The Continuous Spectrum of Mutations Spanning Mendelian and Complex Disease

Eric Boerwinkle

NHGRI Large-scale Program

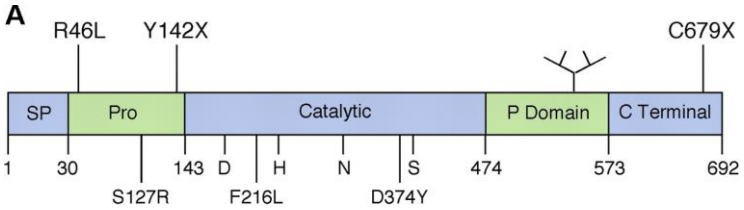
Bethesda, 2016

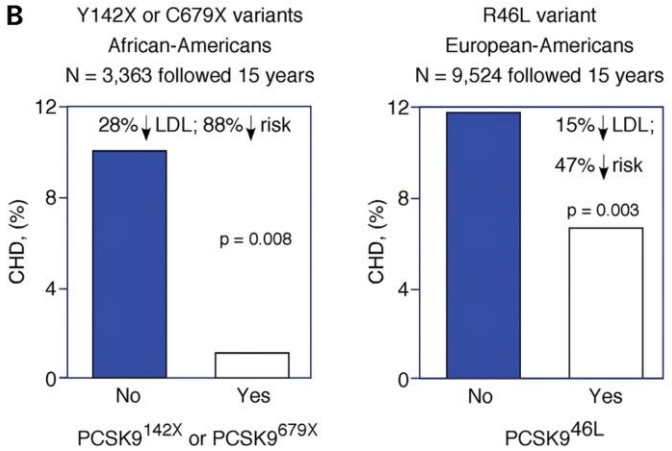
UTHealth
The University of Texas Health Science Center at Houston

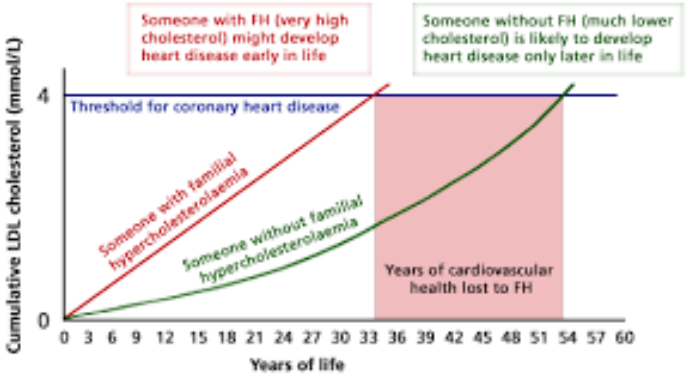
BCM
Baylor College of Medicine

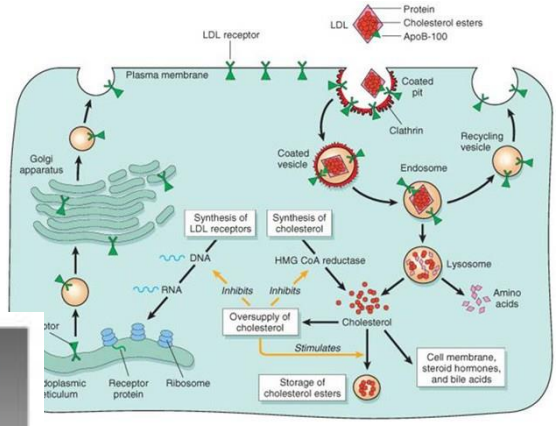
HGSC
HUMAN GENOME SEQUENCING CENTER

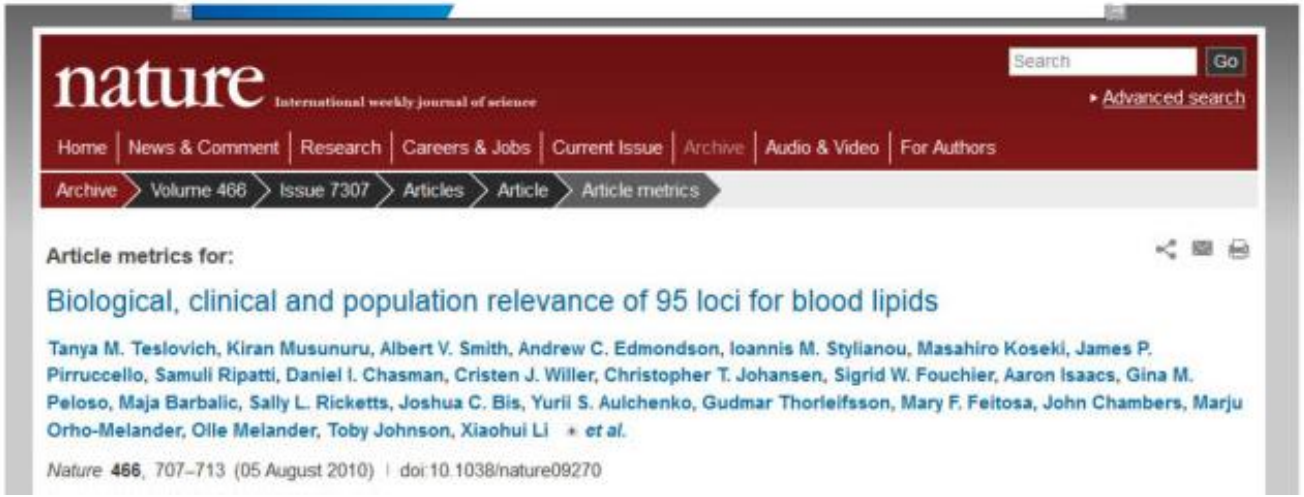
The Highs and Lows LDL Cholesterol











nature international weekly journal of science

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Archive > Volume 466 > Issue 7307 > Articles > Article > Article metrics

Article metrics for:

Biological, clinical and population relevance of 95 loci for blood lipids

Tanya M. Teslovich, Kiran Musunuru, Albert V. Smith, Andrew C. Edmondson, Ioannis M. Stylianou, Masahiro Koseki, James P. Pirruccello, Samuli Ripatti, Daniel I. Chasman, Cristen J. Willer, Christopher T. Johansen, Sigrid W. Fouchier, Aaron Isaacs, Gina M. Peloso, Maja Barbalic, Sally L. Ricketts, Joshua C. Bis, Yurii S. Aulchenko, Gudmar Thorleifsson, Mary F. Feitosa, John Chambers, Marju Orho-Melander, Olle Melander, Toby Johnson, Xiaohui Li + *et al.*

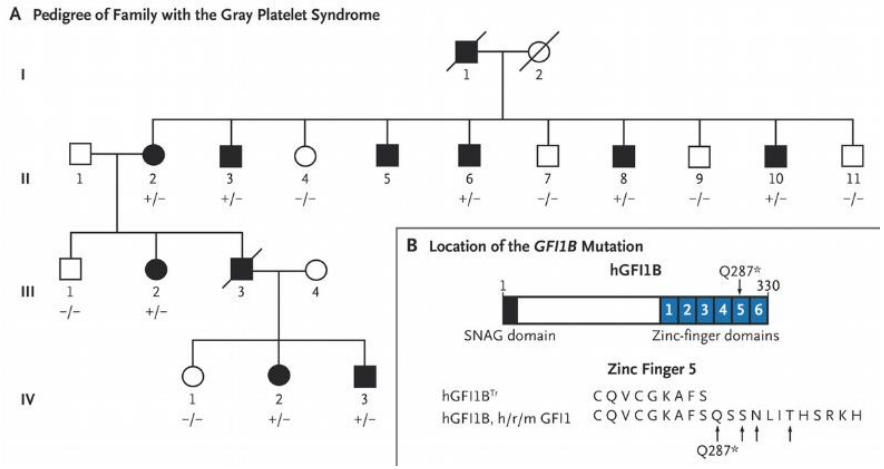
Nature **466**, 707–713 (05 August 2010) | doi:10.1038/nature09270

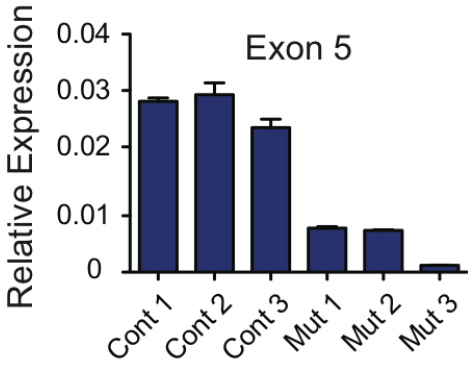
Why is this important?

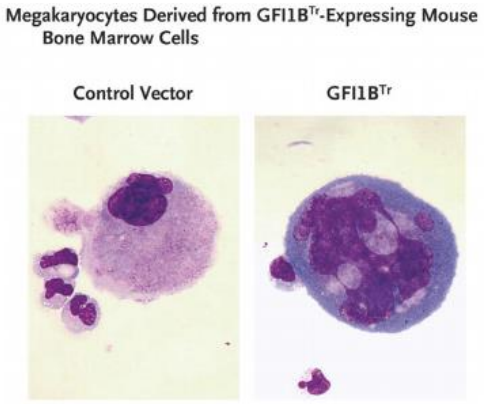
- Shared principles
  - Strategies for gene discovery
    - Ethnic diversity
    - Critical role of phenotype definition and endophenotypes
    - Consortia activities
    - Role of *de novo* mutation
  - Biology of health and disease
  - Pathways to intervention (e.g. drug targets)

GFI1B, growth factor independent 1B

- **Platelet count important for CHD and stroke**
- Transcriptional repressor causing Gray Platelet Syndrome
- CHARGE +ESP + UK10K for Platelet count (14,000 discovery, 32,000 replication)
- Synonymous *GFI1B* variant located in alternatively spliced exon
  - p=4.72x10-8 (EA, MAF=0.009, Beta=-0.4)
- Key to megakaryocyte/ platelet vs erythroid cell development



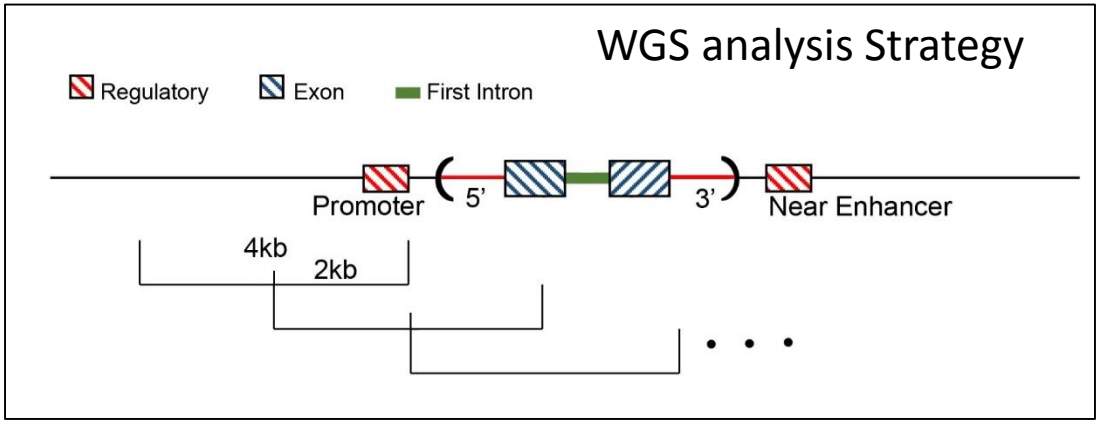




Polfus et al, Submitted

Monteferrario D· **A dominant-negative GFI1B mutation in the gray platelet syndrome.** N Engl J Med. 2014 Jan 16;370(3):245-53.

Asparagine: Critical for Brain Dev't

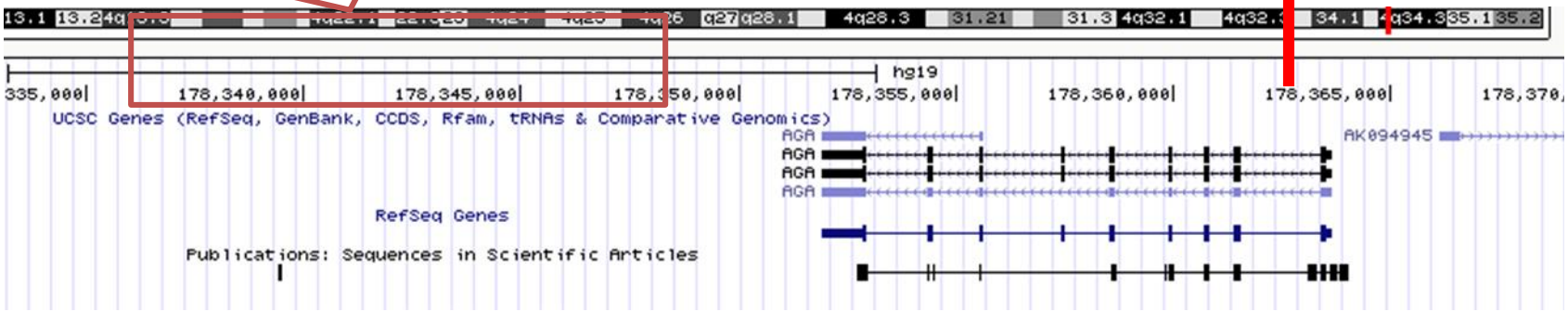


Asparagine:

- A non-essential amino acid;
- Biosynthesis/diet intake;
- Required for development and function of the brain.

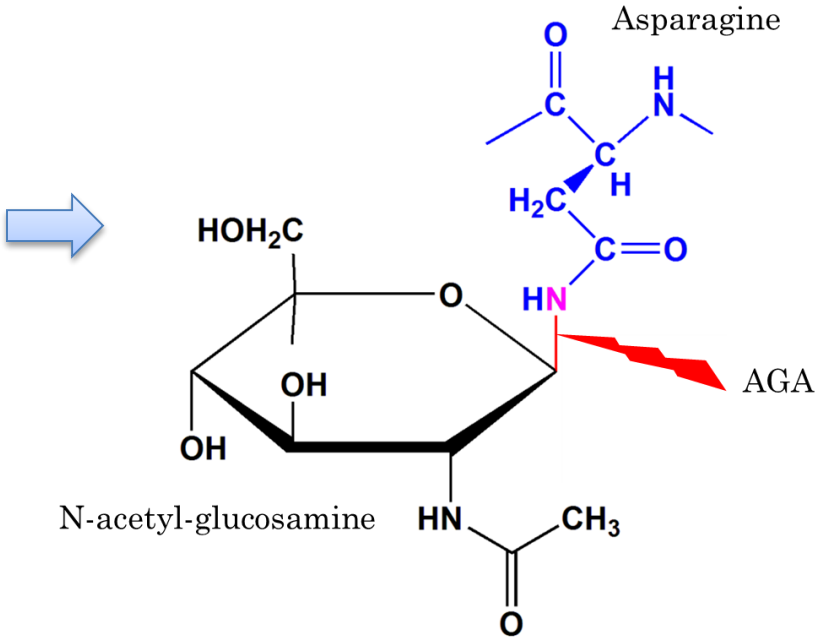
2 significant sliding windows ($p < 4e-8$), 6kb downstream of AGA

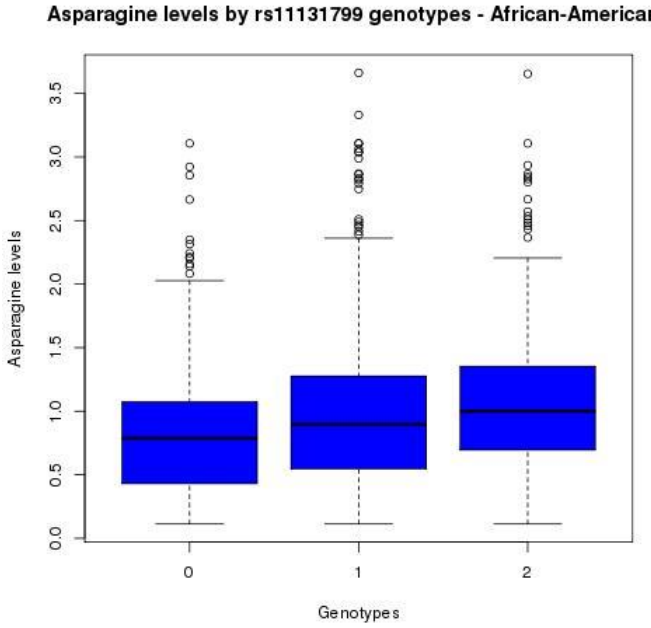
AGA: rs11131799, first intron, the most significant common variant

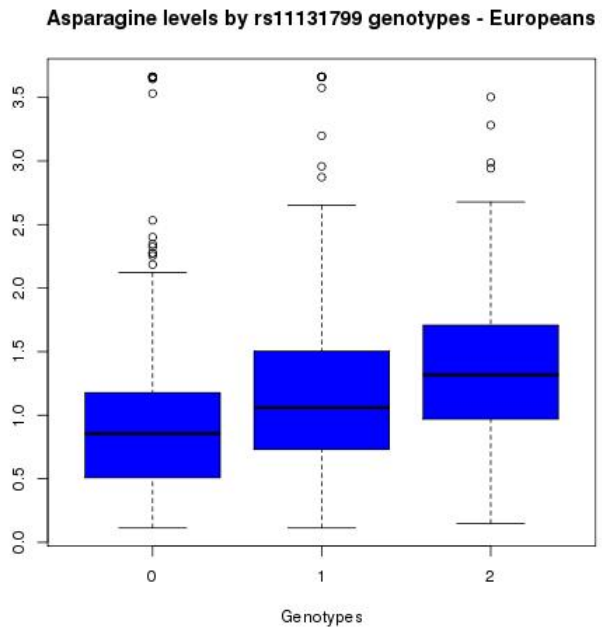


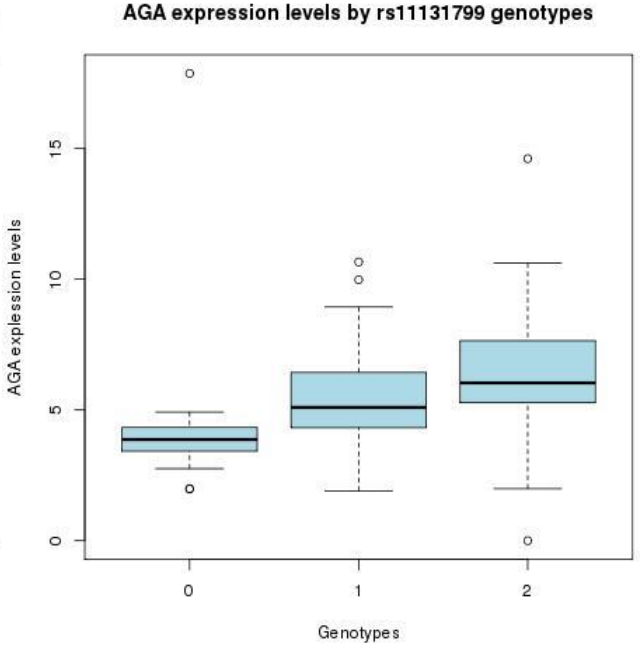
AGA gene:

- Aspartylglucosaminidase, which cleaves *asparagine* from N-acetylglucosamines.









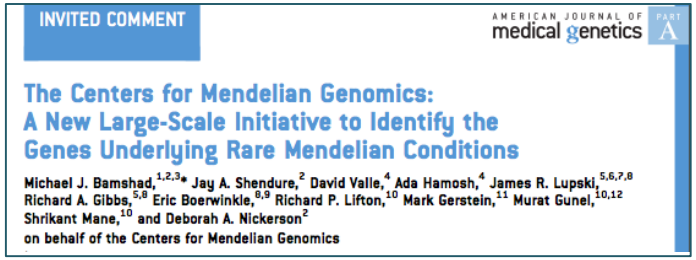
Centers for Mendelian Genomics

Funded by: NHGRI & NHLBI

New 2016-2019!!
- 4 CMGs: All 3 + Broad
- Additionally funded by NEI

BROAD INSTITUTE

2012


INVITED COMMENT

AMERICAN JOURNAL OF medical genetics PART A

The Centers for Mendelian Genomics: A New Large-Scale Initiative to Identify the Genes Underlying Rare Mendelian Conditions

Michael J. Bamshad,[1,2,3]* Jay A. Shendure,[2] David Valle,[4] Ada Hamosh,[4] James R. Lupski,[5,6,7,8] Richard A. Gibbs,[5,8] Eric Boerwinkle,[8,9] Richard P. Lifton,[10] Mark Gerstein,[11] Murat Gunel,[10,12] Shrikant Mane,[10] and Deborah A. Nickerson[2] on behalf of the Centers for Mendelian Genomics

2015


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],

4 Major Goals of the CMGs:

1. **Ascertain samples** for all Mendelian disorders for which genetic basis not yet understood.

2. Improve the efficiency of the sequencing; ongoing **technology innovation**.

3. To determine the **genetic basis** for as many Mendelian conditions as possible.

4. To **disseminate methods and data** to facilitate gene discovery by others

< Previous Article

Volume 97, Issue 3, p457–464, 3 September 2015

Report

Switch to Standard Vie

Mutations in *SPATA5* Are Associated with Microcephaly, Intellectual Disability, Seizures, and Hearing Loss

Akemi J. Tanaka, Megan T. Cho, Francisca Millan, Jane Juusola, Kyle Retterer, Charuta Joshi, Dmitriy Niyazov, Adolfo Garnica, Edward Gratz, Matthew Deardorff, Alisha Wilkins, Xilma Ortiz-Gonzalez, Katherine Mathews, Karin Panzer, Eva Brilstra, Koen L.I. van Gassen, Catharina M.L. Volker-Touw, Ellen van Binsbergen, Nara Sobreira, Ada Hamosh, Dianalee McKnight, Kristin G. Monaghan, Wendy K. Chung

Whole-Exome Sequencing in Familial Parkinson Disease

Janice L. Farlow, PhD[1]; Laurie A. Rob
Eric Boerwinkle, PhD[8,9]; Zeynep H. Co
Shen Gu, PhD[2]; Preti Jain, PhD[7,10]; Jo
Dongbing Lai, PhD[1]; Hai Lin, BS[12]; Hu
Donna Muzny, MS[8]; Paula Porter, MP
Richard M. Myers, PhD[7]; Joshua M. S

[+] Author Affiliations

RESEARCH

POGZ truncating alleles cause syndromic intellectual disability

Ja
Ke
Kl
M
D
Ri

Report

Biallelic Mutations i Encephalopathy, Gr

Asbjørg Stray-Pedersen[18], Jan-Maarten
Marielle Alders, Thorsten Gerstner, Kath
Donna M. Muzny, Maja Tarailo-Graovac
Genomics, James R. Lupski, Dejian Ren

CLINICAL MEDICINE

Molecular etiology of arthrogryposis in multiple families of mostly Turkish origin

Yavuz Bayram,[1] Ender Karaca,[1] Zeynep Coban Akdemir,[1] Elif Ozdamar Yilmaz,[2] Gulsen Akay Tayfun,[3] Hatip Aydin,[4] De
Sevcan Tug Bozdogan,[6] Alper Gezdirici,[7] Sedat Isikay,[8] Mehmed M. Atik,[1] Tomasz Gambin,[1] Tamar Harel,[1] Ayman W. E
Wu-Lin Charng,[1] Davut Pehlivan,[1] Shalini N. Jhangiani,[10] Donna M. Muzny,[10] Ali Karaman,[11] Tamer Celik,[12] Ozge O
Timur Yildirim,[14] Ilhan A. Bayhan,[14] Eric Boerwinkle,[10,15] Richard A. Gibbs,[10] Nursel Elcioglu,[3] Beyhan Tuysuz,[2] and Ja

GENETICS IN MEDICINE | ORIGINAL RESEARCH ARTICLE

The role of combined SNV and CNV burden in patients with distal symmetric polyneuropathy

Davut Pehlivan MD, Christine R. Beck PhD, Yuji Okamoto MD, PhD, Tamar Harel MD, PhD, Zeynep H. C. Akdemir PhD, Shalini N. Jhangiani MS, Marjorie A. Withers BS, Meryem Tuba Goksungur MD, Claudia M. B. Carvalho PhD, Dirk Czesnik MD, Claudia Gonzaga-Jauregui PhD, Wojciech Wiszniewski MD, PhD, Donna M. Muzny MS, Richard A. Gibbs PhD, Bernd Rautenstrauss PhD, Michael W. Sereda MD & James R. Lupski MD, PhD, DSc(hon)

Article

DVL1 Frameshift Mutations Clustering in the Penultimate Exon Cause Autosomal-Dominant Robinow Syndrome

Janson White[1, 17], Juliana F. Mazzeu[2, 3, 17], Alexander Hoischen[4], Shalini N. Jhangiani[5], Tomasz Gambin[1, 6], Michele Calijorne Alcino[7], Samantha Penney[1], Jorge M. Saraiva[8, 9], Hanne Hove[10], Flemming Skovby[10], Hülya Kayserili[11, 12], Elicia Estrella[13], Anneke T. Vulto-van Silfhout[4], Marloes Steehouwer[4], Donna M. Muzny[5], V. Reid Sutton[1, 14], Richard A. Gibbs[1, 5], Baylor-Hopkins Center for Mendelian Genomics, James R. Lupski[1, 5, 14, 15], Han G. Brunner[4, 16], Bregje W.M. van Bon[4], Claudia M.B. Carvalho[1, 7],

Clinical Report

FBN1 contributing to familial congenital diaphragmatic hernia

Tyler F. Beck, Philippe M. Campeau, Shalini N. Jhangiani, Tomasz Gambin, Alexander H. Li, Reem Abo-Zahrah, Valerie K. Jordan, Andres Hernandez-Garcia, Gibbs, Eric Boerwinkle, yl A. Scott

BHCMG Findings…
~200 'new genes + expanded phenotypes'
84+ Publications

…types: Discoveries,

…brinne Boehm[3, 4], Nara Sobreira[3, 4], …ech Wiszniewski[6], Tomasz Gambin[6], …Dimitri Avramopoulos[3], Aravinda …mer[3, 7], Hua Ling[3, 7], Kurt Hetrick[3, 7], Lee

Switch to Standard View

Recurrent Muscle Weakness with Rhabdomyolysis, Metabolic Crises, and Cardiac Arrhythmia Due to Bi-allelic *TANGO2* Mutations

Seema R. Lalani[21], Pe
Yan Ding, Shujuan Pan, Fra
Zeynep Hande Coban Akde
Bradley P. Coe, Mahshid A
Gary Clark, Angus Wilfong,
Jane Crosson, Jessica Duis
Art Beaudet, Christine M. E
[21] These authors contributed equally

Rare Variants in the Notch Signaling Pathway Describe a Novel Type of Autosomal Recessive Klippel–Feil Syndrome

Ender Karaca,[1] Ozge O. Yuregir,[2] Sevcan T. Bozdogan,[3] Huseyin Aslan,[4] Davut Pehlivan,[1] Shalini N. Jhangiani,[1,5] Zeynep C. Akdemir,[1] Tomasz Gambin,[1] Yavuz Bayram,[1] Mehmed M. Atik,[1] Serkan Erdin,[6,7] Donna Muzny,[1,5] Richard A. Gibbs,[1,5] James R. Lupski,[1,5,8,9]* and The Baylor-Hopkins Center for Mendelian Genomics

Nature Genetics 47, 654–

COPA mutations impair ER-Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis

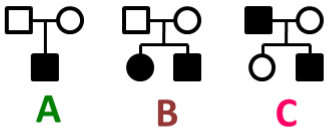
Levi B Watkin , Birthe Jessen , Wojciech Wiszniewski , Timothy J Vece , Max Jan , Youbao Sha , Maike Thamsen , Regie L P Santos-Cortez , Kwanghyuk Lee , Tomasz Gambin , Lisa R Forbes , Christopher S Law , Asbjørg Stray-Pedersen , Mickie H Cheng , Emily M Mace , Mark S Anderson , Dongfang Liu , Ling Fung Tang , Sarah K Nicholas , Karen Nahmod , George Makedonas , Debra L Canter , Pui-Yan Kwok , John Hicks , Kirk D Jones , Samantha Penney , Shalini N Jhangiani , Michael D Rosenblum , Sharon D Dell , Michael R Waterfield , Feroz R Papa , Donna M Muzny , Noah Zaitlen , Suzanne M Leal , Claudia Gonzaga-Jauregui , Eric Boerwinkle , N Tony Eissa , Richard A Gibbs , James R Lupski , Jordan S Orange & Anthony K Shum

Mutation Burden in Complex Neuropothy

Claudia Gonzaga-Jauregui

Tamar Harel

WES of neuropathy cohort



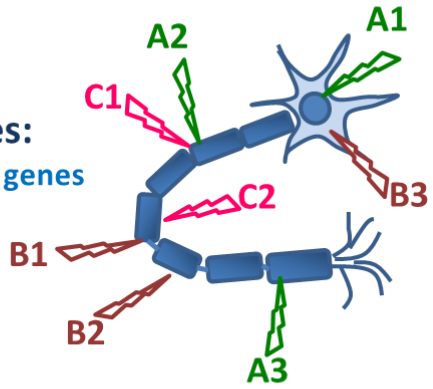
Highly Penetrant Mendelizing Variant, HPMV: A1, B1, C1

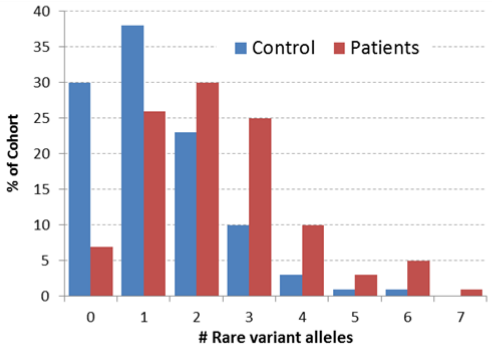
+

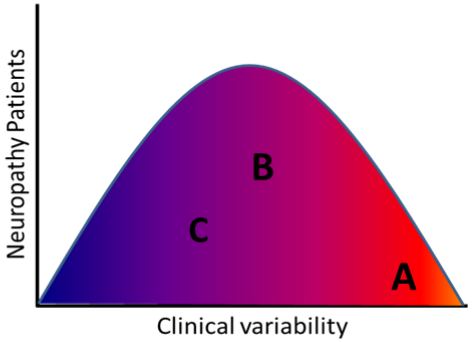
Additional variants in other neuropathy genes
A2, A3, B2, B3, C2

~45% of cases

Mutation load in disease genes:
Aggregation of rare alleles in neuropathy genes within a patient's genome







37 unrelated families CMT-like peripheral neuropathy refractory to molecular Dx

WES, study rare vrnts in neuropathy genes in subjects vs cntrls
evidence for burden NA cohort replicate in 2nd (Turkish) pt pop

Combinatorial effect of rare variants contributes to Dz burden & variable expression of Dz

Sub-optimal dose morpholino A1

Sub-optimal dose morpholino A2

phenotype

Gonzaga-Jauregui, Harel, *et al.* (2015) *Cell Reports 12*:1169-1183
Gibbs, Battaloglu, Boerwinkle, Katsanis & Lupski Labs

Model genetic interactions in zebrafish

Lessons from the BCM Clinical Lab

de novo Mutant Alleles (AD: 74%; XL: 62%)

Mendelian Dz	*'textbook'*	*observations*
AD (n = 280)	family history	*de novo* (208/280; 74%) mosaic (3; 1%) inh, mosaic in parent (2; 1%)
AR (n = 181)	compound HTZ [outbred pop.]	cmpnd HTZ SNV (104; 57%) cmpnd HTZ SNV + CNV (4; 2%) HMZ (68; 37%) (shared ancestry; 50%) HMZ UPD (5; 3%)
XL (n = 65)	males >> females *de novo*	Male 52% : female 48% m,17/34 (50%, 2 mosaic cases) f, 23/31(74%)

De novo Events and Autism

Rare de novo mutations may cause half of autism cases

Study Links Harmful De Novo Gene Mutations to More-Severe Autism

Share 52 Tweet 8 Google + 0 Email 0 Share 0

By contrast, milder forms of autism are more strongly associated with family history of psychiatric issues

November 04, 2014

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Published online 2012 Apr 4. doi: 10.1038/nature11011
PMCID: PMC3613847
NIHMSID: NIHMS361899

Patterns and rates of exonic *de novo* mutations in autism spectrum disorders

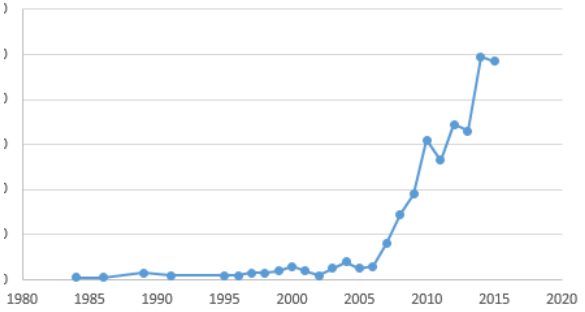
Benjamin M. Neale,[1,2] Yan Kou,[3,4] Li Liu,[5] Avi Ma'ayan,[3] Kaitlin E. Samocha,[1,2] Aniko Sabo,[6] Chiao-Feng Lin,[7] Christine Stevens,[2] Li-San Wang,[7] Vladimir Makarov,[4,8] Paz Polak,[2,9] Seungtai Yoon,[4,8] Jared Maguire,[2] Emily L. Crawford,[10] Nicholas G. Campbell,[10] Evan T. Geller,[7] Otto Valladares,[7] Chad Shafer,[5] Han Liu,[11] Tuo Zhao,[11] Guiqing Cai,[4,8] Jayon Lihm,[4,8] Ruth Dannenfelser,[3] Omar Jabado,[12] Zuleyma Peralta,[12] Uma Nagaswamy,[6] Donna Muzny,[6] Jeffrey G. Reid,[6] Irene Newsham,[6] Yuanqing Wu,[6] Lora Lewis,[6] Yi Han,[6] Benjamin F. Voight,[2,13] Elaine Lim,[1,2] Elizabeth Rossin,[1,2] Andrew Kirby,[1,2] Jason Flannick,[2] Menachem Fromer,[1,2] Khalid Shakir,[2] Tim Fennell,[2] Kiran Garimella,[2] Eric Banks,[2] Ryan Poplin,[2] Stacey Gabriel,[2] Mark DePristo,[2] Jack R. Wimbish,[14] Braden E. Boone,[14] Shawn E. Levy,[14] Catalina Betancur,[15] Shamil Sunyaev,[2,9] Eric Boerwinkle,[6,16] Joseph D. Buxbaum,[4,8,12,17,*] Edwin H. Cook, Jr.,[18] Bernie Devlin,[19] Richard A. Gibbs,[6] Kathryn Roeder,[5,*] Gerard D. Schellenberg,[7] James S. Sutcliffe,[10] and Mark J. Daly[1,2,*]

Nat Genet. 2014 Sep;46(9):944-50. doi: 10.1038/ng.3050. Epub 2014 Aug 3.

A framework for the interpretation of de novo mutation in human disease.

Samocha KE[1], Robinson EB[2], Sanders SJ[3], Stevens C[4], Sabo A[5], McGrath LM[6], Kosmicki JA[7], Rehnström K[8], Mallick S[9], Kirby A[10], Wall DP[11], MacArthur DG[10], Gabriel SB[12], DePristo M[13], Purcell SM[14], Palotie A[15], Boerwinkle E[16], Buxbaum JD[17], Cook EH Jr[18], Gibbs RA[5], Schellenberg GD[19], Sutcliffe JS[20], Devlin B[21], Roeder K[22], Neale BM[2], Daly MJ[2].

Pubmed search: "de novo" and "autism"



Nature. 2014 Nov 13;515(7526):216-21. doi: 10.1038/nature13908. Epub 2014 Oct 29.

The contribution of de novo coding mutations to autism spectrum disorder.

Iossifov I[1], O'Roak BJ[2], Sanders SJ[3], Ronemus M[1], Krumm N[4], Levy D[1], Stessman HA[4], Witherspoon KT[4], Vives L[4], Patterson KE[4], Smith JD[4], Paeper B[4], Nickerson DA[4], Dea J[5], Dong S[6], Gonzalez LE[7], Mandell JD[5], Mane SM[8], Murtha MT[7], Sullivan CA[7], Walker MF[5], Waqar Z[7], Wei L[9], Willsey AJ[3], Yamrom B[1], Lee YH[1], Grabowska E[10], Dalkic E[11], Wang Z[1], Marks S[1], Andrews P[1], Leotta A[1], Kendall J[1], Hakker I[1], Rosenbaum J[1], Ma B[1], Rodgers L[1], Troge J[1], Narzisi G[10], Yoon S[1], Schatz MC[1], Ye K[12], McCombie WR[1], Shendure J[4], Eichler EE[13], State MW[14], Wigler M[1].

Nat Commun. 2014 Nov 24;5:5595. doi: 10.1038/ncomms6595.

Recurrent de novo mutations implicate novel genes underlying simplex autism risk.

O'Roak BJ[1], Stessman HA[1], Boyle EA[1], Witherspoon KT[1], Martin B[1], Lee C[1], Vives L[1], Baker C[1], Hiatt JB[1], Nickerson DA[1], Bernier R[2], Shendure J[1], Eichler EE[3].

Author information

Abstract

Autism spectrum disorder (ASD) has a strong but complex genetic component. Here we report on the resequencing of 64 candidate neurodevelopmental disorder risk genes in 5,979 individuals: 3,486 probands and 2,493 unaffected siblings. We find a strong burden of de novo point mutations for these genes and specifically implicate nine genes. These include CHD2 and SYNGAP1, genes previously reported in related disorders, and novel genes TRIP12 and PAX5. We also show that mutation carriers generally have lower IQs and enrichment for seizures. These data begin to distinguish genetically distinct subtypes of autism important for aetiological classification and future therapeutics.

PMID: 25418537 [PubMed - indexed for MEDLINE] PMCID: PMC4249945 Free PMC Article

J Hum Genet. 2015 May;60(5):277-9. doi: 10.1038/jhg.2015.13. Epub 2015 Feb 19.

A case of autism spectrum disorder arising from a de novo missense mutation in POGZ.

Fukai R[1], Hiraki Y[2], Yofune H[3], Tsurusaki Y[4], Nakashima M[4], Saitsu H[4], Tanaka F[5], Miyake N[4], Matsumoto N[4].

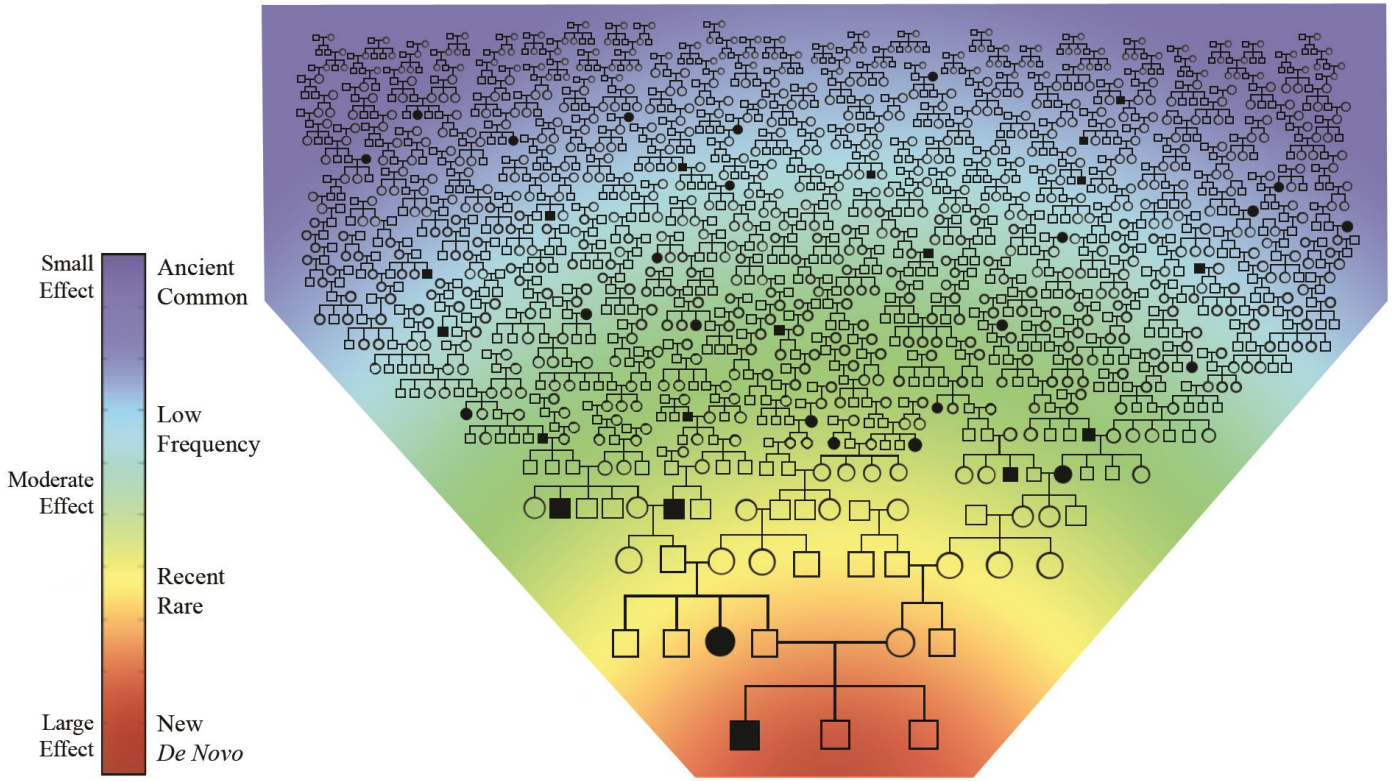
Author information

Abstract

Autism spectrum disorder (ASD) is a clinically heterogeneous psychiatric disorder with various genetic backgrounds. Here, we report a novel mutation in the pogo transposable element-derived protein with zinc finger domain gene (POGZ) identified by trio-based whole exome sequencing. To date, a total of seven de novo POGZ mutations in ASD have been reported. POGZ contains a total of five functional domains, and this study reports the first de novo missense mutation in the centromere protein B-like DNA-binding domain. POGZ is highly expressed in the human fetal brain and is involved in mitosis and the regulation of neuronal proliferation. Therefore its loss-of-function or pathogenic missense mutations are likely to be causative of ASD.

PMID: 25694107 [PubMed - indexed for MEDLINE]

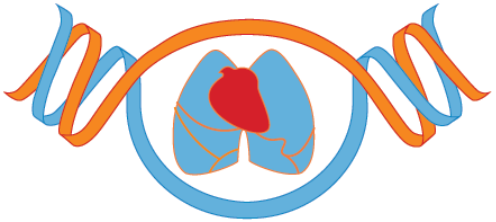
Genomics in a Deep Historic Context



Lupski et al (2011) Cell

Consortium Efforts

COHORTS FOR HEART AND AGING RESEARCH IN GENOMIC EPIDEMIOLOGY



T2D

ICBP

stands for

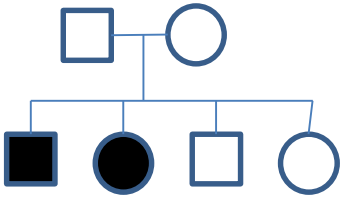
International Consortium for Blood Pressure

Abbreviations.com

Genetic Architecture of Human Disease

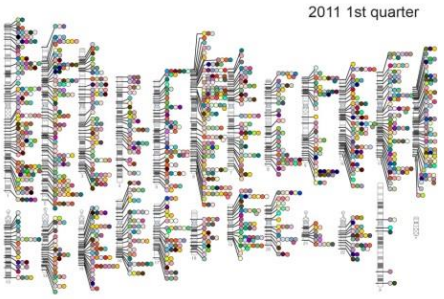
Mendel…….. ‘Oligogenic’ ……CD/CV (GWAS)

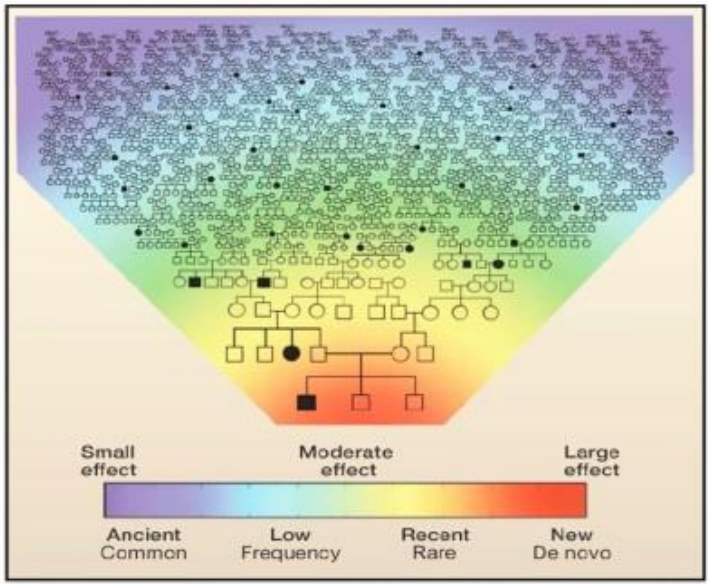
Low frequency/High impact
Not related to sporadic cases in a simple way

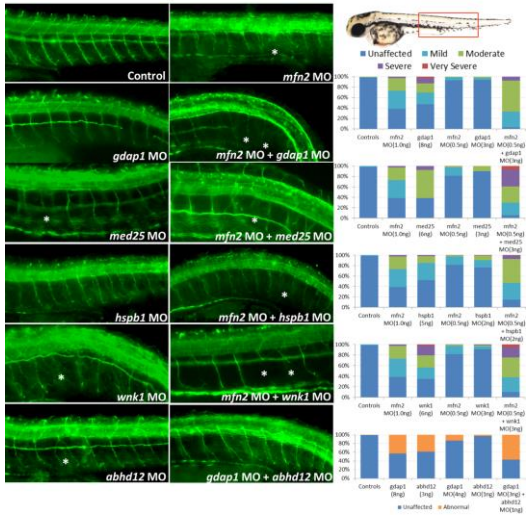


The ‘missing heritability’?

High frequency
Few Actionable Alleles
Missing ‘Heritability’







Joint Challenges and Opportunities

- **Shared challenges:**
  - Gene discovery approaches: for instance, exomes vs genomes
  - Variant discovery: structural variants, indels, etc.
  - Variant annotation: splicing, non-coding
  - How to share data ethically and impactfully
- **Shared opportunities:**
  - Overview of the genetic architecture of human disease
  - Are there phenotypes where CCDG and CMG will provide complementary insights into disease biology?
  - CCDG data will provide a critical reference for CMG (following model of ExAC) – but requires data harmonization and availability of frequency resource