Discovering the Genetic Bases of Mendelian Disorders

David Valle, MD

McKusick-Nathans Institute of Genetic Medicine
Johns Hopkins University
13 April 2016

dvalle@jhmi.edu

Current Topics in Genome Analysis 2016

David Valle

No Relevant Financial Relationships with Commercial Interests

Disclosures and objectives

- Disclosure: I am enthusiastic about genetics!
- Objectives:
  - ✓ Some features of Mendelian disease
  - ✓ Review the rapidly evolving field of clinical DNA sequencing
  - ✓ Disease gene discovery and the Baylor-Hopkins Center for Mendelian Genomics

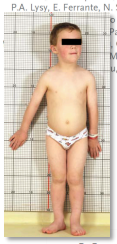
NEJM: Mendelian disease this month

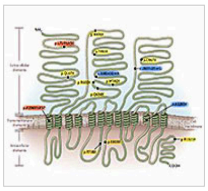
The NEW ENGLAND JOURNAL of MEDICINE

HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS | CME

Gigantism and Acromegaly Due to Xq26 Microduplications and *GPR101* Mutation

G. Trivellin, A.F. Daly, F.R. Faucz, B. Yuan, L. Rostomyan, D.O. Larco, M.H. Schernthaner-Reiter, E. Szarek, L.F. Leal, J.-H. Caberg, E. Castermans, C. Villa, A. Dimopoulos, P. Chittiboina, P. Xekouki, N. Shah, D. Metzger, P.A. Lysy, E. Ferrante, N. Strebkova, N. Mazerkina, M.C. Zatelli, M. Lodish, de Alexandre, A.D. Manning, I. Levy, M.F. Keil, Palmeira, W. Coppieters, M. Georges, L.A. Naves, C.S. Choong, J. Bertherat, P. Chanson, P. Kamenicky, M. Quezado, I. Bjelobaba, S.S. Stojilkovic, J. Wess, J.R. Lupski, A. Beckers, and C.A. Stratakis





ORIGINAL ARTICLE ONLINE FIRST

NPC1L1 Mutations and Coronary Heart Disease

November 12, 2014 |The Myocardial Infarction Genetics Consortium Investigators
(DOI: 10.1056/NEJMoa1405386)

Inactivating mutations in *NPC1L1* were identified on exon sequencing and genotyping in 16 cohorts of patients with coronary heart disease and controls. Mutation carriers had lower LDL cholesterol levels and a lower risk of coronary heart disease than did noncarriers.

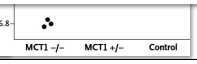
SPECIALTY Cardiology

Biologically Inactive Leptin and Early-Onset Extreme Obesity

Martin Wabitsch, M.D., Ph.D., Jan-Bernd Funcke, M.Sc., Belinda Lennerz, M.D., Ursula Kuhnle-Krahl, M.D., Georgia Lahr, Ph.D., Klaus-Mich... Petra Vatter, Ph.D., Peter Gierschik, M.D., Barbara M... and Pamela Fischer-Posovszky, Ph.D.

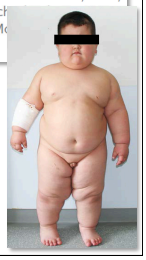
Monocarboxylate Transporter 1 Deficiency and Ketone Utilization

Peter M. van Hasselt, M.D., Ph.D., Sach... Glen R. Monroe, M.Sc., Jos P.N. Ruiter, B.Sc. Maartje J. Geerlings, M.Sc., Karen Duran, B.Sc., M... Bert van der Zwaag, Ph.D., Ardeshir A. Monava... Mark J. Sharrard, F.R.C.P.C.H., Maureen Cleary, M... Valerie Walker, M.D., M. Estela Rubio-Gozalbo, M.... Gepke Visser, M.D., Ph.D., Roderick H... Jasper J. van der Smagt, M.D., Nanda M. Verhoeven-Duif, Ph.D., Ronald J.A. Wanders, Ph.D., and Gijs van Haaften, Ph.D.



Screening an Asymptomatic Person for Genetic Risk — Polling Results

Joann Schulte, D.O., M.P.H., Carla S. Rothaus, M.D., Jonathan N. Adler, M.D., and Elizabeth G. Phimister, Ph.D.



Increasing prominence of Mendelian Disease

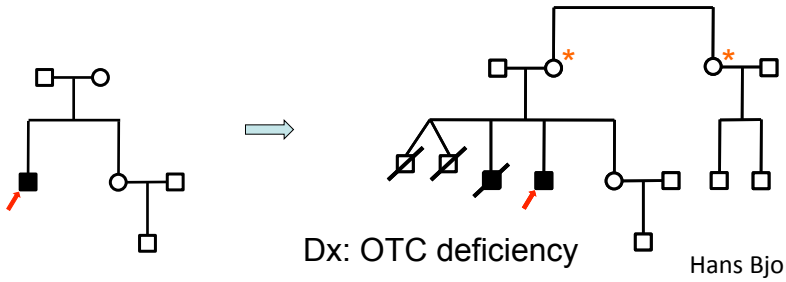
- Human genome project provides a reference human genome sequence
- Availability of sequencing technology that dramatically decreases cost and increases throughput
- Appreciation of the extent of "normal" human genetic variation
- Development of genomic and genetic strategies to identify responsible variants and genes

When to think of Mendelian disease

- Phenotype often includes multiple systems not usually co-occurring
- Relatively early onset
- Consanguinity
- Multiple affected sibs and/or generations

Case 1: 34 yr old male

- 10 day history of fever and pharyngitis Rx'ed with antibiotics and steroids; 2 day history of confusion
- Outside hospital ER: NH_4 of 280 μM; mild respiratory alkalosis
- JHH MICU – Coma with cerebral edema; NH_4 = 420 μM
- Family history – "negative"

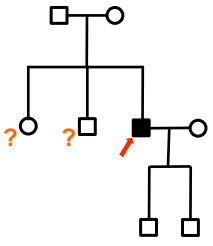


Dx: OTC deficiency

Hans Bjornsson

Case 2: 54 yr old male

- Severe DCM (EF ~20%), early dementia
- Labs include mild elevation homocystine (Hyc), methylmalonic acid (MMA)
- Partial response to hydroxycobalamin
- Gene sequencing – compound heterozygote for 2 LOF mutations in Cbl C gene
- Dx: CblC form of Methylmalonic Acidemia



Tracy Fehr
Stuart Russell
Hilary Vernon

Finding the responsible variants and genes

Finding the responsible variants and genes

Targeted capture and massively parallel sequencing of 12 human exomes

Sarah B. Ng[1], Emily H. Turner[1], Peggy D. Robertson[1], Steven D. Flygare[1], Abigail W. Bigham[2], Choli Lee[1], Tristan Shaffer[1], Michelle Wong[1], Arindam Bhattacharjee[4], Evan E. Eichler[1,3], Michael Bamshad[2], Deborah A. Nickerson[1] & Jay Shendure[1]

Nat Genet, Sept 09

Whole-Genome Sequencing of a Single Proband Together with Linkage Analysis Identifies a Mendelian Disease Gene

Nara L. M. Sobreira[1,2☯], Elizabeth T. Cirulli[3☯], Dimitrios Avramopoulos[1,4☯], Elizabeth Wohler[5], Gretchen L. Oswald[1], Eric L. Stevens[1,2], Dongliang Ge[3], Kevin V. Shianna[3], Jason P. Smith[3], Jessica M. Maia[3], Curtis E. Gumbs[3], Jonathan Pevsner[6,7], George Thomas[1,5], David Valle[1,8¶], Julie E. Hoover-Fong[1,8,9¶], David B. Goldstein[2¶*]

PLoS Genetics 6:1, 2010

The rise of clinical DNA sequencing

Some types of sequencing by target

- Single disease gene
- Disease gene panel – a collection of genes each known to be responsible for a particular disease
- Whole exome sequencing (WES) – sequencing the entire exome together with the splice sites flanking each exon; ~85% of Mendelian variants
- Whole genome sequencing (WGS) – sequencing the entire genome; exons, introns, regulatory sequences

Clinical vs. research whole exome sequencing (WES)

- Research WES
  - ✓ Diagnosis +/-; molecular basis unknown
  - ✓ Typically done in multiple members of a family or in a large cohort; speed not critical
  - ✓ Surveys all 21,000 protein coding genes
  - ✓ Requires validation, segregation, functional studies for confirmation
- Clinical WES
  - ✓ Diagnosis not known
  - ✓ Patient +/- immediate family
  - ✓ Depends on known disease genes

Some unanticipated consequences of DNA sequencing

- Variants of unknown significance (VUS)
- Incidental findings of medical consequence

Characteristics of current sequencing approaches

TYPE	e.g.	COST ($)	COMMENTS
Single gene	BRCA1	100s – 1000s	Less expensive if correct; fewer VUS; no incidental findings
Panel	Cardiomyopathy (~25 proven cardiomyopathy genes)	100s – 1000s	Broader net; less expensive; more VUS; no incidental findings
WES	A "Clinical WES"	5000 - 8000	Much broader net; a bargain; many VUS; incidental findings
WGS	Largely a research tool at this time	5000 - 15000	Broader still; harder to interpret; VUS and incidental findings galore

*Clinical WES: BCM first 2000 samples**

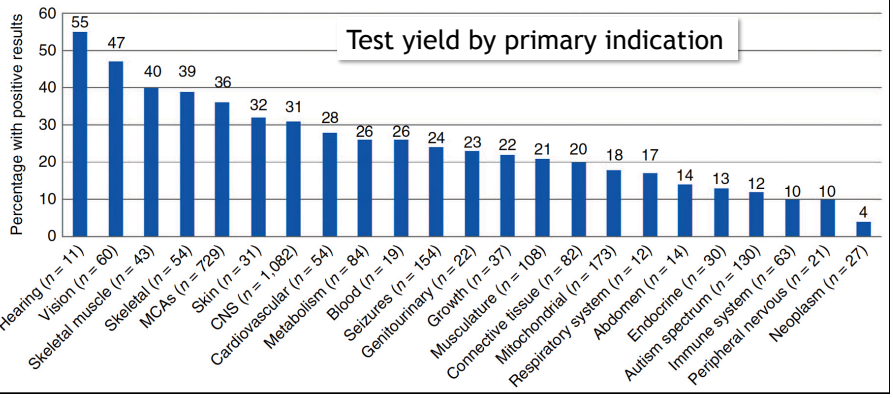
- 2000 consecutive patient samples, June 2012- Aug 2014
- 88% pediatric age range
- Molecular diagnosis in 504 (25.2%), with 58% of the diagnostic mutations not previously reported
- Inheritance pattern of solved cases
  - ✓ AD – 53%
  - ✓ AR – 34%
  - ✓ X-linked – 12%
  - ✓ mtDNA – 0.2%
- 23 of the patients (4.6%) had blended phenotypes from 2 Mendelian disorders

~30% of diagnoses involved a disease gene identified in last 3 years

* Yang et al., JAMA 2014

*Clinical WES: GeneDx first 3528 probands**

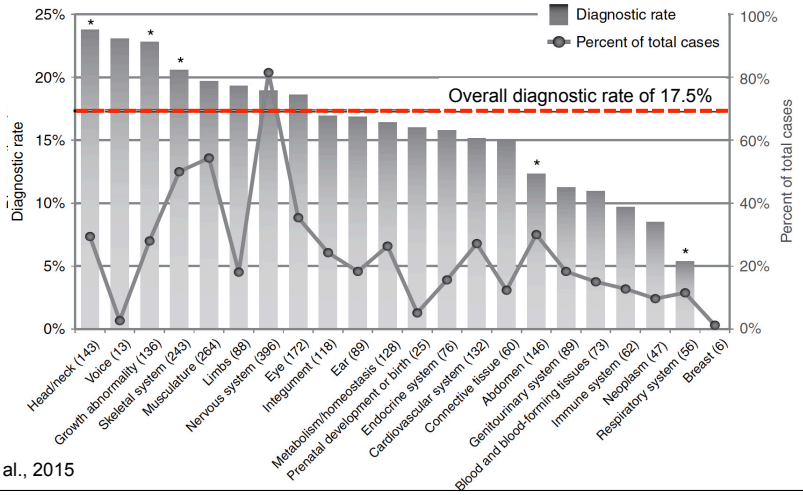
- 3040 consecutive probands, 2013- 2015
- Nearly all in pediatric age range
- Molecular diagnosis in 851(28.8%)
- 28 of the patients (3.3%) had 2 or 3 Mendelian disorders



* Retterer et al., 2015

*Clinical WES: BCM first 486 adult patients**

- 486 consecutive adult probands
- Molecular diagnosis in 85 (17.5%); 6 (7%) with 2 disorders



* Posey et al., 2015

The Value of a Precise Diagnosis

- Short cuts the diagnostic work up
- Ends the uncertainty of the "diagnostic odyssey"
- Provides a biological explanation for the problem
- Focuses patient management
- Informs family of recurrence risk

The value of a diagnosis

- 39 yr old male followed by me for 36 yr
- Recurrent episodes of lactic acidosis
- Intellectual disability (IQ 65) with cortical atrophy
- Cardiomyopathy
- Autonomic dysfunction

Age 37: Homozygous nonsense mutation in *FBXL4;* mtDNA depletion syndrome, type 13 (OMIM 605654)

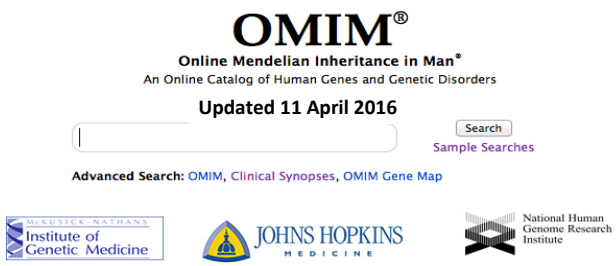
A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders

Stark et al, GIM, 2016

- 119 infants considered; 80 participated
- 2,830 genes evaluated by single clinical WES
- 122 genes with late onset phenotypes excluded
- 46 infants (57.5%) had a molecular diagnosis
- Of these, 32% had a change in management
- 28 couples (61%) received a high (25%, 50%) recurrence rate

Mendelian disease: current scorecard

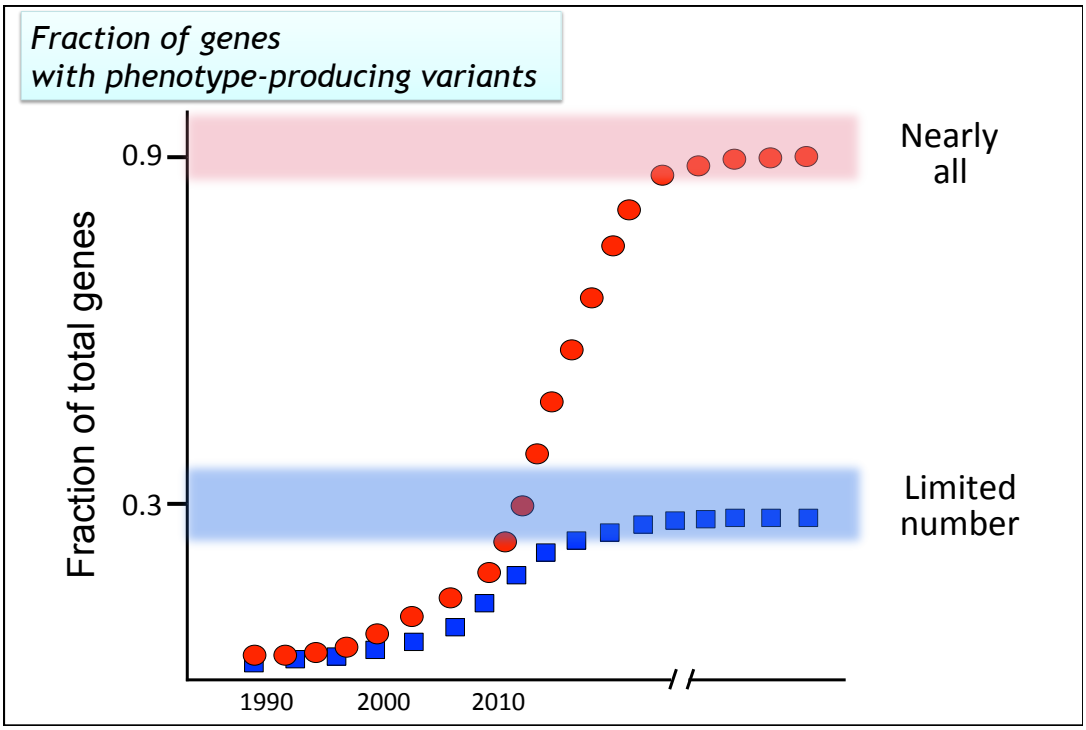
OMIM.org



- Mendelian phenotypes ~7,500
- "Disease" genes ~3,543 (~18% of total)
- Explained phenotypes ~5,722
- Unexplained phenotypes ~1,800 ~300/yr

How many Mendelian disease genes ?

- Those genes in which some fraction of variants produce highly penetrant phenotypes
- How many phenotypes?
  - ✓ OMIM currently lists ~7,500 total with ~1.8 phenotypes/disease gene; 1,800 unexplained predicts ~ 900 more disease genes
  - ✓ But many phenotypes are conditional on environmental variables, e.g. G6PD deficiency
  - ✓ Vast number of unrecognized phenotypes; ~300 "new" phenotypes in OMIM/year



If the fraction of Mendelian genes is large, why are they difficult to identify ?

- Unrecognized developmental lethals
  - ✓ High frequency of spontaneous 1st trimester spontaneous abortions; how many Mendelian?
  - ✓ ~30% mouse knockouts
- Incomplete and/or insensitive phenotyping
  - ✓ Routine or uninformed vs. directed or iterative
  - ✓ Technological limitations; what can we measure?
- Conditional nature of some phenotypes
- Buffering, robustness and redundancy of biological systems

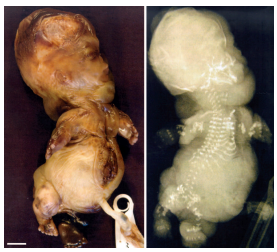
Fraction of genes with phenotype-producing variants

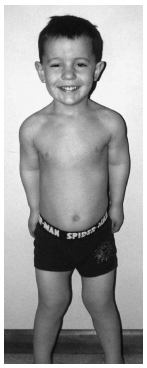
- Mouse experience - 8,793 genes ko'ed
  - ✓ 19% lethal E0 - E18.5
  - ✓ 11% lethal E18.5 – P1
  - ✓ 96.6% targeted viable mice show one or more phenotypic features*
- Other model systems

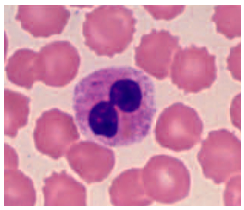
* MGI per J Eppig

Developmental lethals

- At any locus there is a collection of variants with a spectrum of functional consequences from null to GOF
- Examples:
  - ✓ *LBR* mutations







- Solution – Cast a wide net, including sequencing spontaneous abortuses and/or their parents

Incomplete phenotyping: Olfaction

- Cursorily addressed in history and physical exam
- Humans have 500-1000 olfactory receptor genes
- A few "inborn errors" are known *

Table 1 | Genomic variation in OR genes are known to contribute to variance in perception of an odour ligand

Odour(s)	Receptor	Consequence of SNP(s)	Perception tested	Phenotypic variance
Androstenone and androstadienone	OR7D4	R88W, T133M	Intensity, sensitivity	39%, 19%
Isovaleric acid	OR11H7P	X226Q	Threshold	8%
cis-3-Hexen-1-ol	OR2J3	T113A, R226Q	Threshold	26.4%
β-Ionone	OR5A1	N183D	Sensitivity	96.3%
Guaiacol	OR10G4	ALTYMGPVRK>ALICVSSEGQ	Intensity, valence	15.4%, 10.3%

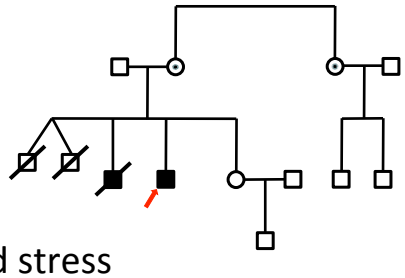
* See Logan DW, Biochem Soc Trans 42:861, 2014

"Conditional" Phenotypes

- The example of MCAD deficiency
- Seizures, hypoglycemia, hyperammonemia, 36 hours in to an episode of viral gastroenteritis in an 18 month old
- Can we learn from the UDN program and KOMP ?
- Value of education
- Many other examples:
  - ✓ G6PD deficiency
  - ✓ Deficiency of urate oxidase (gout); ascorbate oxidase (scurvy)

Buffering and systems biology

- Develop the mind set of developmental and homeostatic vulnerabilities
  - ✓ Disease = exceeding a limited homeostatic capacity:
  - ✓ The example of adult-onset OTC deficiency



- Improved methods for controlled stress
  - ✓ In patients
  - ✓ In model organisms with subsequent translation to humans
  - ✓ In cellular systems

How many Mendelian genes?

Hypothesis:

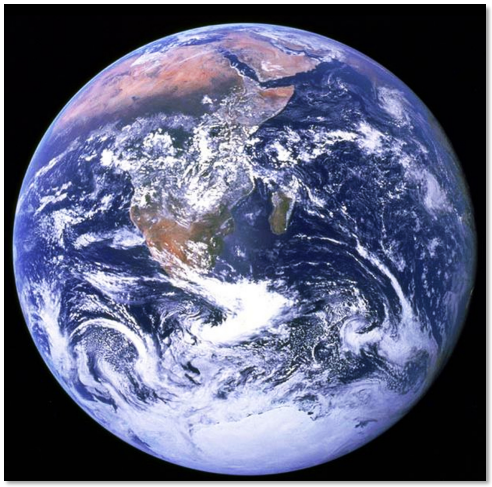
If we look carefully and across large populations, nearly all in our genome….

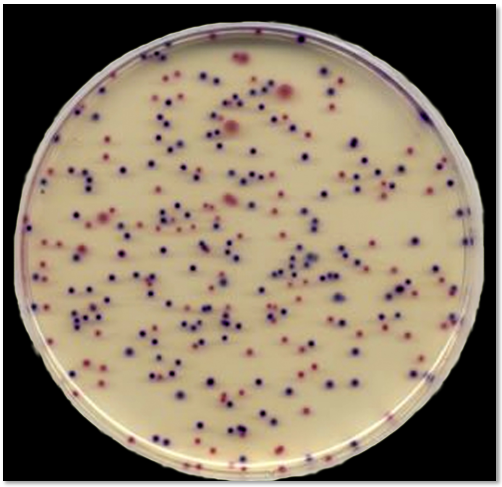
CMGs: Overall strategy

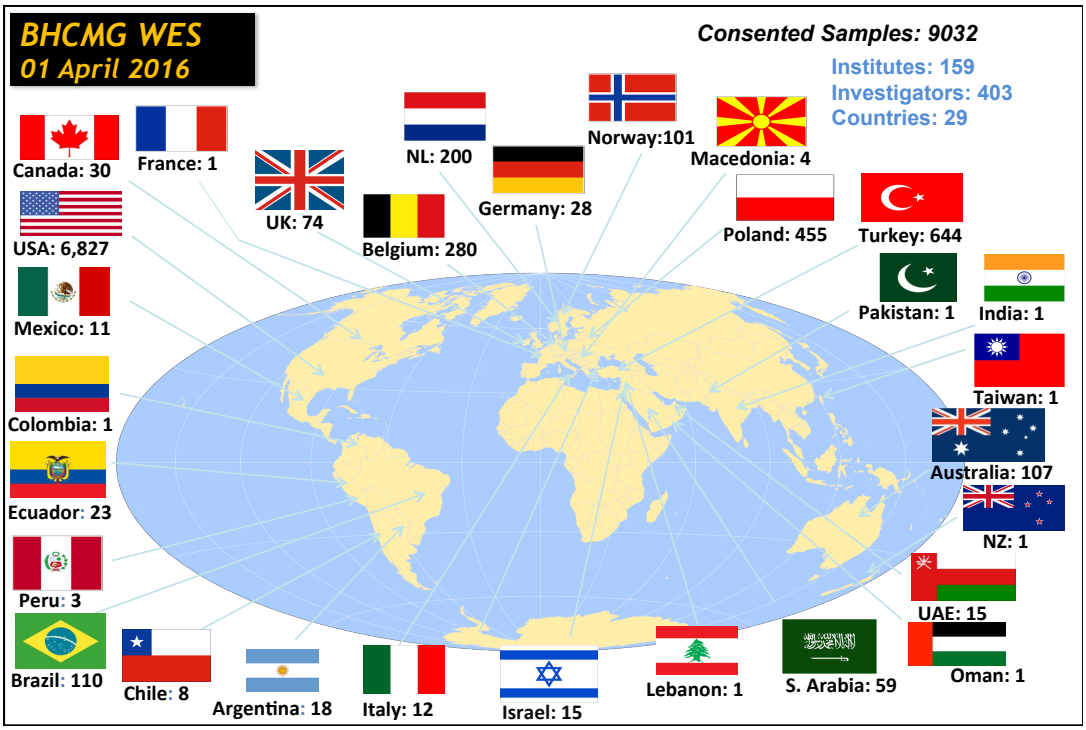
- Find well-phenotyped cases and families
- Perform whole exome sequencing on relevant family members
- Use family relationships, allele frequency data, functional predictions, model organism results and functional studies to identify the responsible genes and variants
- Return the information to submitter for publication

BHCMG
mendeliangenomics.org

CMGs: Searching for disease genes







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

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

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

Hum Mut 34:561, 2013

New Tools for Mendelian Disease Gene Identification: PhenoDB Variant Analysis Module; and GeneMatcher, a Web-Based Tool for Linking Investigators with an Interest in the Same Gene

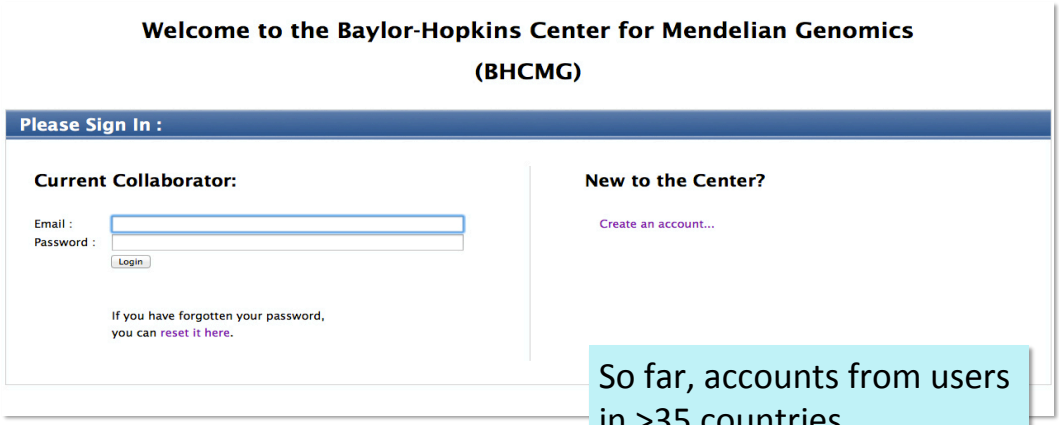
Nara Sobreira,[1]* François Schiettecatte,[2] Corinne Boehm,[1] David Valle,[1,3] and Ada Hamosh[1,3]

[1]McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205; [2]FS Consulting LLC, Salem, Massachusetts 01970; [3]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

Hum Mut 36:425, 2015

http://phenodbresearch.net
http://phenodb.org

BHCMG: PhenoDb – Submitter view



So far, accounts from users in >35 countries

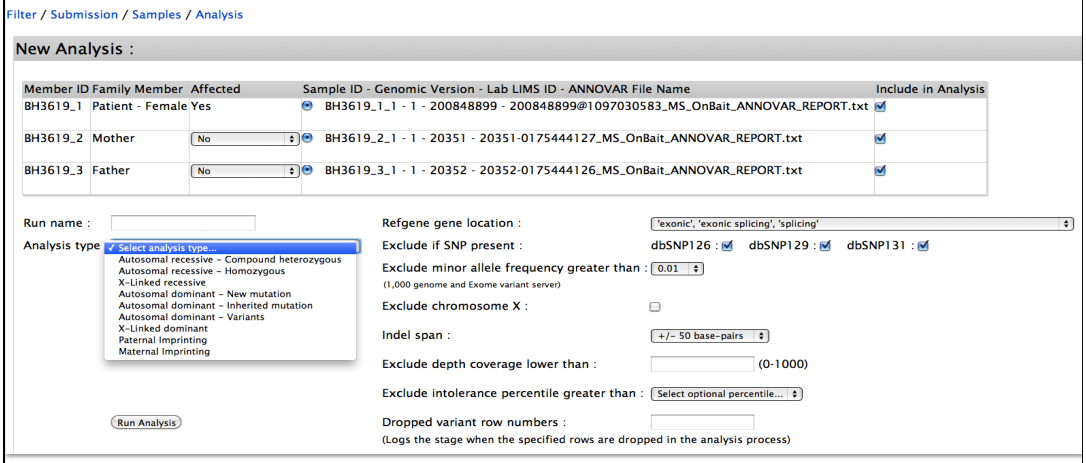
mendeliangenomics.org

PhenoDB Status for BHCMG*

- Data on 4,426 projects including 53 cohorts ranging from 5-295 subjects/cohort
- Phenotypic data from more than 10,284 individuals
- WES VCF and ANNOVAR files on > 6,225 samples
- Analysis performed with PhenoDB analysis tool
- Continually adding enhancements
- PhenoDB has been downloaded by more than 367 centers

* www.mendeliangenomics.org

PhenoDB Variant Analysis Tool



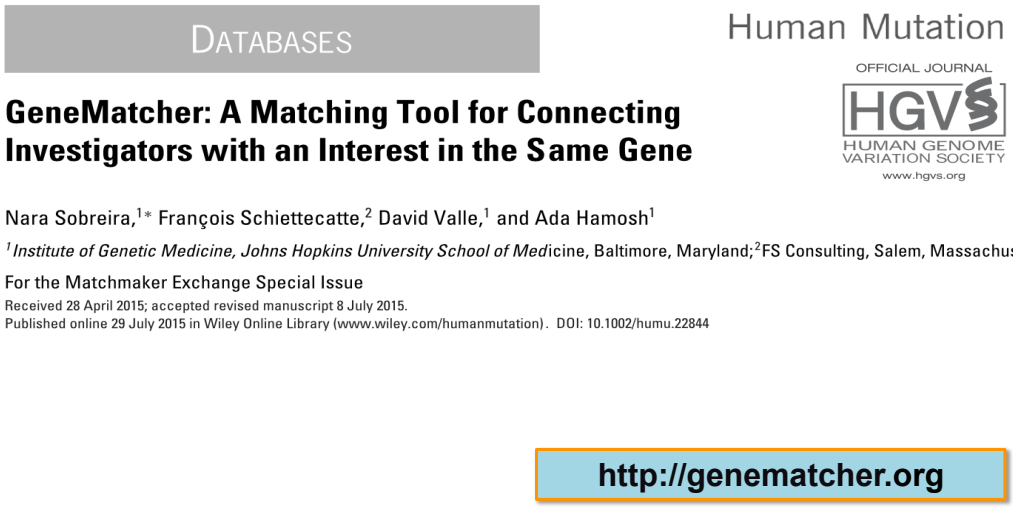
PhenoDB Features

- ANNOVAR files are created as VCFs are uploaded, and 3 standard analyses (AD, AR homozyg, AR cpd het) are generated
- Automatically creates a file for pathogenic or likely pathogenic incidental findings in the ACMG 56 genes
- Utilizes phenotypic info and OMIM algorithm to suggest possible diagnoses and to flag relevant known Mendelian disease genes in the candidate gene list
- An API allows transfer of final results (gene names, genomic coordinates, features) from PhenoDB to GeneMatcher

PhenoDB Features (continued)

- Proband information fully searchable including:
  - ✓ One or a combination of clinical features
  - ✓ Phenotypic features algorithm identifies other probands with similar features
  - ✓ Selected by shared variants, genes, genomic coordinates
- VCFs, analysis results files, final results files all searchable by genes or variants

GeneMatcher



DATABASES

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

GeneMatcher: A Matching Tool for Connecting Investigators with an Interest in the Same Gene

Nara Sobreira,[1]* François Schiettecatte,[2] David Valle,[1] and Ada Hamosh[1]

[1] *Institute of Genetic Medicine, Johns Hopkins University School of Med*icine, Baltimore, Maryland;[2]FS Consulting, Salem, Massachusetts

For the Matchmaker Exchange Special Issue

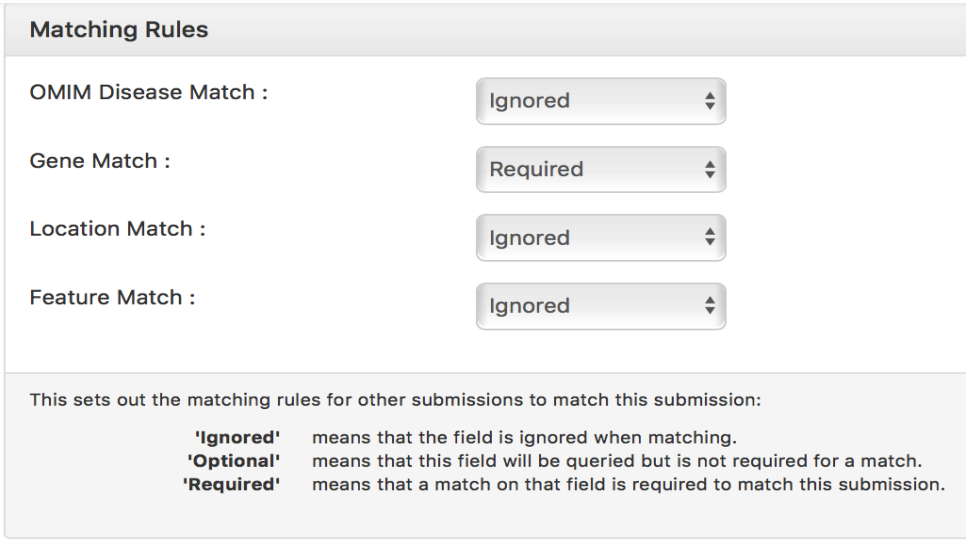
Received 28 April 2015; accepted revised manuscript 8 July 2015.
Published online 29 July 2015 in Wiley Online Library (www.wiley.com/humanmutation). DOI: 10.1002/humu.22844

http://genematcher.org

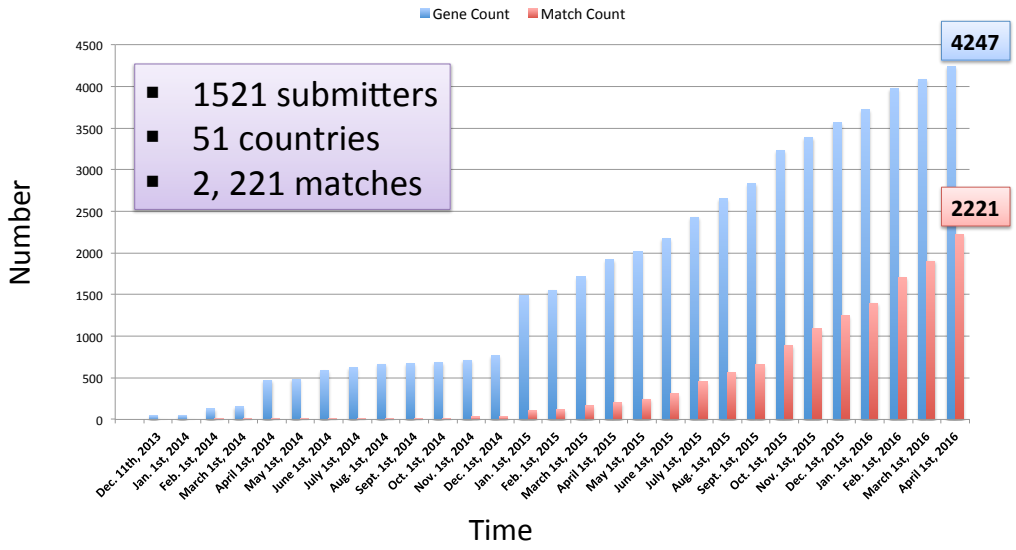
GeneMatcher Overview

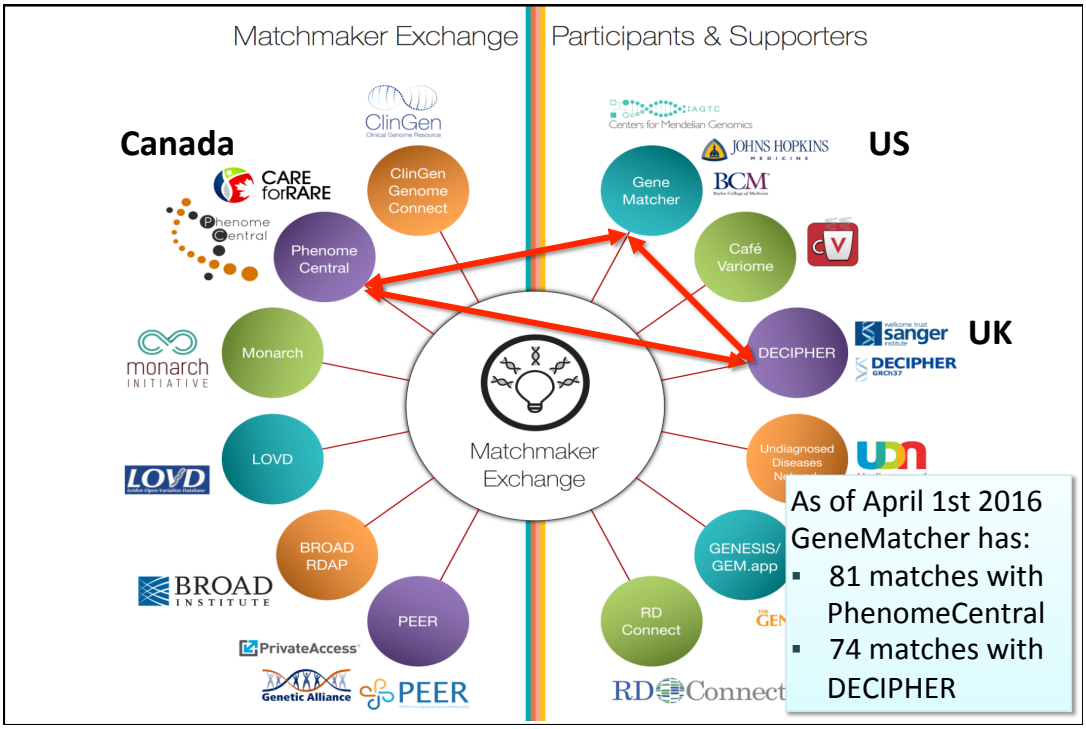
- Designed to connect investigators (clinicians, basic scientists) with an interest in the same gene
- All data de-identified so IRB not required
- Automated and continuous matching
- Submitters connected by a match can choose to collaborate at their own discretion
- Matching on phenotypic features added on 1 Oct 2015
- Connected to MME

GeneMatcher: Matching Options



GeneMatcher: Growth in Genes & Matches





BHCMG Summary Data at 4 Years

Category	Number
Consented samples	9032
Phenotypes (56% novel)	776
Exomes	6769
Disease genes -- total	468 *
Novel	222
Known (55% with pheno exp)	246
Publications	124

Finding disease genes: Some immediate consequences

- Connects genes to phenotypes
- Connects phenotype to biological system, normal and perturbed
- Unravels locus heterogeneity
- Enables precise diagnosis and counseling
- First step in path towards informed treatment
- Research stimulus, bench to bedside

Finding disease genes: Some long term consequences

- Suppose we had phenotypes for > 50% of the genes in our genome……
- What questions could we ask?

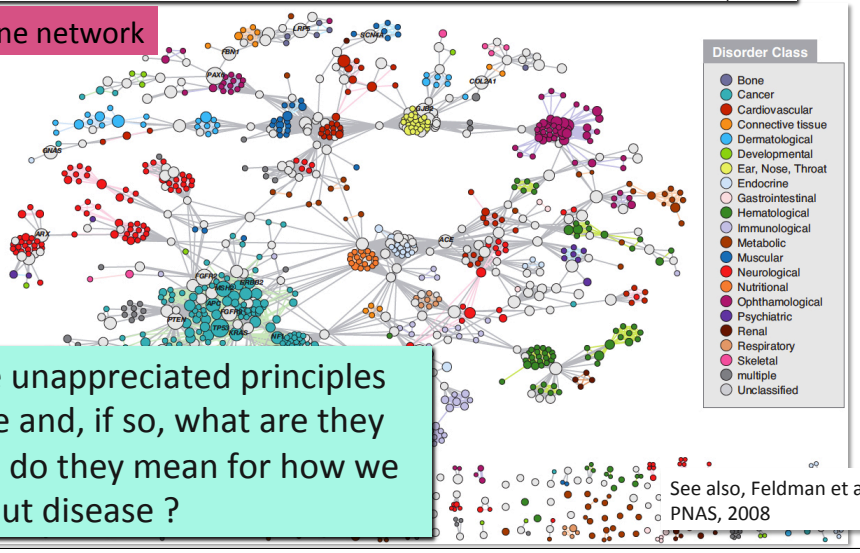
The human disease network

Kwang-Il Goh*†‡§, Michael E. Cusick†‡¶, David Valle‖, Barton Childs‖, Marc Vidal†‡¶**, and Albert-László Barabási*†‡**

*Center for Complex Network Research and Department of Physics, University of Notre Dame, Notre Dame, IN 46556; †Center for Cancer Systems Biology (CCSB) and ¶Department of Cancer Biology, Dana–Farber Cancer Institute, 44 Binney Street, Boston, MA 02115; ‡Department of Genetics, Harvard Medical School, 77 Avenue Louis Pasteur, Boston, MA 02115; §Department of Physics, Korea University, Seoul 136-713, Korea; and ‖Department of Pediatrics and the McKusick–Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205

PNAS, 2007

Disease gene network



Are there unappreciated principles of disease and, if so, what are they and what do they mean for how we think about disease ?

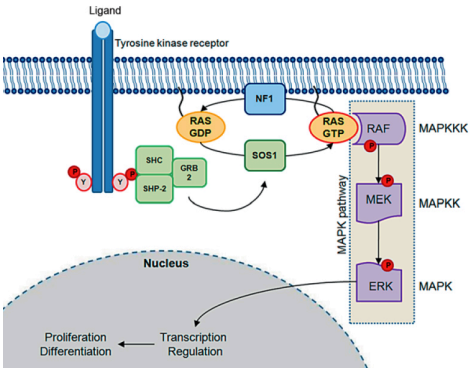
See also, Feldman et al, PNAS, 2008

Biological networks and disease: some questions

- Are all networks equally vulnerable; if not what are the rules?
- Are all components of a system equally vulnerable; if not what are the rules?
- Can we predict the consequences of variation in one component on the behavior of a system?

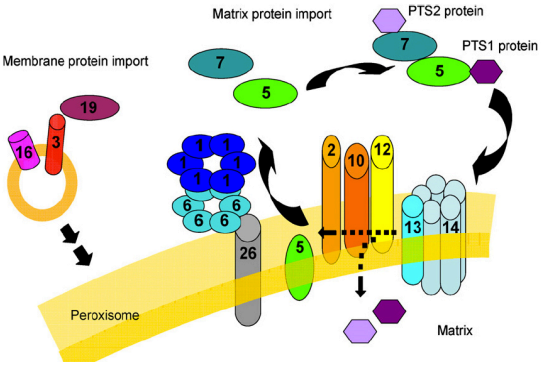
All components equally vulnerable?

Ras/MAPK



~30 genes
>15 phenotypes
No one gene predominates

Peroxisome biogenesis

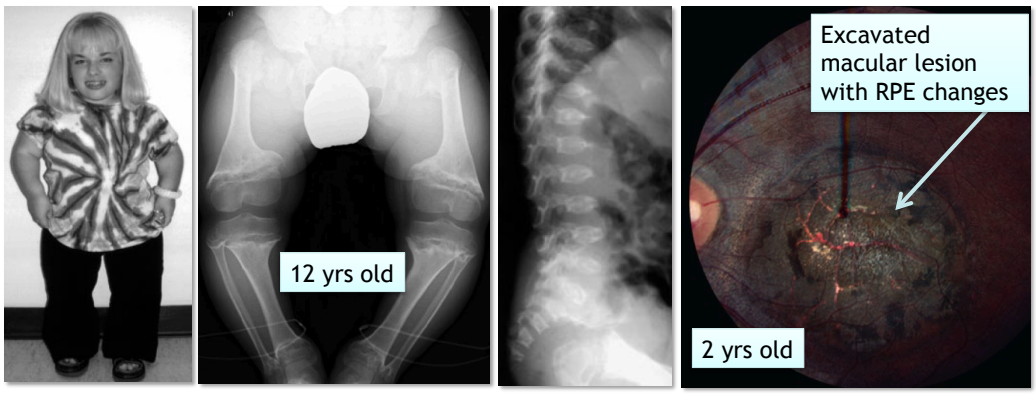


~30 genes
1-2 phenotypes
~65% *PEX1*

Some examples of short and long term consequences of disease gene identification

Predictive power of Mendelian disease

- Spondylometaphyseal dysplasia – cone/rod dystrophy
  - » Postnatal short stature and loss of visual function
  - » Rare autosomal recessive trait



* Julie Hoover-Fong, Nara Sobreira, Julie Juergens et al

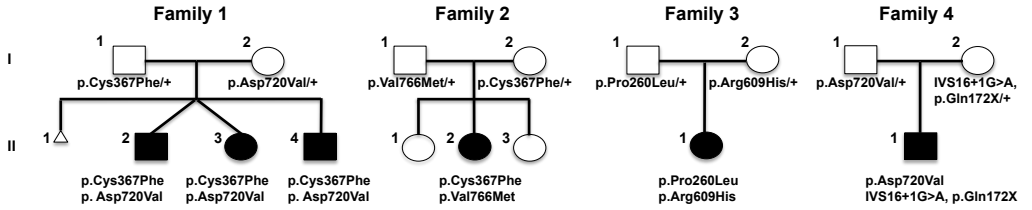
PCYT1A and SMD-CRD

- Three unrelated SMD-CRD pedigrees segregating two missense mutations, A99V and P150A, in *PCYT1A* at 3q29
- Encodes Phosphocholine cytidylytransferase
- Both residues conserved to fish
- Catalyzes synthesis of phosphatidylcholine, a major membrane structural lipid

CTP + Choline phosphate ⟶ CDP-choline + PPi

Identifying new systems:

TELO2: Pedigrees and Clinical Features*

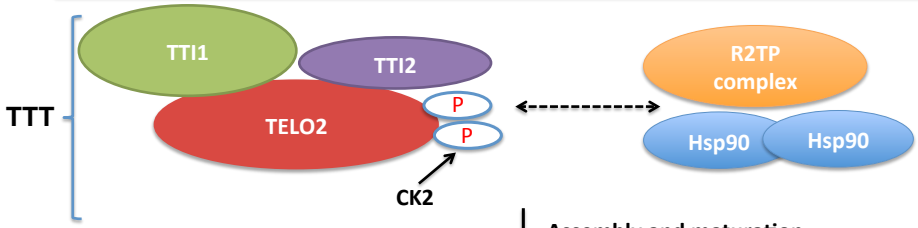


B

- Severe ID
- Seizures
- Abnormalities of the great vessels ?

* Jing You

TELO2 and the TTT Complex



Assembly and maturation

Phosphatidylinositol 3-kinase-related protein kinases (PIKKs)

ATM	ATR	PRKDC	mTOR	SMG1	TRRAP
DNA DSB repair	Replication stress	DNA DSB repair	Cell growth control	Nonsense mediated decay	Gene expression control

Ataxia Telangiectasia **Seckel syndrome I**

Lovejoy CA et al., 2009; Hořejší et al.,2010; Takai et al.,2007

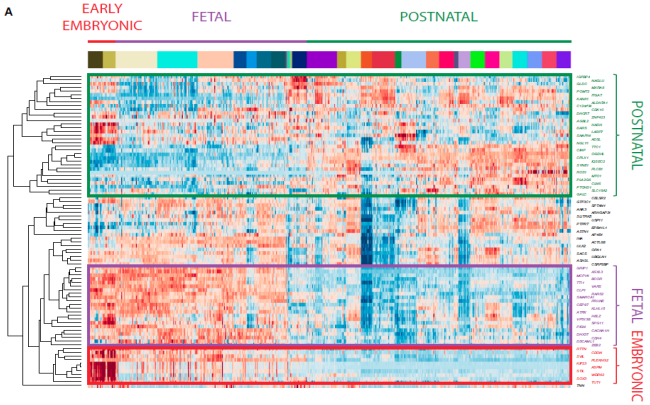
Neuron
Article

***Neuron 88*: 499-513**

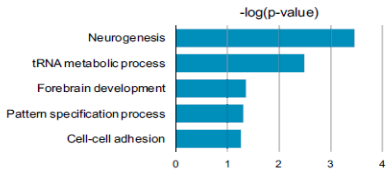
CellPress

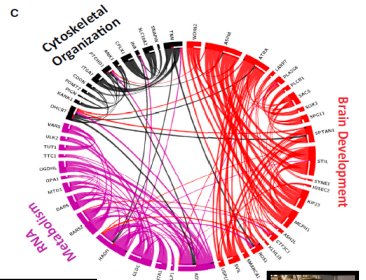
Genes that Affect Brain Structure and Function Identified by Rare Variant Analyses of Mendelian Neurologic Disease

Ender Karaca,[1] Tamar Harel,[1] Davut Pehlivan,[1] Shalini N. Jhangiani,[1,2] Tomasz Gambin,[1] Zeynep Coban Akdemir,[1] Claudia Gonzaga-Jauregui,[3] Serkan Erdin,[4,5] Yavuz Bayram,[1] Ian M. Campbell,[1] Jill V. Hunter,[6] Mehmed M. Atik,[1] Hilde Van Esch,[7] Bo Yuan,[1] Wojciech Wiszniewski,[1] Sedat Isikay,[8] Gozde Yesil,[9] Ozge O. Yuregir,[10] Sevcan Tug Bozdogan,[11] Huseyin Aslan,[12] Hatip Aydin,[13] Tulay Tos,[14] Ayse Aksoy,[15] Darryl C. De Vivo,[16] Preti Jain,[17] B. Bilge Geckinli,[18] Ozlem Sezer,[19] Davut Gul,[20] Burak Durmaz,[21] Ozgur Cogulu,[21] Ferda Ozkinay,[21] Vehap Topcu,[22] Sukru Candan,[23] Alper Han Cebi,[24] Mevlit Ikbal,[24] Elif Yilmaz Gulec,[25] Alper Gezdirici,[25] Erkan Koparir,[26] Fatma Ekici,[25] Salih Coskun,[26] Salih Cicek,[27] Kadri Karaer,[28] Asuman Koparir,[29] Mehmet Bugrahan Duz,[29] Emre Kirat,[29] Elif Fenercioglu,[29] Hakan Ulucan,[29] Mehmet Seven,[29] Tulay Guran,[30] Nursel Elcioglu,[31] Mahmut Selman Yildirim,[32] Dilek Aktas,[33] Mehmet Alikasifoglu,[33] Mehmet Ture,[34] Tahsin Yakut,[34] John D. Overton,[3] Adnan Yuksel,[35] Mustafa Ozen,[35] Donna M. Muzny,[1,2] David R. Adams,[36] Eric Boerwinkle,[2,37] Wendy K. Chung,[38] Richard A. Gibbs,[1,2] and James R. Lupski[1,2,39,40,*]



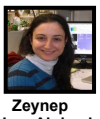
expression, annotation, and pathway analysis of known and candidate brain genes



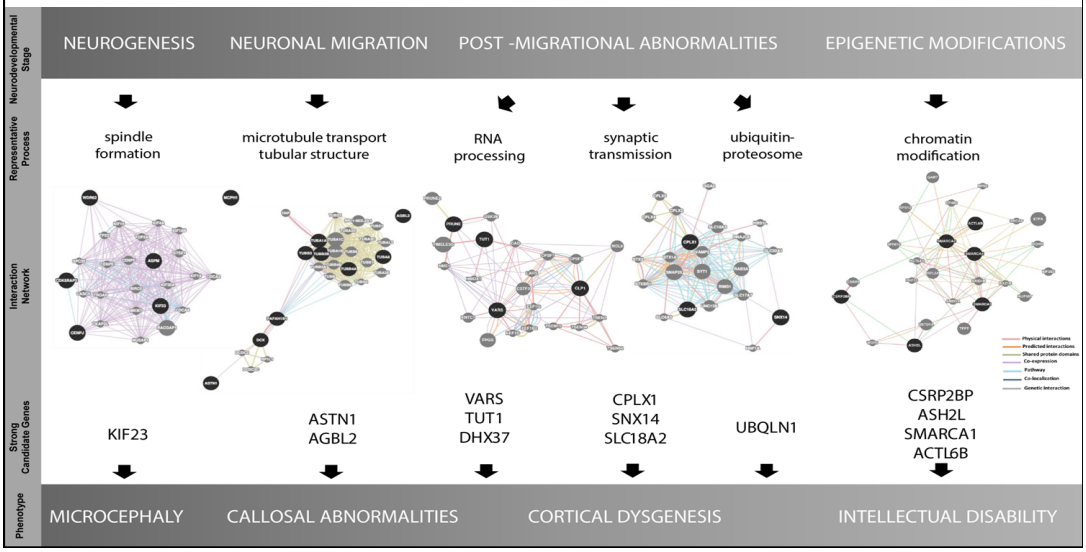



Ender Karaca


Tamar Harel


Zeynep Coban Akdemir

Suggested Correlation among Neurodevelopmental Stage, Representative Process, Strong Candidate Genes, and Phenotype



Cell Reports
Article

Gonzaga-Jauregui, *et al* (2015)
***Cell Reports* 12: 1169-1183**

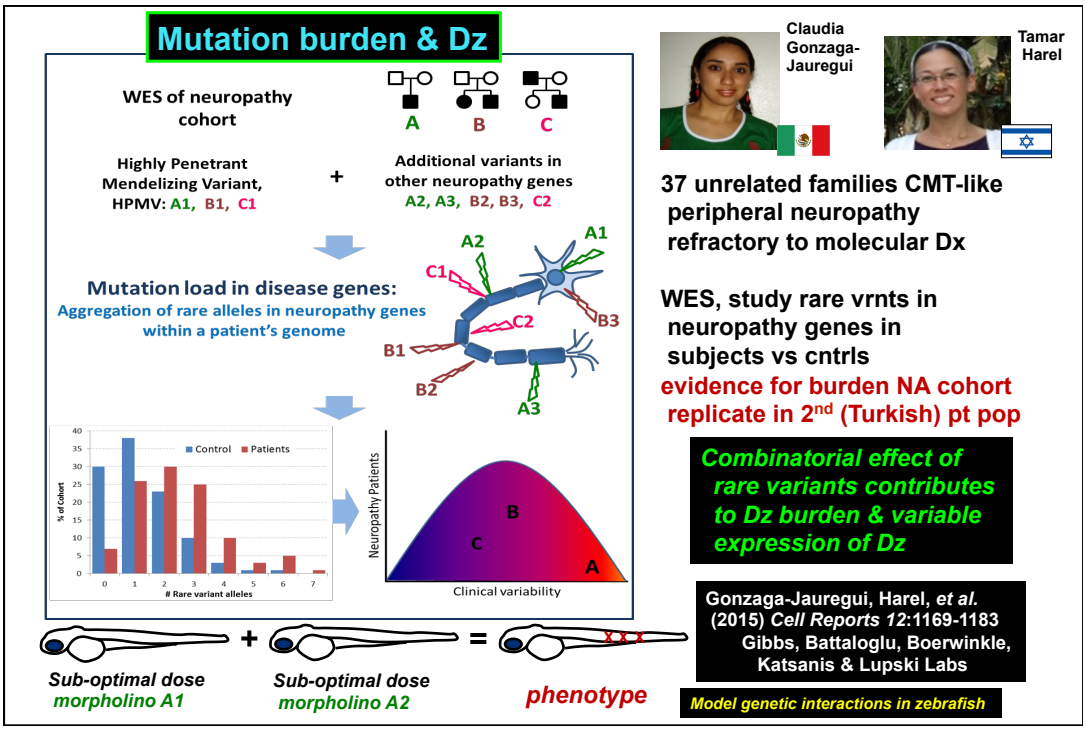
OPEN ACCESS
CellPress

Exome Sequence Analysis Suggests that Genetic Burden Contributes to Phenotypic Variability and Complex Neuropathy

Claudia Gonzaga-Jauregui,[1,2,21] Tamar Harel,[1,21] Tomasz Gambin,[1] Maria Kousi,[2] Laurie B. Griffin,[3,4] Ludmila Francescatto,[2] Burcak Ozes,[5] Ender Karaca,[1] Shalini N. Jhangiani,[6] Matthew N. Bainbridge,[6] Kim S. Lawson,[7] Davut Pehlivan,[1] Yuji Okamoto,[1] Marjorie Withers,[1] Pedro Mancias,[8] Anne Slavotinek,[9] Pamela J. Reitnauer,[10] Meryem T. Goksungur,[11] Michael Shy,[12] Thomas O. Crawford,[13] Michel Koenig,[14,15] Jason Willer,[2] Brittany N. Flores,[3] Igor Pediaditrakis,[2] Onder Us,[16] Wojciech Wiszniewski,[1] Yesim Parman,[11] Anthony Antonellis,[3,17,18] Donna M. Muzny,[6] Baylor-Hopkins Center for Mendelian Genomics, Nicholas Katsanis,[2] Esra Battaloglu,[5] Eric Boerwinkle,[6,7] Richard A. Gibbs,[1,6] and James R. Lupski[1,6,19,20,*]

Highlights:

- **WES of a neuropathy cohort identifies causal variants in ~45% of patients**
- **Three candidate peripheral neuropathy disease genes (*PMP2*, *DNAJB5*, *SPTLC3*) proposed**
- **Evidence for genetic mutation burden found in two independent cohorts**
- **Variant combinatorial effects may contribute to clinical variability and expressivity**



*Some unexpected emerging ideas**

- The extent and distribution of genetic variation
- Extent of locus heterogeneity
- The many examples of phenotypic expansion
- Unexpectedly large role for CNVs and *de novo* mutations
- Relatively high frequency of 2 diseases occurring in the same, difficult to diagnose, individual
- Genetic architecture and burden

REVIEW

The Genetic Basis of Mendelian Phenotypes: Discoveries, Challenges, and Opportunities

Jessica X. Chong,[1] Kati J. Buckingham,[1] Shalini N. Jhangiani,[2] Corinne Boehm,[3,4] Nara Sobreira,[3,4] Joshua D. Smith,[5] Tanya M. Harrell,[1] Margaret J. McMillin,[1] Wojciech Wiszniewski,[6] Tomasz Gambin,[6] Zeynep H. Coban Akdemir,[6] Kimberly Doheny,[3,7] Alan F. Scott,[3] Dimitri Avramopoulos,[3] Aravinda Chakravarti,[3] Julie Hoover-Fong,[3,4] Debra Mathews,[8] P. Dane Witmer,[3,7] Hua Ling,[3,7] Kurt Hetrick,[3,7] Lee Watkins,[3,7] Karynne E. Patterson,[5] Frederic Reinier,[5] Elizabeth Blue,[9] Donna Muzny,[2] Martin Kircher,[5] Kaya Bilguvar,[10] Francesc López-Giráldez,[10] V. Reid Sutton,[6] Holly K. Tabor,[1,5,11] Suzanne M. Leal,[6,12] Murat Gunel,[10] Shrikant Mane,[10] Richard A. Gibbs,[2,6] Eric Boerwinkle,[2,13] Ada Hamosh,[3,4] Jay Shendure,[5] James R. Lupski,[2,6,14] Richard P. Lifton,[10,15] David Valle,[3,4] Deborah A. Nickerson,[5] Centers for Mendelian Genomics, and Michael J. Bamshad[1,5,16,*]

AJHG, 2015

Thanks for your attention

BCM:
Jim Lupski
Richard Gibbs
Eric Boerwinkle
Shalini Jhangiani
Reid Sutton
Zeynep Coban Akdemir
Woj Wiszniewski
Wu-Lin Charng
Donna Muzny
Amy McGuire
Chad Shaw
Matt Bainbridge
Betty Fernandini

JH:
Ada Hamosh
Julie Hoover-Fong
Corinne Boehm
Dimitri Avramopoulos
Nara Sobreira
Dane Witmer
Kim Doheny
Kurt Hetrick
Hua Ling
Lee Watkins
Alan Scott
Aravinda Charavarti
Debra Mathews
Sandra Muscelli