

The NHGRI Intramural Research Program: A Quarter Century of Genomics at the NIH

Dan Kastner, MD, PhD

NHGRI/NIH/DHHS

May 21, 2018

In the beginning . . .

- Established by Francis Collins in 1993 when he became Director of what was then the NCHGR
- Goals:
 - To capitalize on the unique resources of the Intramural environment to establish a world-class program in genetics, genomics, and genomic medicine
 - To catalyze the ‘genomic transformation’ of the Intramural Programs of the other NIH Institutes
 - To serve as an incubator for programs that could be exported to the broader genomics community
- Deliberately larger than other Intramural Programs, relative to the size of the Institute

Distinctive Features of Intramural NIH

- Institutional commitment to researchers over projects
- Quadrennial heavily retrospective review
- Long-term studies that require stable funding
- High-risk, high-reward projects that would be difficult to do with R01 funding
- Specialized resources

The NIH Clinical Center



Nuts and Bolts of the NHGRI IRP

- 22 Tenured Senior-Investigators (5 NAM, 2 NAS), 3 Tenure-Track Investigators, 3 Senior Scientists, 13 Associate Investigators, 9 Adjunct Investigators
- 8 cores (Bioethics, Bioinformatics, Flow Cytometry, Gene Expression, Genomics, Microscopy, Transgenic Mouse, Zebrafish)
- NIH Intramural Sequencing Center (Illumina NovaSeq 6000, PacBio Sequel, Oxford Nanopore GridION)
- ~ 540 total staff
- FY2018 appropriated budget of ~\$113.7 M
- 7 buildings on the NIH campus, plus off-campus facilities in Rockville and Baltimore

NIH Leaders with Labs in the NHGRI DIR



Diana Bianchi, NICHD



Francis Collins, NIH



Gary Gibbons, NHLBI



**Harold Varmus, NIH,
NCI**



Betsy Nabel, NHLBI

Positional Cloning of *MEFV*, the Gene Mutated in Familial Mediterranean Fever (FMF)

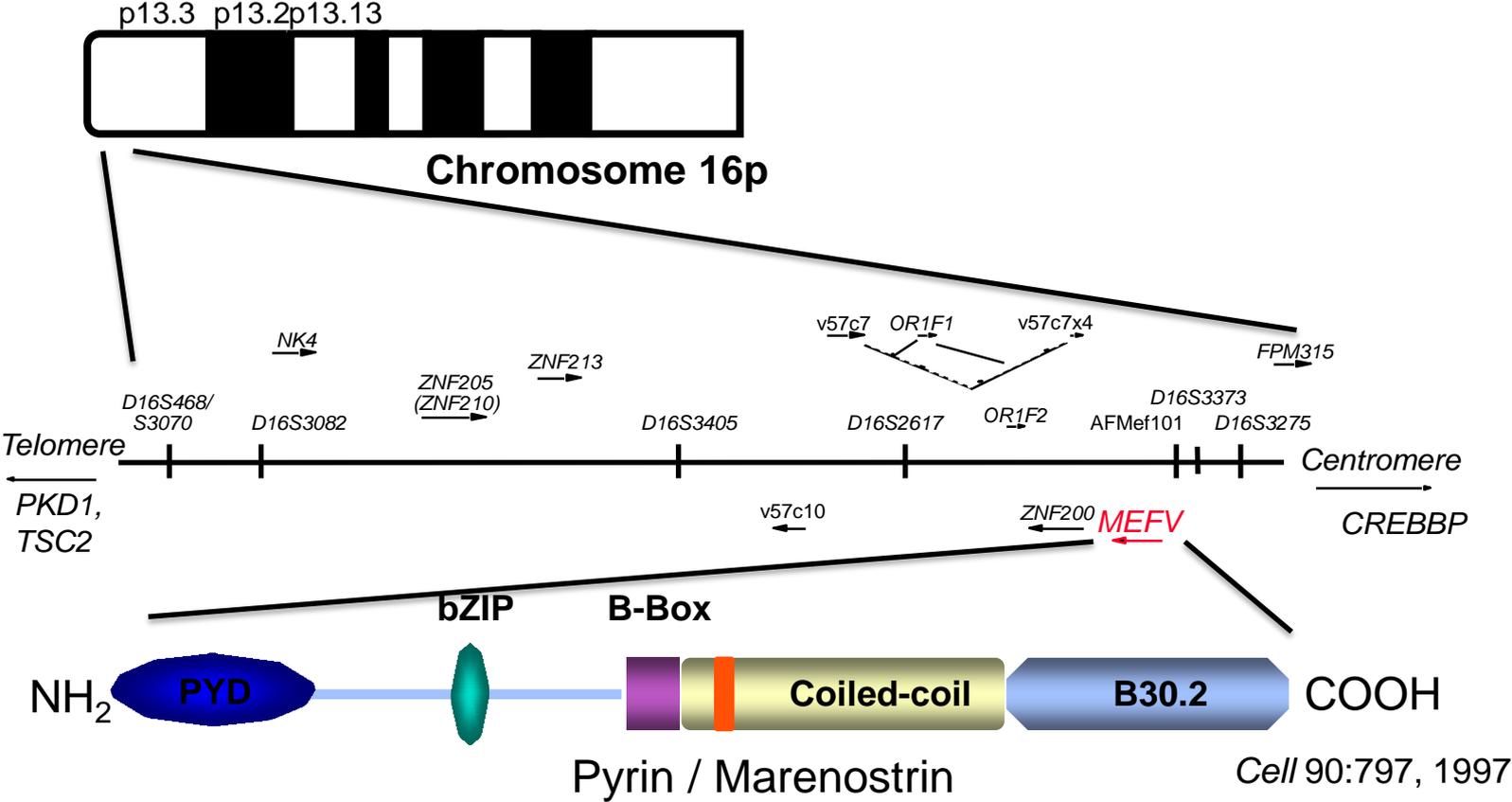
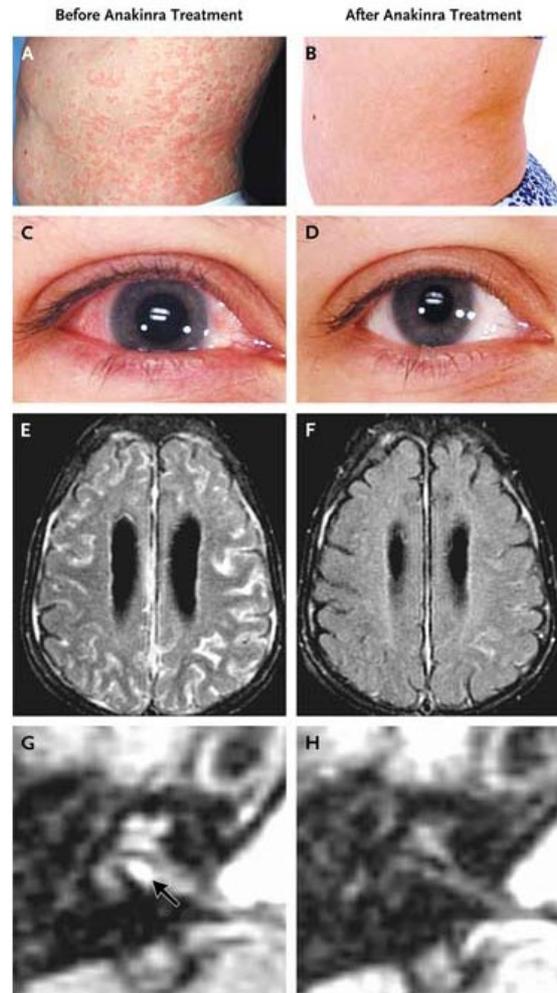


Table 1 Autoinflammatory diseases

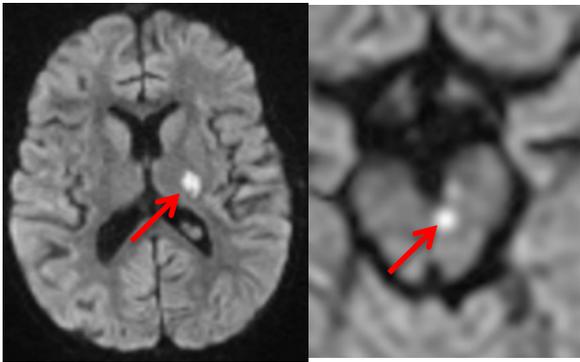
Disease	Gene/protein	Phenotype	Mechanism of disease
FMF	<i>MEFV</i> /Pyrin	Fever, serositis, rash, SAA amyloidosis	Activation of pyrin inflammasome; IL-1 β ↑
PAAND	<i>MEFV</i> /Pyrin	Fever, pyoderma, acne, arthralgia, myalgia	Constitutive activation of pyrin inflammasome; IL-1 β ↑
FKLC,MSPC	<i>NLRP1</i> /NLRP1	Hyperkeratotic ulcerative skin lesions on palms and soles	Constitutive activation of NLRP1 inflammasome; IL-1 β ↑
CAPS	<i>NLRP3</i> /NLRP3	Spectrum from cold-induced urticaria and fever to CNS inflammation and bone overgrowth	Constitutive activation of NLRP3 inflammasome; IL-1 β ↑
Majeed syndrome	<i>LPIN2</i> /LPIN2	Dyserythropoietic anemia, osteomyelitis, neutrophilic dermatosis	Increased K ⁺ efflux through P2X7R, NLRP3 inflammasome activation; IL-1 β ↑
FCAS2	<i>NLRP12</i> /NLRP12	Cold-induced fever, rash, arthralgia, myalgia	Defect in inhibitory function of NLRP12; NF- κ B activity↑
NLRC4-MAS	<i>NLRC4</i> /NLRC4	Recurrent MAS, enterocolitis, cold-induced fever and urticaria, CNS inflammation	Activation of NLRC4 inflammasome; IL-1 β ↑/IL-18↑
PAPA	<i>PSTPIP1</i> /PSTPIP1	Pyoderma, pyogenic arthritis, severe cystic acne	Constitutive activation of pyrin inflammasome; IL-1 β ↑
HIDS,MKD	<i>MVK</i> /MVK	Fever, gangrenosum, rash, lymphadenopathy, abdominal pain, vomiting	Defect in geranylgeranylation of RhoA resulting in activation of pyrin inflammasome; IL-1 β ↑
PFIT	<i>WDR1</i> /WDR1	Fever, immunodeficiency, thrombocytopenia	Dysregulation of actin cytoskeleton resulting in activation of pyrin inflammasome; IL-18↑
DIRA	<i>IL1RN</i> /IL-1RA	Pustular rash, osteomyelitis	Deficiency in IL-1-receptor antagonist; IL-1↑
DITRA	<i>IL36RN</i> /IL-36RA	Pustular psoriasis, fever	Deficiency in IL-36-receptor antagonist; IL-36↑
IL-10 deficiency	<i>IL10</i> /IL-10 and <i>IL10RA</i> , <i>IL10RB</i> /IL-10 receptor	Early-onset inflammatory bowel disease	Loss of inhibitory function of IL-10; STAT3 phosphorylation↓ TNF↑
Blau	<i>NOD2</i> /NOD2	Granulomatous arthritis, uveitis, rash, camptodactyly	Constitutive NOD2 activation; NF- κ B↑
CAMPS,PSORS2	<i>CARD14</i>	Psoriasis, pityriasis rubra pilaris, pustular psoriasis	Constitutive NF- κ B activation; IL-17↑/IL-23↑
HA20	<i>TNFAIP3</i> /A20	Fever, ulcers (oral and genital), ocular inflammation, arthritis	Defect in hydrolysis of Lys63-linked ubiquitin chains; NF- κ B↑; multiple cytokines
Otulipenia,ORAS	<i>OTULIN</i> /OTULIN	Fever, neutrophilic dermatosis, lipodystrophy, failure to thrive	Defect in hydrolysis of linear Met1-linked ubiquitin chains; NF- κ B↑; multiple cytokines
LUBAC deficiency	<i>RBCK1</i> /HOIL-1 and <i>RNF31</i> /HOIP	Immunodeficiency, fever, amylopectinosis, lymphangiectasia	Impaired linear ubiquitination; NF- κ B↓/IL-6↑; hyper-responsiveness to IL-1 and TNF in peripheral blood mononuclear cells
AGS	Multiple genes/proteins	CNS inflammation, brain calcifications	Dysregulation in intracellular sensing of nucleic acids; type I IFN↑
PRAAS,CANDLE	Multiple proteasome genes/proteins	Fever, lipodystrophy, arthropathy, brain calcifications, rash	Defects in proteasome assembly; type I IFN↑
SAVI	<i>TMEM173</i> /STING	Fever, vasculitis, interstitial lung disease	Constitutive activation of STING; type I IFN↑
TRAPS	<i>TNFRSF1A</i> /TNFR1	Fever, serositis, rash, myalgia, orbital inflammation, SAA amyloidosis	Misfolding of mutant protein, unfolded-protein response; MAPK↑; IL-1↑ and other cytokines
Vibratory urticaria	<i>ADGRE2</i> /ADGRE2	Urticarial rash in response to mechanostimulation	Defect in ADGRE2-mediated inhibition of mast-cell degranulation
DADA2	<i>CECR1</i> /ADA2	Fever, lacunar strokes, livedo, vasculitis, immunodeficiency, anemia	Lack of anti-inflammatory (M2) macrophages; TNF↑/IL-1↑
APLAID	<i>PLCG2</i> / PLC γ 2	Rash, arthralgia, ocular inflammation, interstitial lung disease	Increased production of inositol trisphosphate, diacylglycerol and Ca ²⁺ ; IL-1↑ and other cytokines
SIFD	<i>TRNT1</i> /TRNT1	Sideroblastic anemia, B cell immunodeficiency, fevers, developmental delay	Defect in tRNA maturation, protein synthesis; multiple cytokines

PSORS2, familial psoriasis; CAMPS, CARD14-mediated pustular psoriasis; SAA, serum amyloid A; CNS, central nervous system.

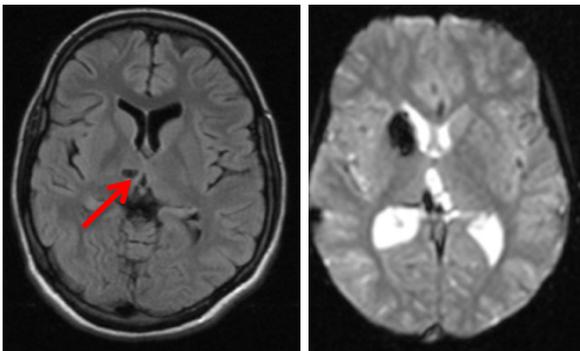
Neonatal-Onset Multisystem Inflammatory Disease Responsive to Interleukin-1 β Inhibition



Early-Onset Stroke and Vasculopathy Associated with Mutations in ADA2



Zhou, Yang et al. *NEJM* 370:911, 2014

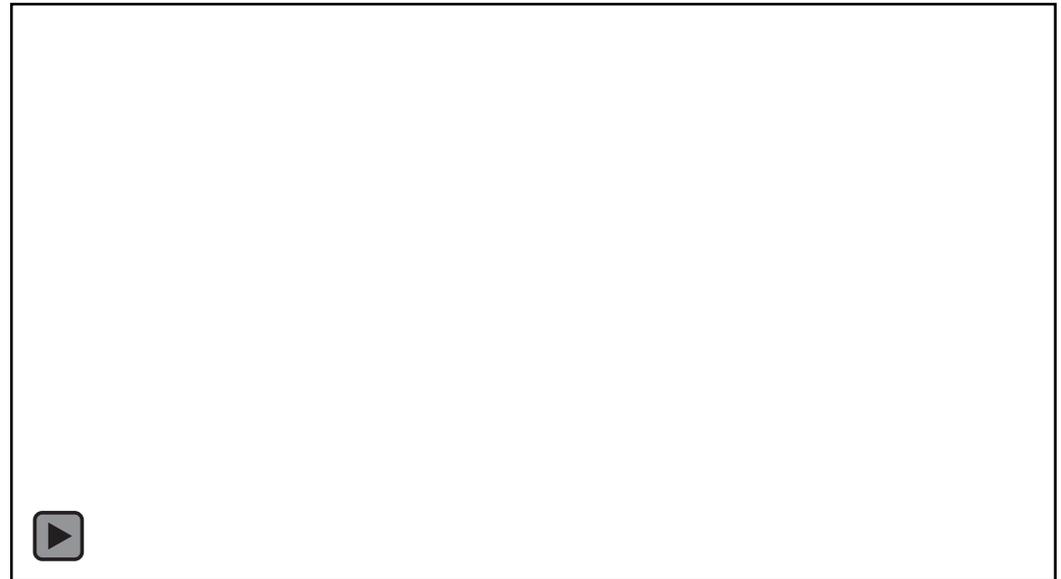
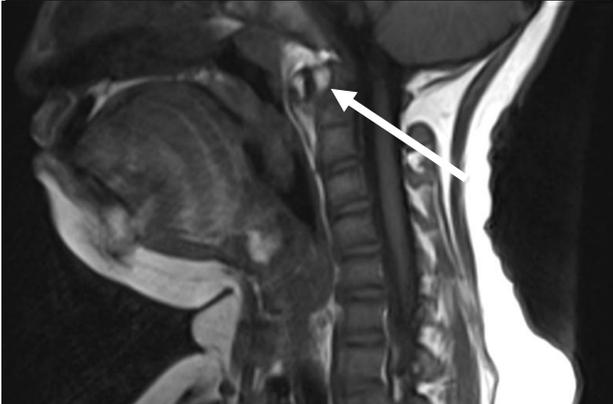
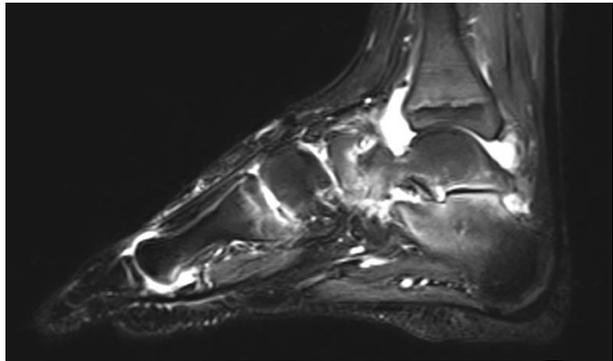
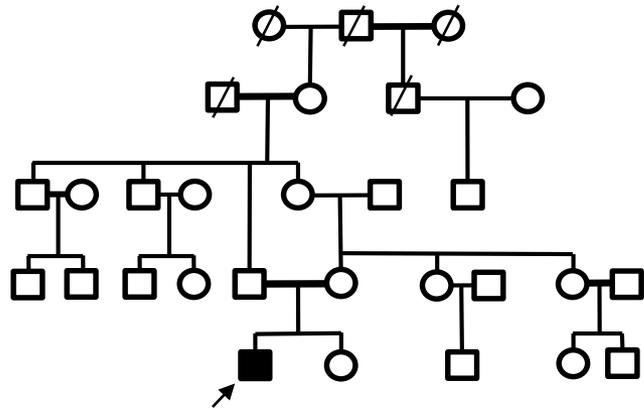


Before anti-TNF: 55 strokes, 2077 patient-months

Since anti-TNF: 0 strokes, 583 patient-months

A. Ombrello et al., submitted

The Boy from Bangaluru



ORIGINAL ARTICLE

Multicenter Analysis of Glucocerebrosidase Mutations in Parkinson's Disease

Sidransky et al., *NEJM* 361:1651, 2009



Ellen Sidransky



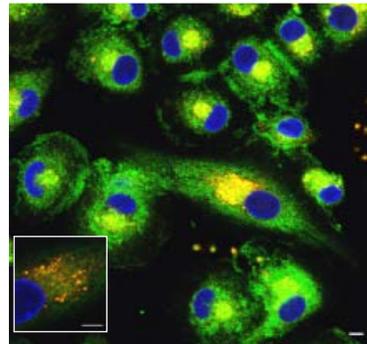
GBA1 is now the most common genetic risk factor for PD and related disorders

- Rare patients with Gaucher disease and parkinsonism
- Parkinson disease in relatives of Gaucher probands - heterozygotes

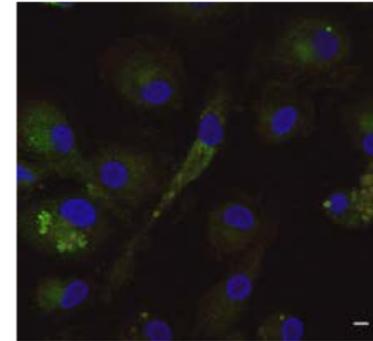
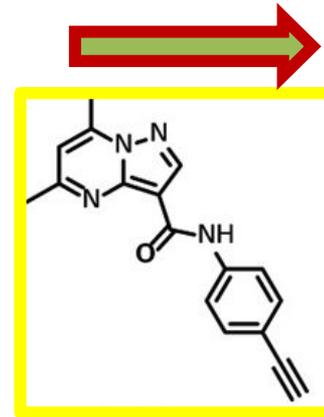
High Throughput Screening For Small Molecule Chaperones



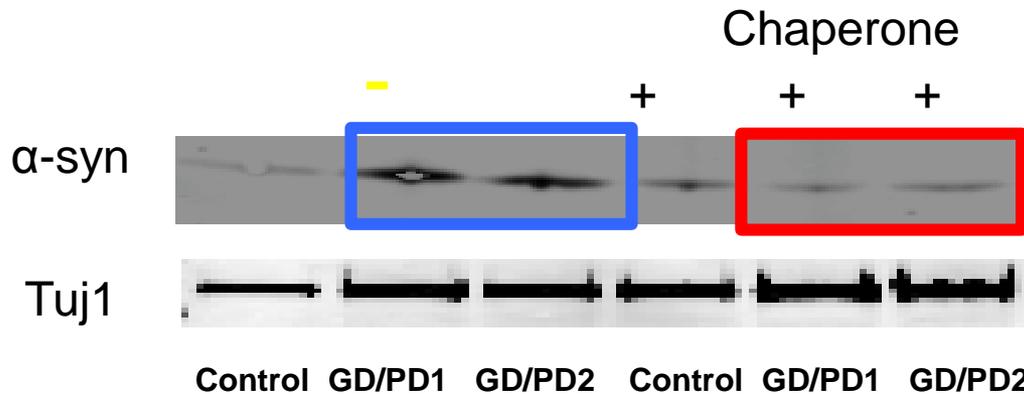
NCATS



Lipid engorged Gaucher
macrophage



Compounds clear out the
stored lipid



iPSC-derived
dopaminergic neurons



Philip Shaw

White Matter Microstructure and the Variable Adult Outcome of Childhood Attention Deficit Hyperactivity Disorder

Philip Shaw^{*,1,2,4}, Gustavo Sudre^{1,4}, Amy Wharton¹, Daniel Weingart¹, Wendy Sharp² and Joelle Sarlls³

¹Section on Neurobehavioral Clinical Research, Social and Behavioral Research Branch, National Human Genome Research Institute, Bethesda, MD, USA; ²Intramural Program of the National Institute of Mental Health, Bethesda, MD, USA; ³NIH MRI Research Facility/National Institute of Neurological Disorders and Stroke/National Institutes of Health, Bethesda, MD, USA

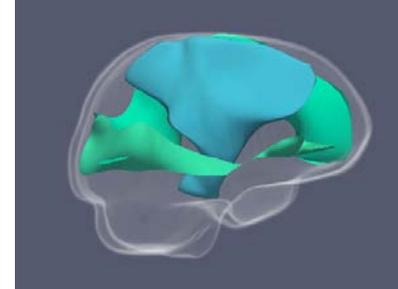
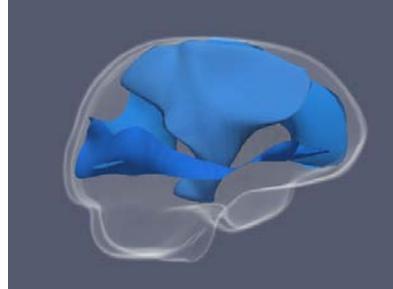
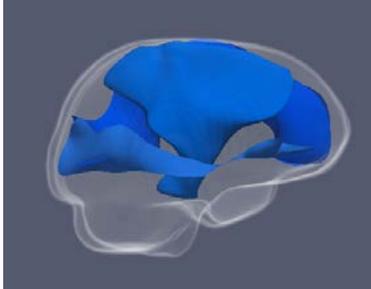
Neuropsychopharmacology 40:746, 2015

Never Affected

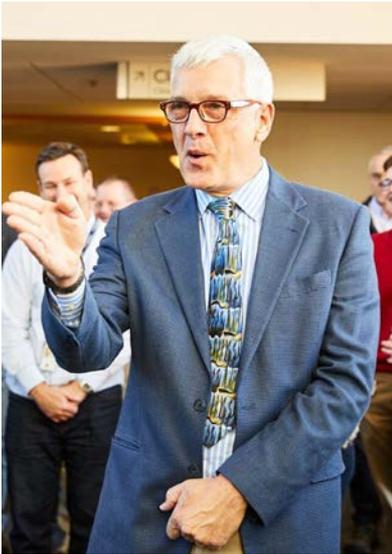
Remitted

Persistent

Z score
1 2



548 children (198 with ADHD) followed for 14 years on the same scanner



Les Biesecker

ORIGINAL ARTICLE

A Mosaic Activating Mutation in *AKT1* Associated with the Proteus Syndrome

Lindhurst et al., *NEJM* 365:611, 2011

COMMENTARY

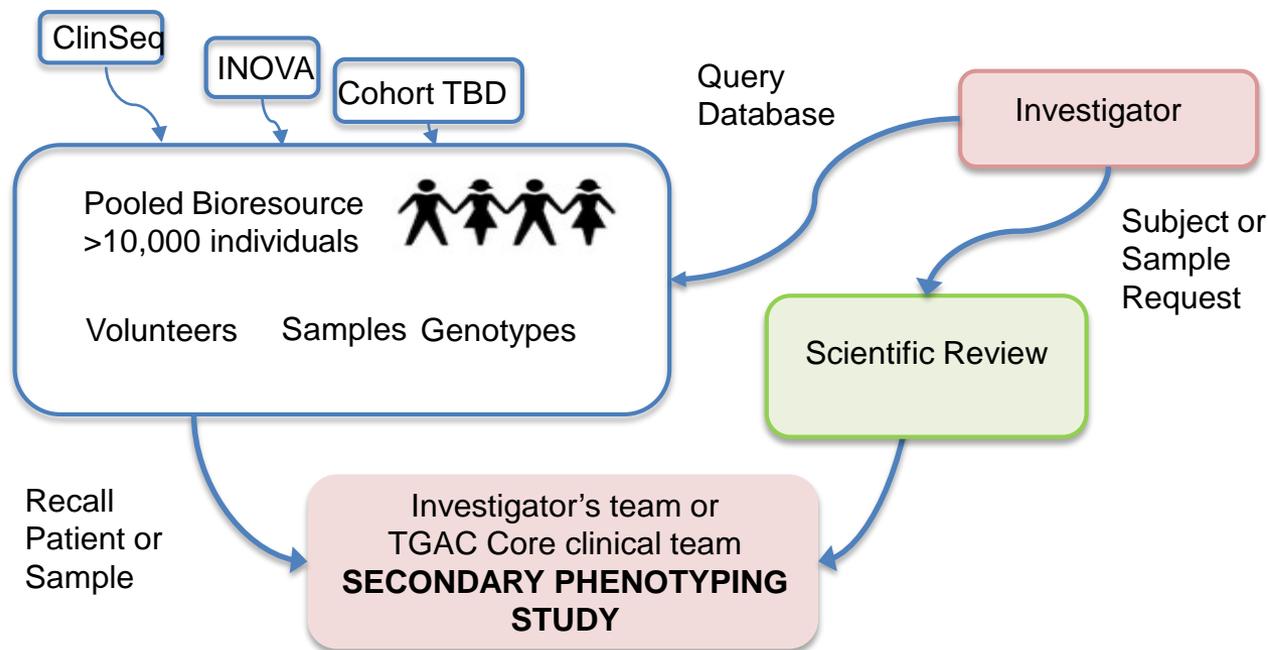
A Clinical Service to Support the Return of Secondary Genomic Findings in Human Research

Andrew J. Darnell,¹ Howard Austin,² David A. Bluemke,³ Richard O. Cannon III,⁴ Kenneth Fischbeck,⁵ William Gahl,⁶ David Goldman,⁷ Christine Grady,⁸ Mark H. Greene,⁹ Steven M. Holland,¹⁰ Sara Chandros Hull,^{8,11} Forbes D. Porter,¹² David Resnik,¹³ Wendy S. Rubinstein,¹⁴ and Leslie G. Biesecker^{15,*}

Am J Hum Genet 98:435, 2016

The Genomic Ascertainment Cohort (TGAC)

- Aggregate WES and WGS data
- Re-align & Call
- Display data in local browser
- Genotype-driven hypotheses
- Secondary clinical studies and deep phenotyping
- Refer to protocol
- Collect sample for investigator
- TGAC performs phenotyping





Bill Gahl

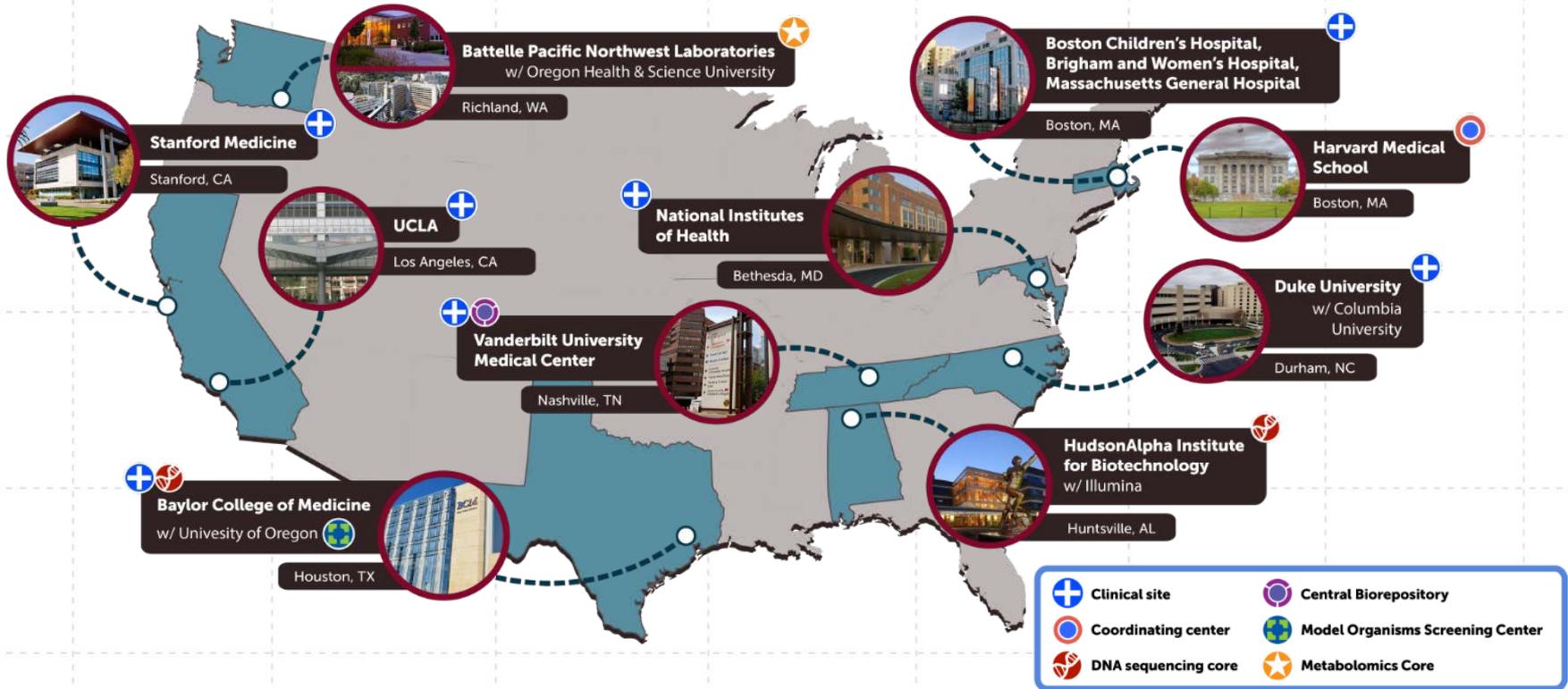
ORIGINAL ARTICLE

NT5E Mutations and Arterial Calcifications

St. Hilaire et al., *NEJM* 364:432, 2011

The Undiagnosed Diseases Program Turns 10

- Medical records: >4000
- Admitted and evaluated ~1100
- Children ~40%
- Neurological ~50%
- Some diagnosis ~30%
- Publications >80
- Two in *NEJM*, two in *JAMA*



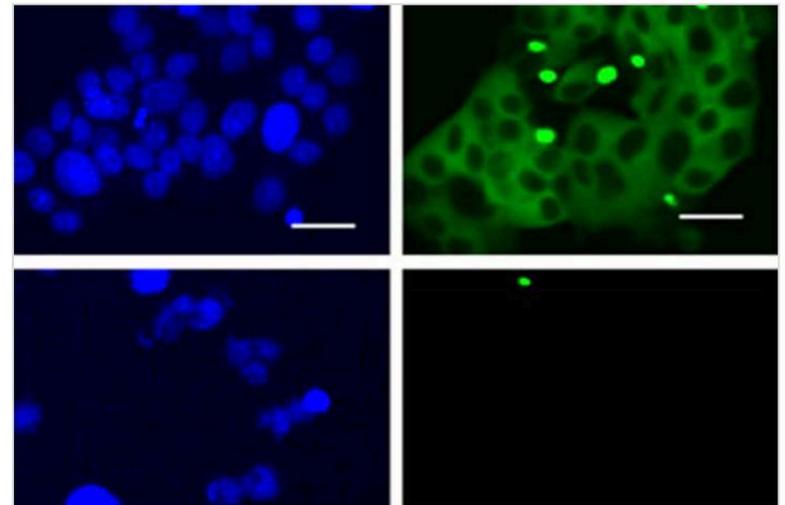
The NIH site will continue to enroll about 150 patients per year, each of the clinical sites will ultimately enroll about 50 patients per year.

NCATS Chemical Genomics Center (NCGC)

NCGC researchers advance small molecule therapeutic development through assay (test) design, high-throughput screening and medicinal chemistry. [Learn more.](#)

NCATS-Led Team Finds Potential Strategy to Fight Huntington's Disease

Al-Ramahi et al., eLIFE 6:e29129, 2017



Center for Inherited Disease Research (CIDR)



Larry Brody
Government
Scientific Officer

ARTICLES

<https://doi.org/10.1038/s41588-018-0057-4>

nature
genetics

Genome-wide mapping of global-to-local genetic effects on human facial shape

LETTER

doi:10.1038/nature24284

Association analysis identifies 65 new breast cancer risk loci

nature
genetics

Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer

LETTERS

nature
genetics

Genome-wide association analyses identify new susceptibility loci for oral cavity and pharyngeal cancer

ARTICLE

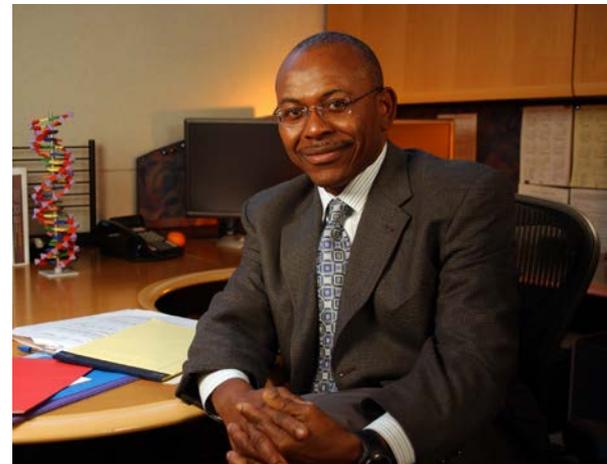
OPEN

doi:10.1038/nature13997

The African Genome Variation Project shapes medical genetics in Africa

Deepti Gurdasani^{1,2*}, Tommy Carstensen^{1,2*}, Fasil Tekola-Ayele^{3*}, Luca Pagani^{1,4*}, Ioanna Tachmazidou^{1*}, Konstantinos Hatzikotoulas¹, Savita Karthikeyan^{1,2}, Louise Iles^{1,2,5}, Martin O. Pollard¹, Ananyo Choudhury⁶, Graham R. S. Ritchie^{1,7}, Yali Xue¹, Jennifer Asimit¹, Rebecca N. Nsubuga⁸, Elizabeth H. Young^{1,2}, Cristina Pomilla^{1,2}, Katja Kivinen¹, Kirk Rockett⁹, Anatoli Kamali⁸, Ayo P. Doumatey³, Gershon Asiki⁸, Janet Seeley⁸, Fatoumatta Sisay-Joof¹⁰, Muminatou Jallow¹⁰, Stephen Tollman^{11,12}, Ephrem Mekonnen¹³, Rosemary Ekong¹⁴, Tamiru Oljira¹⁵, Neil Bradman¹⁶, Kalifa Bojang¹⁰, Michele Ramsay^{6,17,18}, Adebowale Adeyemo³, Endashaw Bekele¹⁹, Ayesha Motala²⁰, Shane A. Norris²¹, Fraser Pirie²⁰, Pontiano Kaleebu⁸, Dominic Kwiatkowski^{1,9}, Chris Tyler-Smith^{1,9}§, Charles Rotimi³§, Eleftheria Zeggini¹§ & Manjinder S. Sandhu^{1,2}§

Nature 517:327, 2015



Charles Rotimi

ARTICLE

OPEN

doi:10.1038/nature15393

A global reference for human genetic variation

The 1000 Genomes Project Consortium*

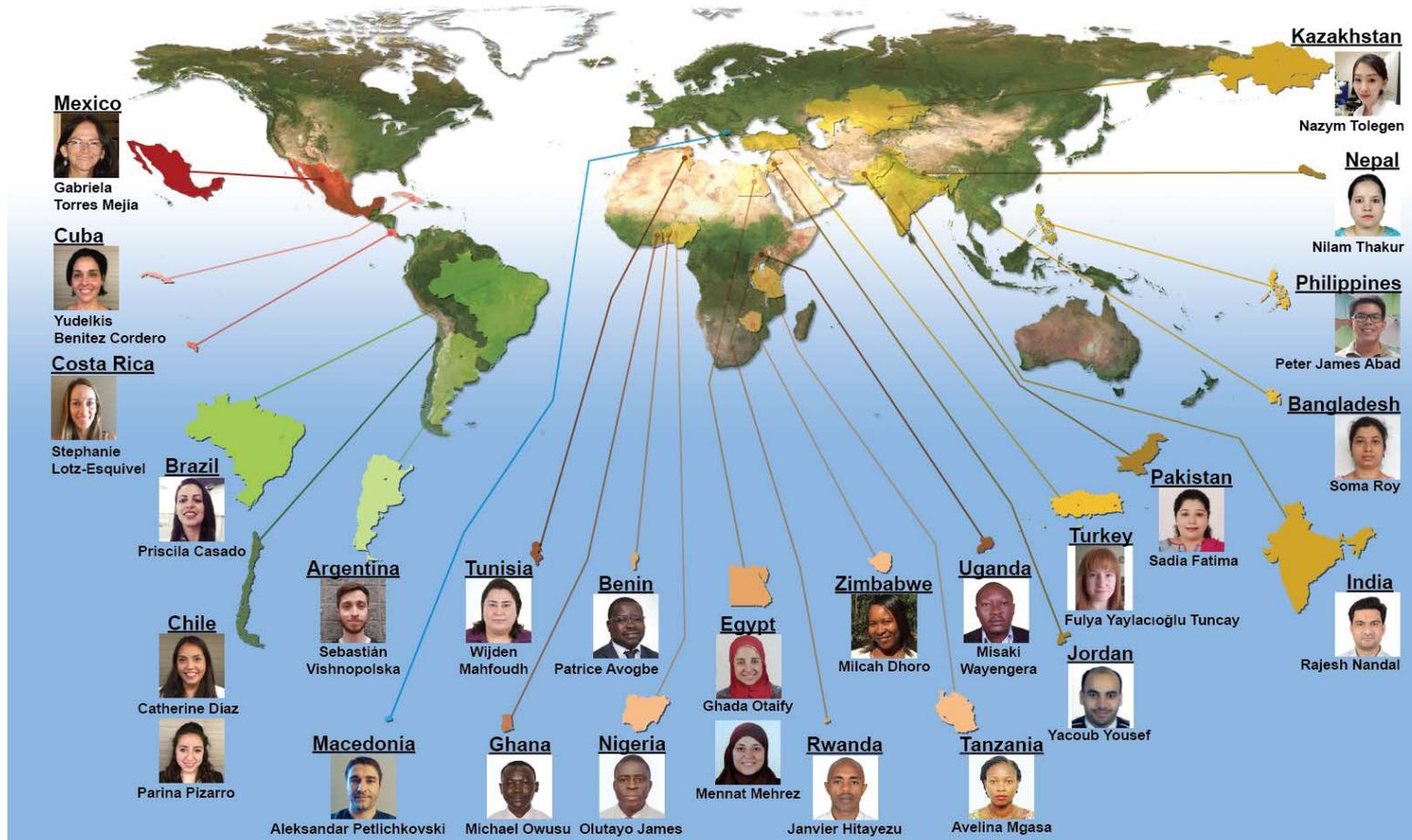
Nature 526:68, 2015



Max Muenke

Second International Summit in Human Genetics and Genomics

National Institutes of Health, Bethesda, Maryland, September 1 - 29, 2017
26 participants, 24 countries



NHGRI Social and Behavioral Research Branch



Laura Koehly, Chief



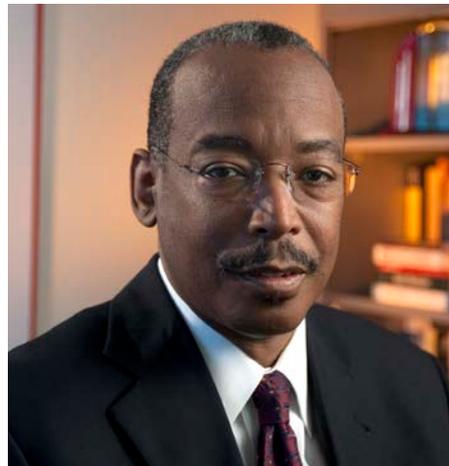
Philip Shaw



Larry Brody



Lori Erby



Vence Bonham



Susan Persky



Julie Segre

ANTIBIOTIC RESISTANCE

Single-molecule sequencing to track plasmid diversity of hospital-associated carbapenemase-producing Enterobacteriaceae

Sean Conlan,¹ Pamela J. Thomas,² Clayton Deming,¹ Morgan Park,² Anna F. Lau,³ John P. Dekker,³ Evan S. Snitkin,¹ Tyson A. Clark,⁴ Khai Luong,⁴ Yi Song,⁴ Yu-Chih Tsai,⁴ Matthew Boitano,⁴ Jyoti Dayal,² Shelise Y. Brooks,² Brian Schmidt,² Alice C. Young,² James W. Thomas,² Gerard G. Bouffard,² Robert W. Blakesley,² NISC Comparative Sequencing Program,² James C. Mullikin,² Jonas Korlach,⁴ David K. Henderson,³ Karen M. Frank,^{3*} Tara N. Palmore,^{3*} Julia A. Segre^{1*}

Sci Transl Med 6:254ra126, 2014



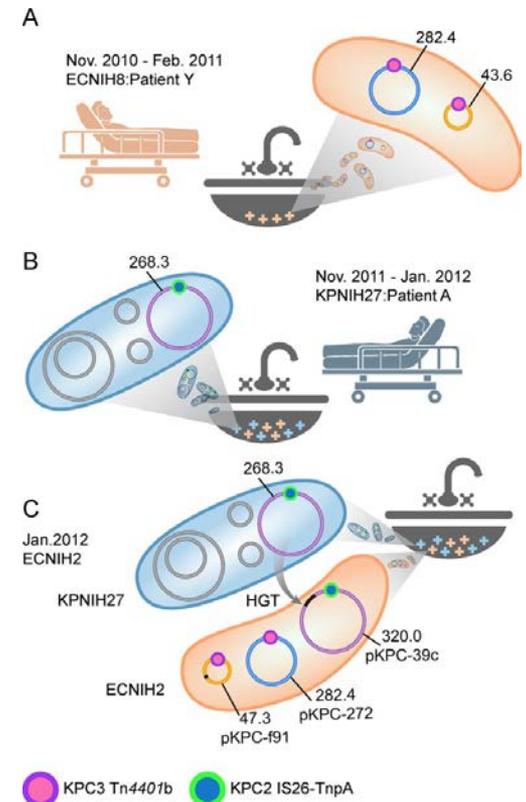
RESEARCH ARTICLE



Genomic Analysis of Hospital Plumbing Reveals Diverse Reservoir of Bacterial Plasmids Conferring Carbapenem Resistance

Rebecca A. Weingarten,^a Ryan C. Johnson,^b Sean Conlan,^b Amanda M. Ramsburg,^a John P. Dekker,^a Anna F. Lau,^a Pavel Khil,^a Robin T. Odom,^a Clay Deming,^b Morgan Park,^c Pamela J. Thomas,^c NISC Comparative Sequencing Program,^c David K. Henderson,^a Tara N. Palmore,^a Julia A. Segre,^b Karen M. Frank^a

MBio 9:e02011, 2018

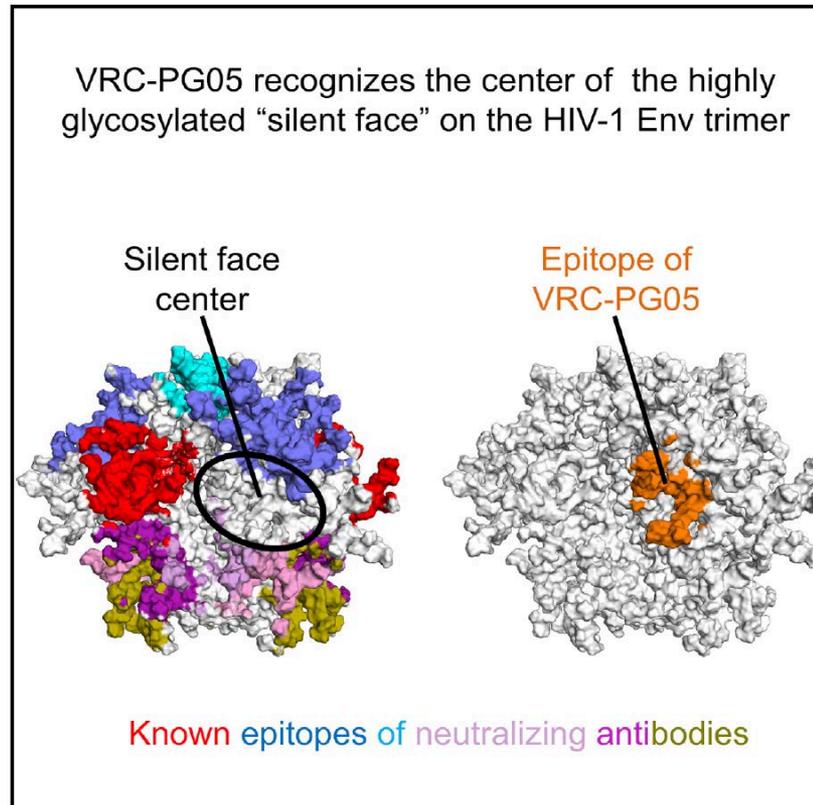


Immunity

A Neutralizing Antibody Recognizing Primarily N-Linked Glycan Targets the Silent Face of the HIV Envelope



Jim Mullikin





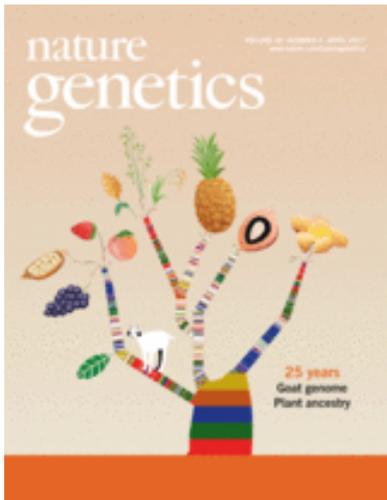
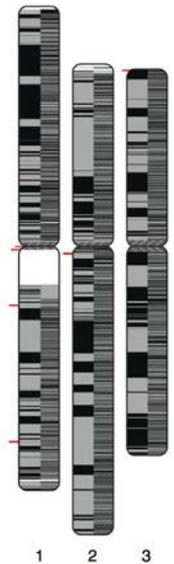
Adam Phillippy

nature
biotechnology

Assembling large genomes with single-molecule sequencing and locality-sensitive hashing

Konstantin Berlin^{1-3,6}, Sergey Koren^{4,6}, Chen-Shan Chin⁵, James P Drake⁵, Jane M Landolin⁵ & Adam M Phillippy⁴

Nat Biotechnol 33:623, 2015



nature
genetics

OPEN

Single-molecule sequencing and chromatin conformation capture enable *de novo* reference assembly of the domestic goat genome

Bickhart et al., *Nat Genet* 49:643, 2017



Shawn Burgess

A high-throughput functional genomics workflow based on CRISPR/Cas9-mediated targeted mutagenesis in zebrafish

Gaurav K Varshney^{1,2,8}, Blake Carrington^{3,8}, Wuhong Pei¹, Kevin Bishop³, Zelin Chen¹, Chunxin Fan⁴, Lisha Xu¹, Marypat Jones⁵, Matthew C LaFave^{1,7}, Johan Ledin⁶, Raman Sood³ & Shawn M Burgess¹

Nat Protoc 11:2357, 2016

A Defined Zebrafish Line for High-Throughput Genetics and Genomics: NHGRI-1

Matthew C. LaFave,^{*} Gaurav K. Varshney,^{*} Meghana Vemulapalli,[†] James C. Mullikin,^{†,*}
and Shawn M. Burgess^{*.1}

Genetics 198:167, 2014

CRISPRz: a database of zebrafish validated sgRNAs

Gaurav K. Varshney¹, Suiyuan Zhang², Wuhong Pei¹, Ashrifia Adomako-Ankomah¹, Jacob Fohitung¹, Katherine Schaffer¹, Blake Carrington³, Anoo Maskeri¹, Claire Slevin¹, Tyra Wolfsberg², Johan Ledin⁴, Raman Sood³ and Shawn M. Burgess^{1,*}

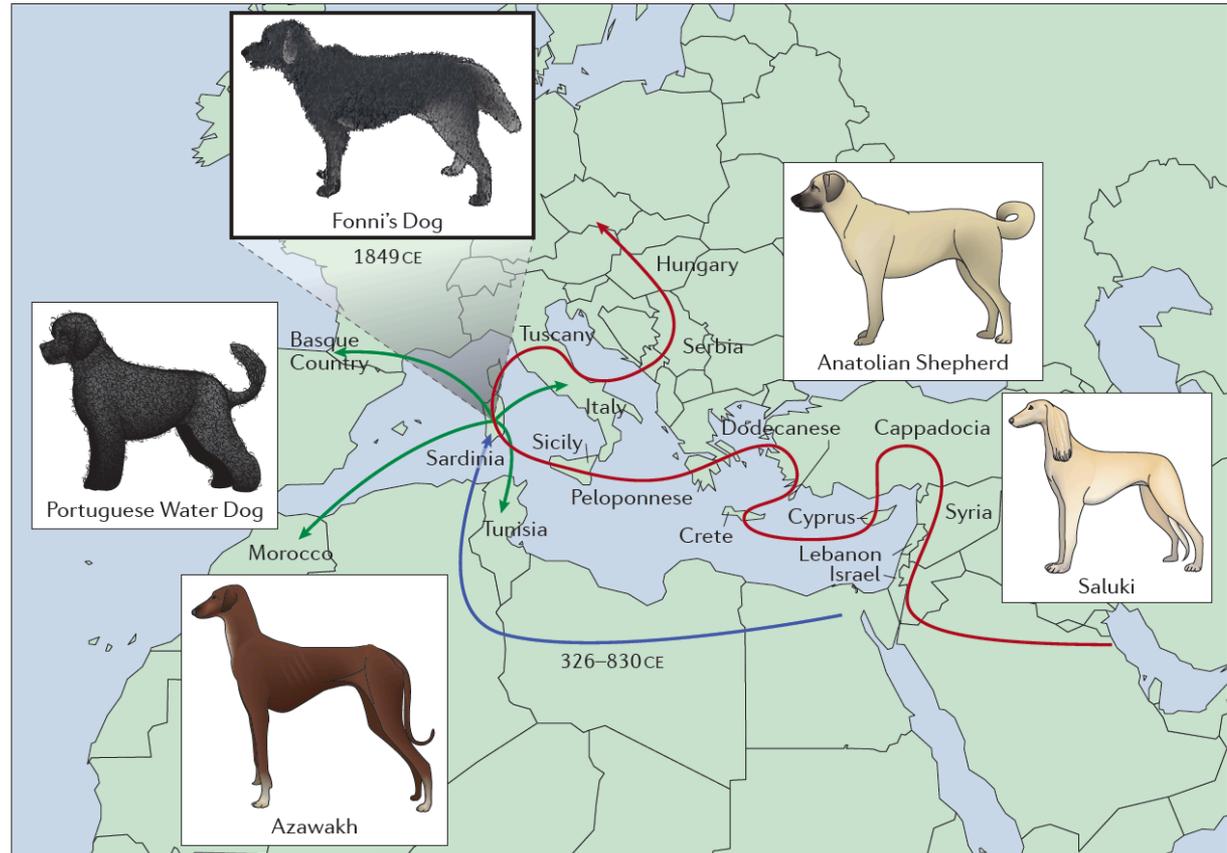
Nucleic Acids Res 44:D822, 2016



Elaine Ostrander

Demographic history, selection and functional diversity of the canine genome

Elaine A. Ostrander¹, Robert K. Wayne², Adam H. Freedman³ and Brian W. Davis^{1,4}

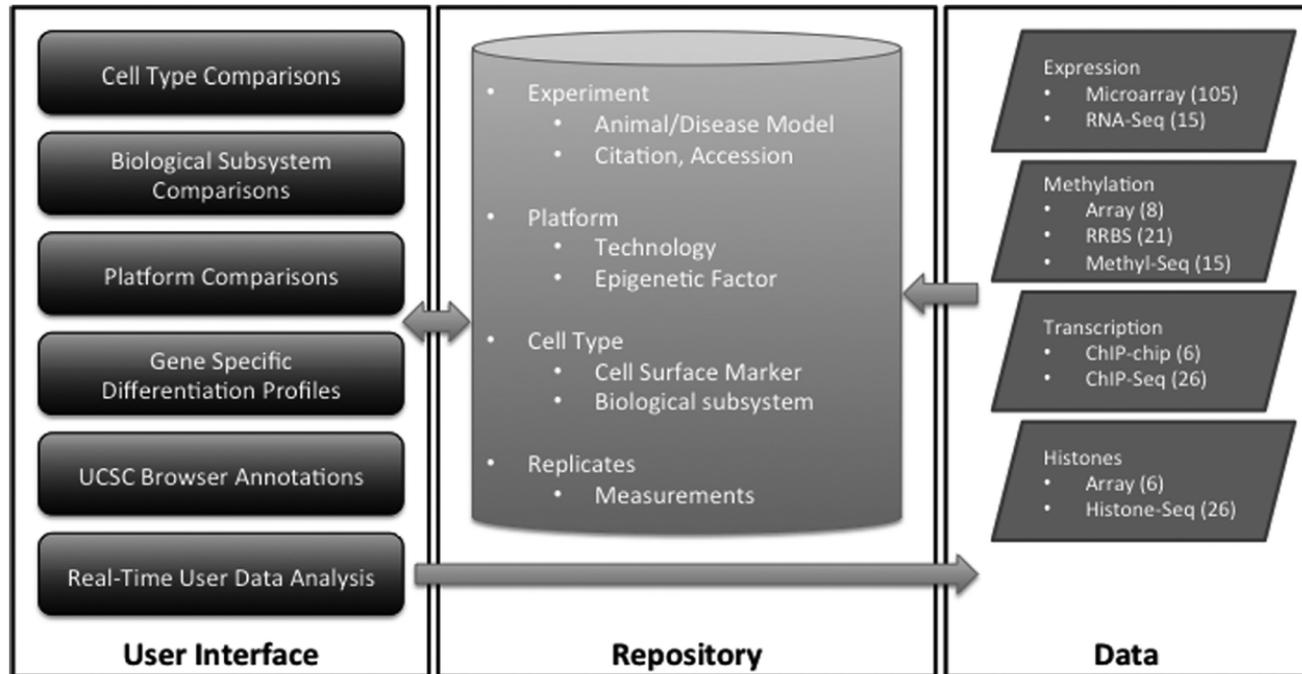




Dave Bodine

SBR-Blood: systems biology repository for hematopoietic cells

Jens Lichtenberg^{1,*}, Elisabeth F. Heuston¹, Tejaswini Mishra², Cheryl A. Keller², Ross C. Hardison² and David M. Bodine¹





Scientific Productivity Since 2/1/2016

- 6 *Science*
- 4 *Nature*
- 6 *Cell*
- 8 *NEJM*
- 6 *JAMA*
- 1 *Lancet*
- 9 *Nature Genetics*
- 4 *Nature Immunology*
- 1 *Nature Medicine*
- 1 *Nature Biotechnology*
- 1 *Nature Protocols*
- 2 *Nature Reviews Genetics*
- 9 *Nature Communications*
- 4 *Science Translational Medicine*
- 1 *Cell Metabolism*
- 6 *PNAS*
- 2 *JCI*
- 26 *American J Human Genetics*
- 7 *Blood*
- 1 *Immunity*
- 2 *Neuron*
- 1 *Annual Review of Medicine*
- 1 *Ann Rev Genomics Human Genet*

Blue Ribbon Panel Review of the Intramural Research Program

- 2011 – 2012, Chaired by David Page
- Members: Wylie Burke, Nancy Cox, Bruce Korf, Rick Myers, Bob Waterston, Huda Zoghbi
- Written materials, conference calls, 2 in-person site visits
- Final report, September 2012

Overall Assessment: Outstanding

- Scientific productivity
- Mentoring and training programs
- Dissemination of genomic technologies across the NIH IRP
- Internationally recognized research faculty
- Robust research infrastructure
- Spirit of collaboration and collegiality

Recommendations

- Continue to adhere to the model of investigator-initiated research
- Allocate resources based on rigorous reviews by the Board of Scientific Counselors
- Embrace a risk-taking culture
- Insist on excellence
- Continue to be a 'change agent' on the NIH campus and beyond

Evaluating Science and Allocating Resources in the Intramural Research Program

NHGRI Board of Scientific Counselors

Brendan Lee, Chair (2020)

Baylor College of Medicine

Mark Daly (2019)

Mass General, Broad Institute

Wayne Grody (2019)

UCLA

Lucille Adams-Campbell (2021)

Georgetown

Neal Copeland (2021)

Methodist Research Institute

Tim Townes (2021)

UAB

Barry Coller (2022)

Rockefeller University

Carole Ober (2022)

University of Chicago

Sara Tishkoff (2022)

University of Pennsylvania

Standards of Excellence for IRP Science

- Does the work fundamentally change the way that we think about or understand relevant areas of biomedical science?
- Through the development of new methods, does it change the way that we do science?
- For clinical research, does it change the way that we practice medicine?
- Whether clinical or basic, how would the field look if the Intramural Investigator had not been active for the last five years?
- Is the research worth studying with the special resources associated with the IRP?

Ratings to Date (60 evaluations)

- 38 Outstanding (63%)
- 6 Outstanding to Excellent (10%)
- 1 Excellent to Outstanding (2%)
- 9 Excellent (15%)
- 1 Excellent to Very Good (2%)
- 2 Very Good to Excellent (3%)
- 3 Very Good (5%)

Planning the Next Quarter Century

- Strong commitment to risk-taking, to scientific excellence, and to leading genomics in the NIH IRP
- Merit-based resource allocation
- Strategic tenure-track faculty recruitment
- Succession planning
- Engagement in the Institute-wide strategic planning and a new round of Blue Ribbon Panel review



NHGRI