang
DiaoZhan Yu
Li Zhang
Joe Zhao**