How the new technologies are changing genetic screening of sudden cardiac death?

Lia Crotti, MD, PHD

IRCCS Istituto Auxologico Italiano, Milan
and
University of Pavia

The new technologies have changed and are changing genetic screening both 1) IN THE CLINICAL and 2) IN THE RESEARCH SETTING

Molecular screening in clinical practice

Europace (2011) 13, 1077–1109
doi:10.1093/europace/eur245

HRS/EHRA EXPERT CONSENSUS STATEMENT

HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)

Michael J. Ackerman, MD, PhD[1], Silvia G. Priori, MD, PhD[2], Stephan Willems, MD, PhD[3], Charles Berul, MD, FHRS, CCDS[4], Ramon Brugada, MD, PhD[5], Hugh Calkins, MD, FHRS, CCDS[6], A. John Camm, MD, FHRS[7], Patrick T. Ellinor, MD, PhD[8], Michael Gollob, MD[9], Robert Hamilton, MD, CCDS[10], Ray E. Hershberger, MD[11], Daniel P. Judge, MD[6,12], Hervè Le Marec, MD[13], William J. McKenna, MD[14], Eric Schulze-Bahr, MD, PhD[15], Chris Semsarian, MBBS, PhD[16], Jeffrey A. Towbin, MD[17], Hugh Watkins, MD, PhD[18], Arthur Wilde, MD, PhD[19], Christian Wolpert, MD[20], and Douglas P. Zipes, MD, FHRS[21]

Europace 2011

Canadian Journal of Cardiology 27 (2011) 232–245

Society Position Statement

Recommendations for the Use of Genetic Testing in the Clinical Evaluation of Inherited Cardiac Arrhythmias Associated with Sudden Cardiac Death: Canadian Cardiovascular Society/Canadian Heart Rhythm Society Joint Position Paper

Michael H. Gollob, MD (Chair),[a] Louis Blier, MD,[b] Ramon Brugada, MD,[c] Jean Champagne, MD,[b] Vijay Chauhan, MD,[d] Sean Connors, MD,[c] Martin Gardner, MD,[f] Martin S. Green, MD,[a] Robert Gow, MB, BS,[g] Robert Hamilton, MD,[h] Louise Harris, MB,[d] Jeff S. Healey, MD,[i] Kathleen Hodgkinson, PhD,[j] Christina Honeywell, MSc,[g] Michael Kantoch, MD,[k] Joel Kirsh, MD,[h] Andrew Krahn, MD,[n] Michelle Mullen, PhD,[o] Ratika Parkash, MD,[f] Damian Redfearn, MB,[l] Julie Rutberg, MSc,[a] Shubhayan Sanatani, MD,[m] and Anna Woo, MD[d]

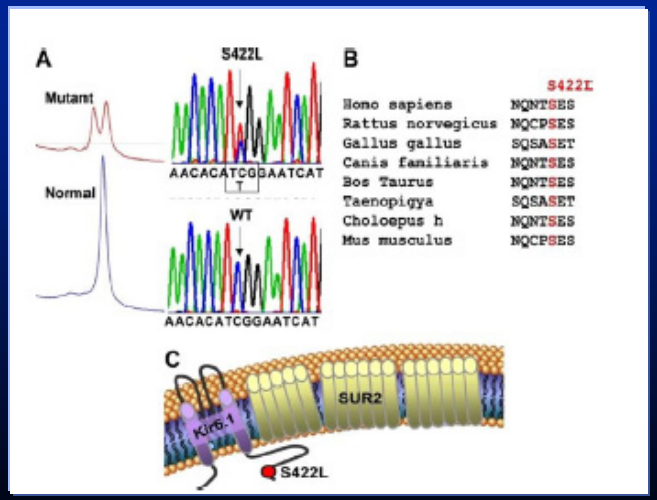
Canadian Journal of Cardiology 2011

Mutation Detection

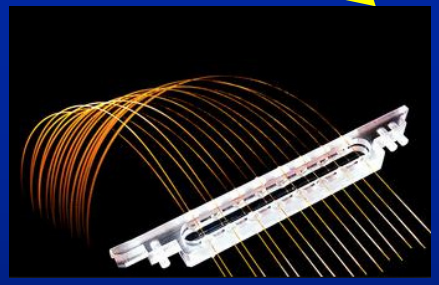
DHPLC

Automated DNA Sequencer

1986: first automated sequencer



Automated Sequencer



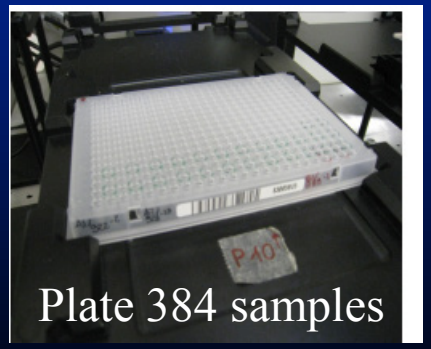


Plate 384 samples

Direct Sequencing

The first human genome was sequenced in 2003 through Sanger Techniques and it took 13 years: Human Genome Project in 1990-2003.

There are around 25.000 genes in our genome.

DNA encoding for proteins < 2%.

We still ignore what the vast majority of our DNA is doing.

Mutation Detection

Direct Sequencing

2005: Next Generation Sequencing

Next Generation Sequencing (NGS)

High throughput sequencing technology providing millions of DNA sequences at once. It lowers the cost of DNA sequencing and allows to scan ultrarapidly large sections of DNA.

1000 Genome Project

International Research effort, launched in January 2008, with the aim of sequence the genome of 1000 individuals of different ethnicities.

1000 Genome Project

A map of human genome variation from population-scale sequencing

The 1000 Genomes Project Consortium*

The 1000 Genomes Project aims to provide a deep characterization of human genome sequence variation as a foundation for investigating the relationship between genotype and phenotype. Here we present results of the pilot phase of the project, designed to develop and compare different strategies for genome-wide sequencing with high-throughput platforms. We undertook three projects: low-coverage whole-genome sequencing of 179 individuals from four populations; high-coverage sequencing of two mother–father–child trios; and exon-targeted sequencing of 697 individuals from seven populations. We describe the location, allele frequency and local haplotype structure of approximately 15 million single nucleotide polymorphisms, 1 million short insertions and deletions, and 20,000 structural variants, most of which were previously undescribed. We show that, because we have catalogued the vast majority of common variation, over 95% of the currently accessible variants found in any individual are present in this data set. On average, each person is found to carry approximately 250 to 300 loss-of-function variants in annotated genes and 50 to 100 variants previously implicated in inherited disorders. We demonstrate how these results can be used to inform association and functional studies. From the two trios, we directly estimate the rate of *de novo* germline base substitution mutations to be approximately 10^{-8} per base pair per generation. We explore the data with regard to signatures of natural selection, and identify a marked reduction of genetic variation in the neighbourhood of genes, due to selection at linked sites. These methods and public data will support the next phase of human genetic research.

Nature 2010

http://exac.broadinstitute.org/

Analysis of protein-coding genetic variation in 60,706 humans

Monkol Lek[1,2,3,4], Konrad J. Karczewski[1,2*], Eric V. Minikel[1,2,5*], Kaitlin E. Samocha[1,2,5,6*], Eric Banks[2], Timothy Fennell[2], Anne H. O'Donnell-Luria[1,2,7], James S. Ware[2,8,9,10,11], Andrew J. Hill[1,2,12], Beryl B. Cummings[1,2,5], Taru Tukiainen[1,2], Daniel P. Birnbaum[2], Jack A. Kosmicki[1,2,6,13], Laramie E. Duncan[1,2,6], Karol Estrada[1,2], Fengmei Zhao[1,2], James Zou[2], Emma Pierce-Hoffman[1,2], Joanne Berghout[14,15], David N. Cooper[16], Nicole Deflaux[17], Mark DePristo[18], Ron Do[19,20,21,22], Jason Flannick[2,23], Menachem Fromer[1,6,19,20,24], Laura Gauthier[18], Jackie Goldstein[1,2,6], Namrata Gupta[2], Daniel Howrigan[1,2,6], Adam Kiezun[18], Mitja I. Kurki[2,25], Ami Levy Moonshine[18], Pradeep Natarajan[2,26,27,28], Lorena Orozco[29], Gina M. Peloso[2,27,28], Ryan Poplin[18], Manuel A. Rivas[2], Valentin Ruano-Rubio[18], Samuel A. Rose[6], Douglas M. Ruderfer[19,20,24], Khalid Shakir[18], Peter D. Stenson[16], Christine Stevens[2], Brett P. Thomas[1,2], Grace Tiao[18], Maria T. Tusie-Luna[30], Ben Weisburd[2], Hong-Hee Won[31], Dongmei Yu[6,25,27,32], David M. Altshuler[2,33], Diego Ardissino[34], Michael Boehnke[35], John Danesh[36], Stacey Donnelly[2], Roberto Elosua[37], Jose C. Florez[2,26,27], Stacey B. Gabriel[2], Gad Getz[18,26,38], Stephen J. Glatt[39,40,41], Christina M. Hultman[42], Sekar Kathiresan[2,26,27,28], Markku Laakso[43], Steven McCarroll[6,8], Mark I. McCarthy[44,45,46], Dermot McGovern[47], Ruth McPherson[48], Benjamin M. Neale[1,2,6], Aarno Palotie[1,2,5,49], Shaun M. Purcell[19,20,24], Danish Saleheen[50,51,52], Jeremiah M. Scharf[2,6,25,27,32], Pamela Sklar[19,20,24,53,54], Patrick F. Sullivan[55,56], Jaakko Tuomilehto[57], Ming T. Tsuang[58], Hugh C. Watkins[44,59], James G. Wilson[60], Mark J. Daly[1,2,6], Daniel G. MacArthur[1,2] & Exome Aggregation Consortium†

Large-scale reference data sets of human genetic variation are critical for the medical and functional interpretation of DNA sequence changes. Here we describe the aggregation and analysis of high-quality exome (protein-coding region) DNA sequence data for 60,706 individuals of diverse ancestries generated as part of the Exome Aggregation Consortium (ExAC). This catalogue of human genetic diversity contains an average of one variant every eight bases of the exome, and provides direct evidence for the presence of widespread mutational recurrence. We have used this catalogue to calculate objective metrics of pathogenicity for sequence variants, and to identify genes subject to strong selection against various classes of mutation; identifying 3,230 genes with near-complete depletion of predicted protein-truncating variants, with 72% of these genes having no currently established human disease phenotype. Finally, we demonstrate that these data can be used for the efficient filtering of candidate disease-causing variants, and for the discovery of human 'knockout' variants in protein-coding genes.

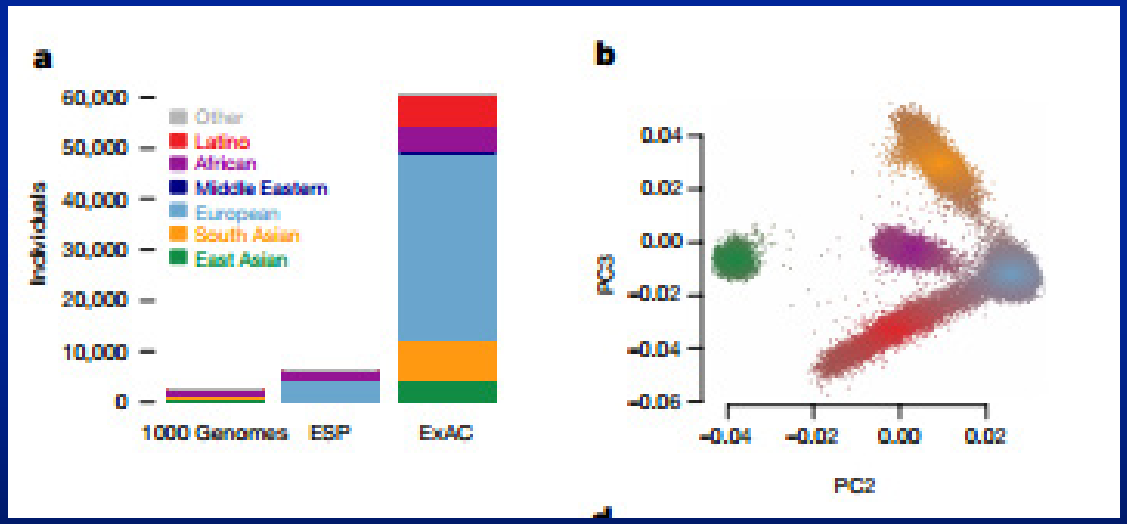
Nature 18 August 2016

http://exac.broadinstitute.org/

ExAC Browser (Beta) | Exome Aggregation Consortium

Search for a gene or variant or region

Examples - Gene: PCSK9, Transcript: ENST00000407236, Variant: 22-46615880-T-C, Multi-allelic variant: rs1800234, Region: 22:46615715-46615880



Contributing projects

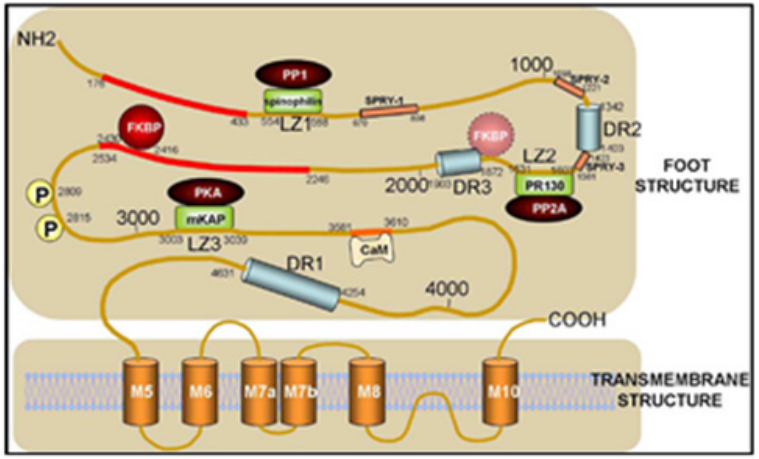
- 1000 Genomes
- Bulgarian Trios
- Finland-United States Investigation of NIDDM Genetics (FUSION)
- GoT2D
- Inflammatory Bowel Disease
- METabolic Syndrome In Men (METSIM)
- Jackson Heart Study
- Myocardial Infarction Genetics Consortium:
  - Italian Atherosclerosis, Thrombosis, and Vascular Biology Working Group
  - Ottawa Genomics Heart Study
  - Pakistan Risk of Myocardial Infarction Study (PROMIS)
  - Precocious Coronary Artery Disease Study (PROCARDIS)
  - Registre Gironi del COR (REGICOR)
- NHLBI-GO Exome Sequencing Project (ESP)
- National Institute of Mental Health (NIMH) Controls
- SIGMA-T2D
- Sequencing in Suomi (SISu)
- Swedish Schizophrenia & Bipolar Studies
- T2D-GENES
- Schizophrenia Trios from Taiwan
- The Cancer Genome Atlas (TCGA)
- Tourette Syndrome Association International Consortium for Genomics (TSAICG)

NEXT GENERATION SEQUENCING

- Many more genes can be sequenced simultaneously
- Reduction of time
- Reduction of costs
- Possibility to screen even very big genes

Molecular screening for CPVT: *RyR2*

Gene: 105 exons – Protein: 4967 amino-acid



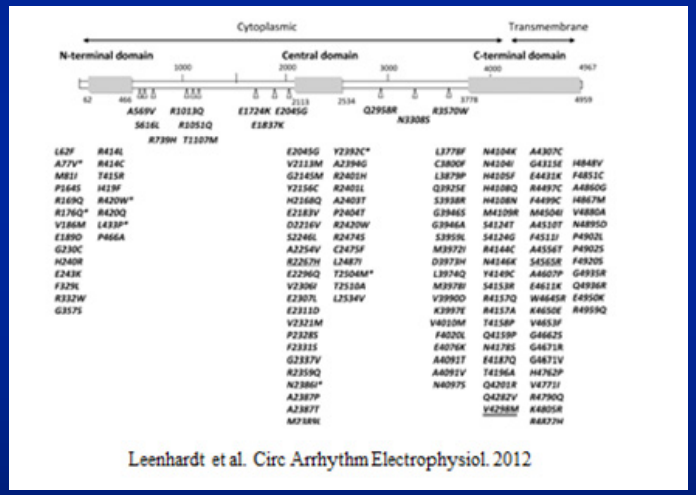
Yano M. et al. Pharmacology and Therapeutics, 2005

To screen through traditional technology the entire gene was too long (105 exons vs 59 exons to screen the 3 major LQTS genes) and expensive.

The reimbursement for the screening we had from our Region was far less than the cost we had only to cover reagents.

Molecular screening for CPVT: *RyR2*

As most of the mutations are located in 3 regions of the proteins, we were using a two step approach:



Leenhardt et al. Circ Arrhythm Electrophysiol. 2012

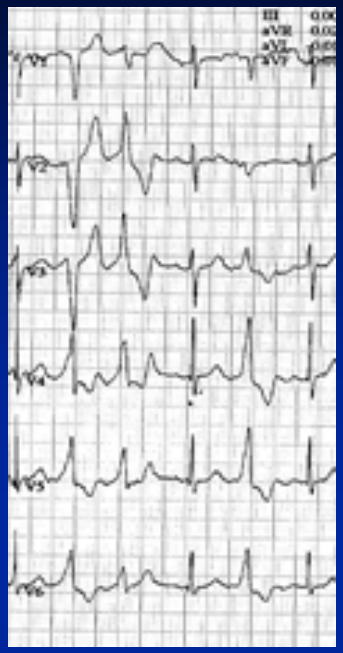
So 57 exons (54% of the gene) were analyzed.

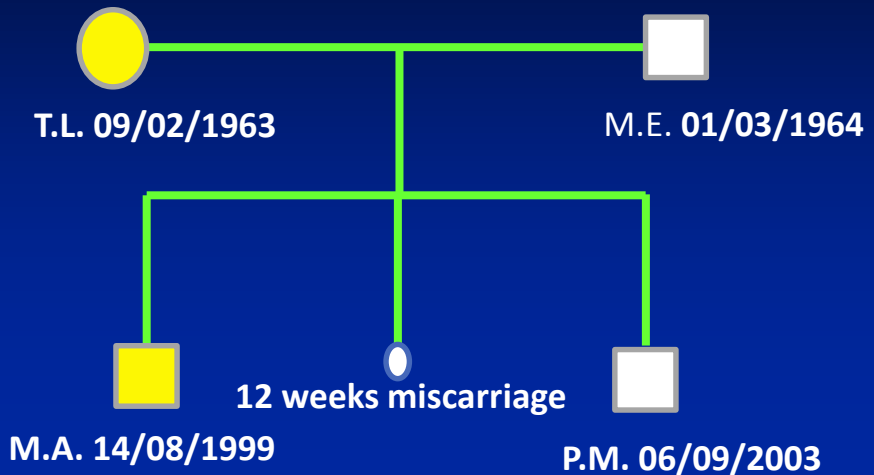
Molecular screening for CPVT: *RyR2*

Gene: 105 exons – Protein: 4967 amino-acid

Through NGS the size of the gene is not a problem any more: we are screening again CPVT patients genotype-negative at the traditional screening.

Fam. CPVT M12





TL: Syncopal events during exercise from 12 to 36 years. At 36 years CPVT was diagnosed and BB therapy started. No recurrences on therapy.

MA: Many syncopal events during exercise from 8 to 10 years. CPVT was diagnosed and BB therapy started. No recurrences on therapy.

Two-step screening on RyR2: negative

Fam. CPVT M12

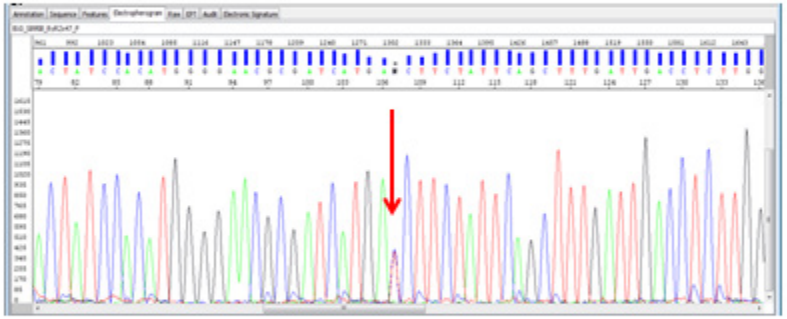
Complete screening of *RyR2*

Next-Generation Sequencing (TruSeq Custom Amplicon – Illumina)

RYR2:NM_001035:exon47:c.C7169T:

p.T2390I

Sanger Sequencing confirmation



RYR2:c.C7169T:**p.T2390I**

Truncations of Titin Causing Dilated Cardiomyopathy

Daniel S. Herman, Ph.D., Lien Lam, Ph.D., Matthew R.G. Taylor, M.D., Ph.D., Libin Wang, M.D., Ph.D., Polakit Teekakirikul, M.D., Danos Christodoulou, B.S., Lauren Conner, B.S., Steven R. DePalma, Ph.D., Barbara McDonough, R.N., Elizabeth Sparks, R.N.P., Debbie Lin Teodorescu, M.A., Allison L. Cirino, C.G.C., Nicholas R. Banner, F.R.C.P., Dudley J. Pennell, M.D., Sharon Graw, Ph.D., Marco Merlo, M.D., Andrea Di Lenarda, M.D., Gianfranco Sinagra, M.D., J. Martijn Bos, M.D., Ph.D., Michael J. Ackerman, M.D., Ph.D., Richard N. Mitchell, M.D., Ph.D., Charles E. Murry, M.D., Ph.D., Neal K. Lakdawala, M.D., Carolyn Y. Ho, M.D., Paul J.R. Barton, Ph.D., Stuart A. Cook, M.D., Luisa Mestroni, M.D., J.G. Seidman, Ph.D., and Christine E. Seidman, M.D.

N Engl J Med 2012

Truncations of Titin Causing Dilated Cardiomyopathy

NGS allowed a complete screening of the titin, a huge gene (363 exons, ~100 kb), encoding for the largest human protein (33.000 amino acids) .

Mutations altering full-length titin were identified in 27% of pts with DCM, 1% of pts with HCM and 3% of controls.

In the research setting next generation sequencing means the possibility to perform whole-exome sequencing or whole-genome sequencing to identify new disease-causing genes not previously anticipated.

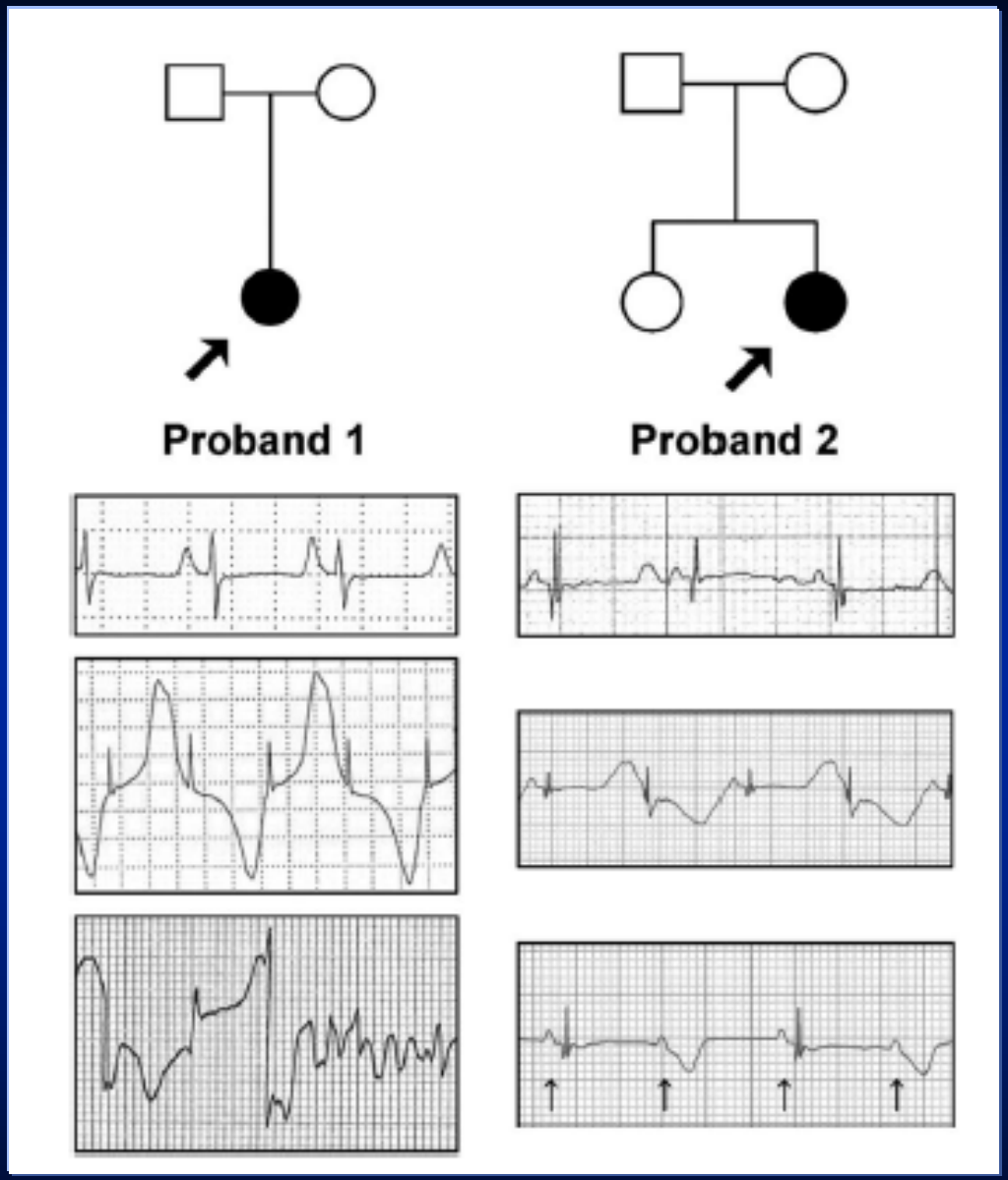
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Calmodulin Mutations Associated with Recurrent Cardiac Arrest in Infants

Lia Crotti, Christopher N. Johnson, Elisabeth Graf, Gaetano M. De Ferrari, Bettina F. Cuneo, Marc Ovadia, John Papagiannis, Michael D. Feldkamp, Subodh G. Rathi, Jennifer D. Kunic, Matteo Pedrazzini, Thomas Wieland, Peter Lichtner, Britt-Maria Beckmann, Travis Clark, Christian Shaffer, D. Woodrow Benson, Stefan Kääb, Thomas Meitinger, Tim M. Strom, Walter J. Chazin, Peter J. Schwartz and Alfred L. George, Jr.

Circulation. published online February 6, 2013;

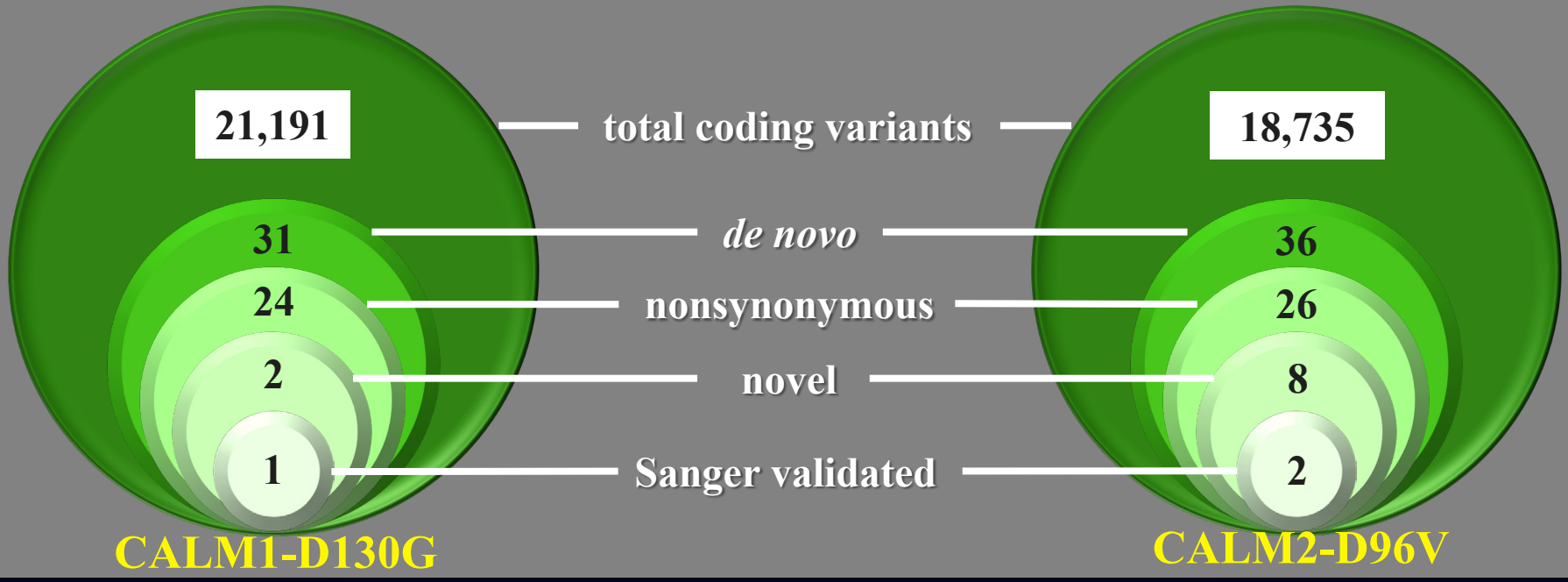


Crotti et al Circulation 2013

Whole Exome Sequencing

- Performed on the 2 probands and their parents
- Searched for novel variants
  1. Not inherited (de novo)
  2. Predicted to have deleterious effects

Proband 1 | **Proband 2**



Mutations in Calmodulin Cause Ventricular Tachycardia and Sudden Cardiac Death

Mette Nyegaard,[1,8,*] Michael T. Overgaard,[2,8] Mads T. Søndergaard,[2] Marta Vranas,[1] Elijah R. Behr,[3] Lasse L. Hildebrandt,[2] Jacob Lund,[2] Paula L. Hedley,[4,5] A. John Camm,[3] Göran Wettrell,[6] Inger Fosdal,[7] Michael Christiansen,[4] and Anders D. Børglum[1,*]

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Calmodulin Mutations Associated with Recurrent Cardiac Arrest in Infants

Lia Crotti, Christopher N. Johnson, Elisabeth Graf, Gaetano M. De Ferrari, Bettina F. Cuneo, Marc Ovadia, John Papagiannis, Michael D. Feldkamp, Subodh G. Rathi, Jennifer D. Kunic, Matteo Pedrazzini, Thomas Wieland, Peter Lichtner, Britt-Maria Beckmann, Travis Clark, Christian Shaffer, D. Woodrow Benson, Stefan Kääb, Thomas Meitinger, Tim M. Strom, Walter J. Chazin, Peter J. Schwartz and Alfred L. George, Jr.

A Mutation in *CALM1* Encoding Calmodulin in Familial Idiopathic Ventricular Fibrillation in Childhood and Adolescence

Roos F. Marsman, MD,* Julien Barc, PhD,*† Leander Beekman, BSc,* Marielle Alders, PhD,‡ Dennis Dooijes, PhD,§ Arthur van den Wijngaard, PhD,‖ Ilham Rathi, MD,¶ Abdelaziz Sefiani, MD, PhD,¶ Zahurul A. Bhuiyan, MD, PhD,‡# Arthur A. M. Wilde, MD, PhD,* ** Connie R. Bezzina, PhD*

CALMODULIN-DISEASE

Are new clinical entity responsible for life-theratening arrhythmias mainly occurring early in life, that can manifest as CPVT, LQTS or IVF

CALMODULIN-REGISTRY

Established in 2015 and currently enrolling 49 patients.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

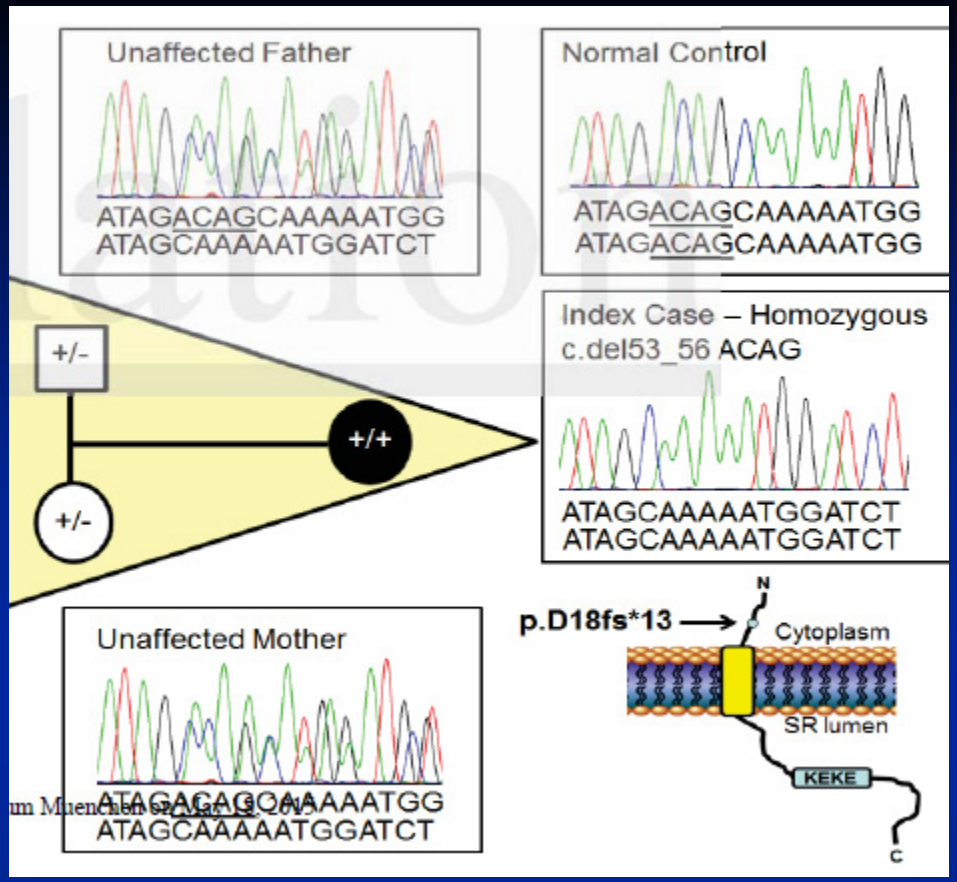
American Heart Association®

Homozygous/Compound Heterozygous Triadin Mutations Associated with Autosomal Recessive Long QT Syndrome and Pediatric Sudden Cardiac Arrest: Elucidation of Triadin Knockout Syndrome

Helene M. Altmann, David J. Tester, Melissa L. Will, Sumit Middha, Jared M. Evans, Bruce W. Eckloff and Michael J. Ackerman

Circulation. published online April 28, 2015;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539



Patients with homozygous or compound heterozygous mutations in Triadin gene (*TRDN*) displayed extensive T-wave inversions in precordial leads V1-V4, with QT-prolongation, severe disease expression of exercise-induced cardiac arrest in early childhood (< 3 years of age), and required aggressive therapy.

"Our ability to generate sequence data currently outstrips our ability to interpret it accurately."

Goldstein, Nature 2013

High prevalence of genetic variants previously associated with Brugada syndrome in new exome data

Risgaard B, Jabbari R, Refsgaard L, Holst AG, Haunsø S, Sadjadieh A, Winkel BG, Olesen MS, Tfelt-Hansen J. High prevalence of genetic variants previously associated with Brugada syndrome in new exome data. Clin Genet 2013. © John Wiley & Sons A/S. Published by Blackwell Publishing Ltd, 2013 Clin. Genet . 2013

High prevalence of genetic variants previously associated with LQT syndrome in new exome data

Eur. J. Hum. Genet. 2012

Lena Refsgaard[1,2], Anders G Holst[1,2], Golnaz Sadjadieh[1,2], Stig Haunso[1,2,3], Jonas B Nielsen[1,2] and Morten S Olesen*[,1,2]

New population-based exome data are questioning the pathogenicity of previously cardiomyopathy-associated genetic variants

Eur. J. Hum .Genet. 2013

Charlotte Andreasen[1,2,5], Jonas B Nielsen[1,2,5], Lena Refsgaard[1,2], Anders G Holst[1,2], Alex H Christensen[1,2], Laura Andreasen[1,2], Ahmad Sajadieh[3], Stig Haunso[1,2,4], Jesper H Svendsen[1,2,4] and Morten S Olesen*[,1,2]

All these articles are highlighting the need to employ solid criteria of evaluation, to identify those genetic variants that are really pathogenetic, reducing the number of false-positive results.

All available databases include heterogeneous populations of individuals and therefore should be viewed as a representative sample of the population at large, containing both healthy and diseased individuals and **cannot be considered as "pure" control populations for any given disease.**

How many controls should be "allowed"?

It depends: - severity of the disease
- age of onset
- penetrance

"It is clear that a central challenge for the field is developing appropriate statistical criteria that incorporate disparate data types in the interpretation of sequenced genomes."

- **Frequency in population**
- **Prediction tools (i.e. SIFT, Polyphen2, Mutation Taster)**
- **OMIM**
- **Biological plausibility**
- **Expression in different tissues**
- **Human Genome Mutation Database (HGMD)**

Benign variant?
VUS?
Disease-causing mutation?

Next generation sequencing improved:

- **Diagnostic screening: - possibility to screen simultaneously multiple genes, without a size limitation.**
- **Research screening: - possibility to identify new-disease causing genes without an a-priori hypothesis (new mechanisms and pathways could be identified)**
- **Availability of genomic data of >60.000 individuals: - improved our ability to discriminate between genetic background and functional variant; - highlighted a big grey area of variants of unknown significance.**

THANK YOU!

HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

Europace (2011) **13**, 1077–1109

Impact of genetic testing for the proband

Disease	Diagnostic	Prognostic	Therapeutic
LQTS	+++	+++	++
CPVT	+++	+	-
BrS	+	+	-
SQTS	+/-	-	-
AF	-	-	-
HCM	+++	++	+
ARVC	+	+/-	-
DCM	+/-	-	-

CONDITION	PROBAND	FAMILY MEMBER
LQTS	Class I (is recommended)	Class I (is recommended)
Brugada Syndrome	Class IIa (can be useful)	Class I (is recommended)
CPVT	Class I (is recommended)	Class I (is recommended)

Cascade screening is always a class I indication, to allow the early identification of affected family members in which preventive strategies could be employed

ORIGINAL ARTICLE

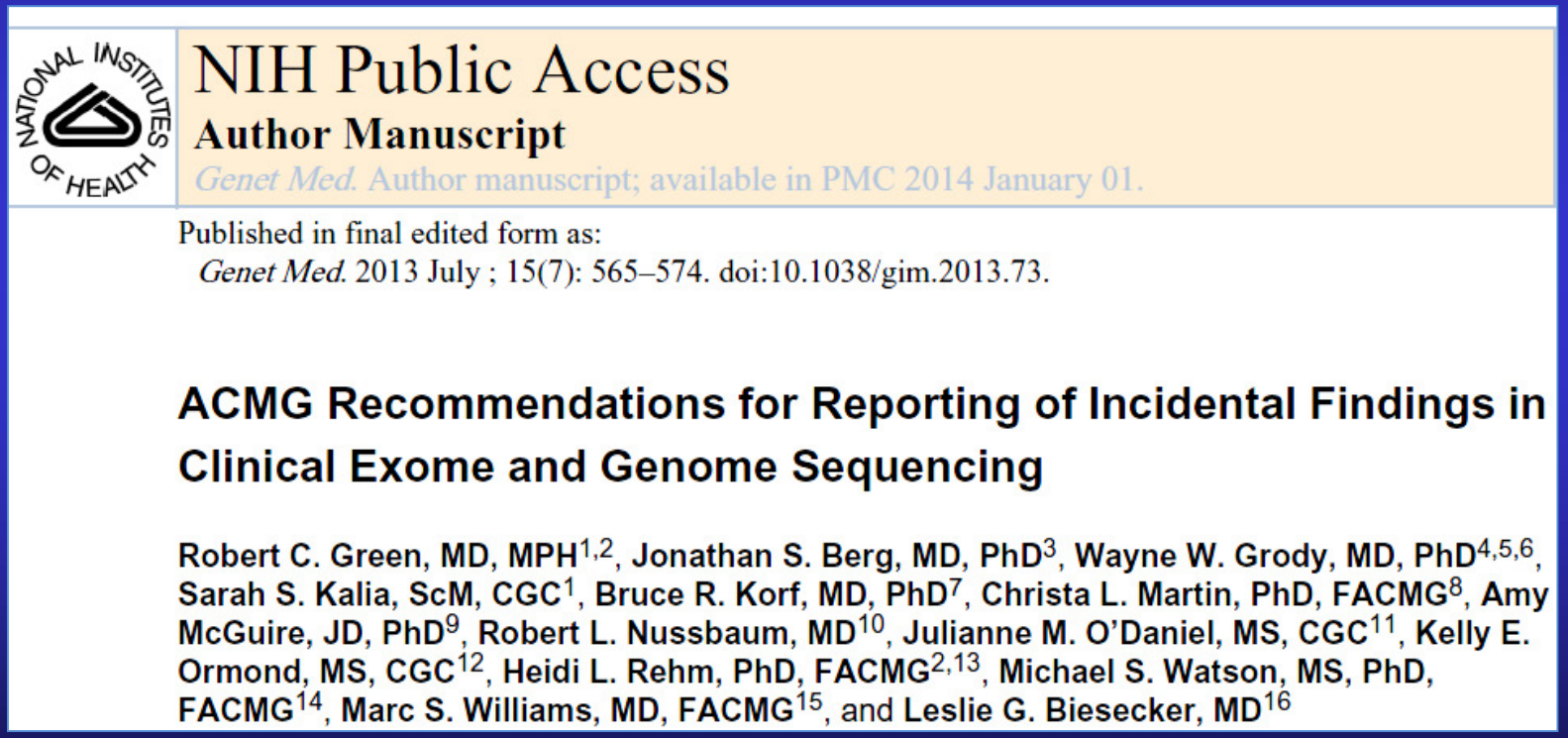
Diagnostic Exome Sequencing in Persons with Severe Intellectual Disability

Joep de Ligt, M.Sc., Marjolein H. Willemsen, M.D., Bregje W.M. van Bon, M.D., Ph.D., Tjitske Kleefstra, M.D., Ph.D., Helger G. Yntema, Ph.D., Thessa Kroes, B.Sc., Anneke T. Vulto-van Silfhout, M.D., David A. Koolen, M.D., Ph.D., Petra de Vries, B.Sc., Christian Gilissen, Ph.D., Marisol del Rosario, B.Sc., Alexander Hoischen, Ph.D., Hans Scheffer, Ph.D., Bert B.A. de Vries, M.D., Ph.D., Han G. Brunner, M.D., Ph.D., Joris A. Veltman, Ph.D., and Lisenka E.L.M. Vissers, Ph.D.

NEJM 2012

An incidental findings is the identification of a genetic defect unrelated to the indication for ordering the sequencing but of medical value for patient care.

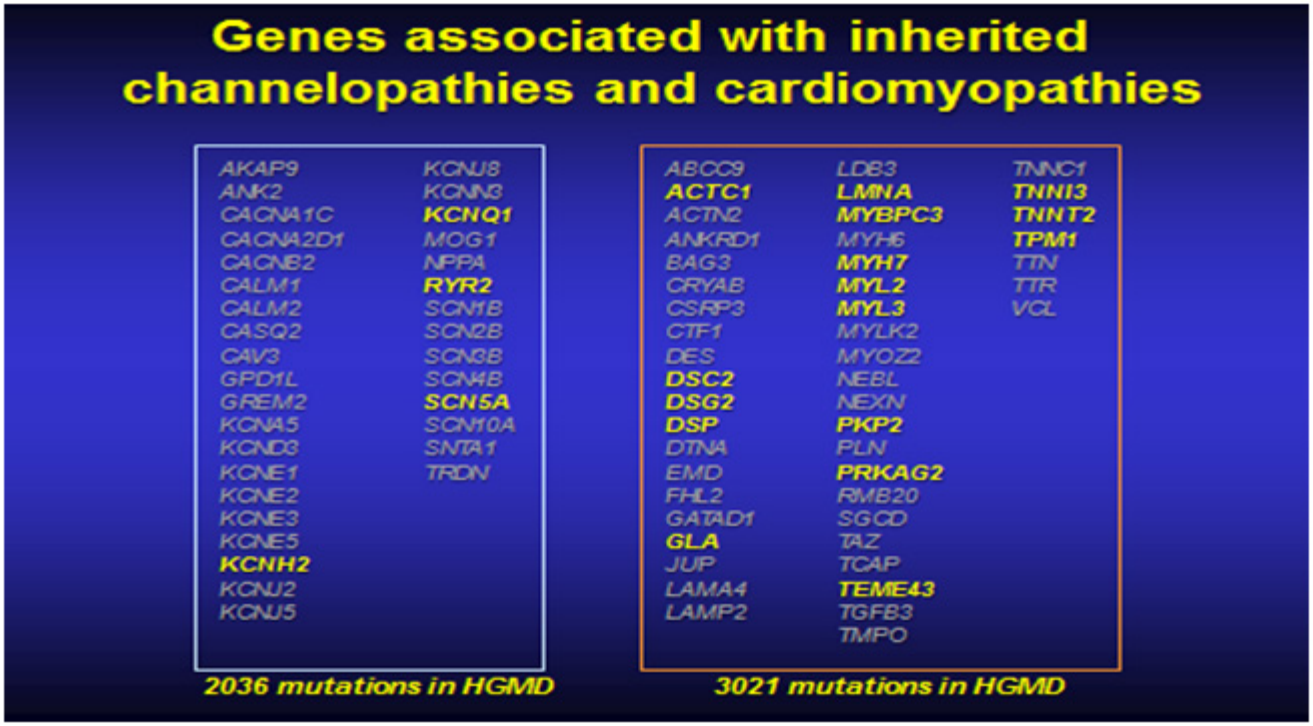
How to manage and when to return incidental findings?



Published in final edited form as:
Genet Med. 2013 July ; 15(7): 565–574. doi:10.1038/gim.2013.73.

ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

Robert C. Green, MD, MPH[1,2], Jonathan S. Berg, MD, PhD[3], Wayne W. Grody, MD, PhD[4,5,6], Sarah S. Kalia, ScM, CGC[1], Bruce R. Korf, MD, PhD[7], Christa L. Martin, PhD, FACMG[8], Amy McGuire, JD, PhD[9], Robert L. Nussbaum, MD[10], Julianne M. O'Daniel, MS, CGC[11], Kelly E. Ormond, MS, CGC[12], Heidi L. Rehm, PhD, FACMG[2,13], Michael S. Watson, MS, PhD, FACMG[14], Marc S. Williams, MD, FACMG[15], and Leslie G. Biesecker, MD[16]



The working group created a "minimum list" of genes for which incidental findings should be reported.

19 February 2016

Blood test breakthrough improves diagnosis of inherited heart conditions

A new genetic test for heart conditions which are passed down through families has been developed by researchers funded by your donations.

The international team of researchers, led by Professor Stuart Cook, in Singapore, Imperial College London and at the MRC Clinical Sciences Centre showed that by looking at a particular group of genes they were able to reliably test for all known inherited heart condition genes with one simple blood test.

Professor Cook has been working on this research, published in the Journal of Cardiovascular Translational Research, since we funded his PhD studies when he first became a researcher.

NEWS FROM THE BHF

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RELATED LINKS

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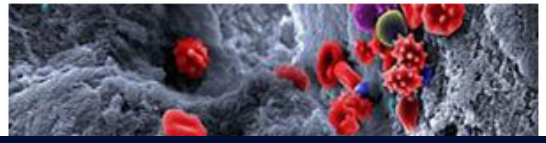


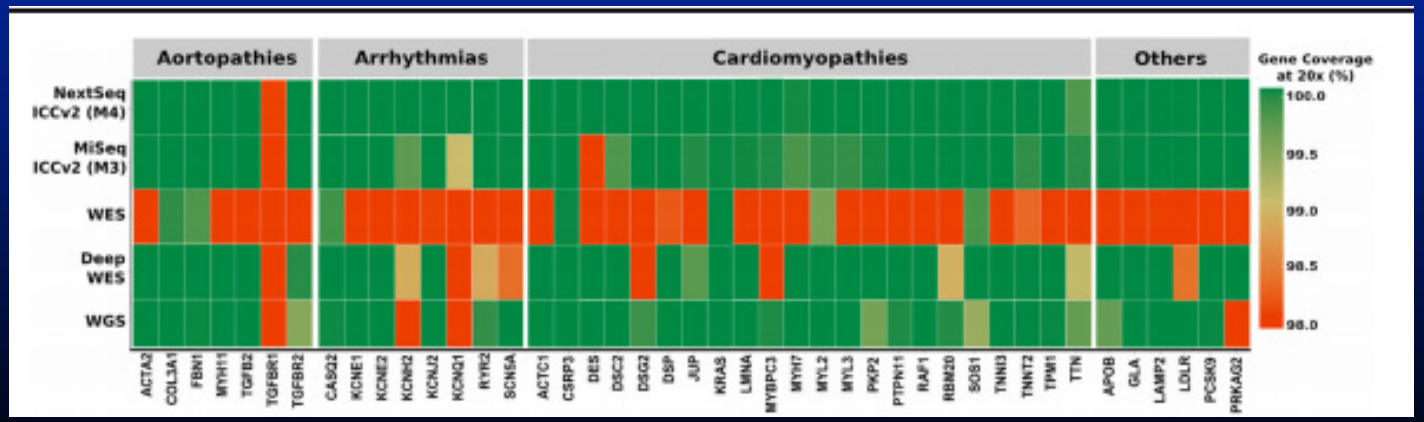
J. of Cardiovasc. Trans. Res. (2016) 9:3–11
DOI 10.1007/s12265-016-9673-5

ORIGINAL ARTICLE

Development of a Comprehensive Sequencing Assay for Inherited Cardiac Condition Genes

Chee Jian Pua[1] · Jaydutt Bhalshankar[1] · Kui Miao[2] · Roddy Walsh[3,4] · Shibu John[3,4] · Shi Qi Lim[1] · Kingsley Chow[1] · Rachel Buchan[3,4] · Bee Yong Soh[1] · Pei Min Lio[1] · Jaclyn Lim[1] · Sebastian Schafer[1] · Jing Quan Lim[5] · Patrick Tan[6,7] · Nicola Whiffin[3,4] · Paul J. Barton[3,4] · James S. Ware[4,8] · Stuart A. Cook[1,2,4,8]

174 genes: channelopathies and cardiomyopathies and other inherited cardiac condition.



Population-Based Variation in Cardiomyopathy Genes

Jessica R. Golbus, BA; Megan J. Puckelwartz, PhD; John P. Fahrenbach, PhD;
Lisa M. Dellefave-Castillo, MS, CGC; Don Wolfgeher, BS; Elizabeth M. McNally, MD, PhD

Circ Cardiovsc Genet 2012

Interrogating the 1000 Genome Project database, the titin gene appears to be very polymorphic, with over 5% of the general population having a 18bp in frame deletion in a region that regulates extensibility of titin.

FROM A CANDIDATE GENE APPROACH TO WHOLE-EXOME/WHOLE-GENOME SEQUENCING

In the candidate gene approach one or more biologically plausible genes are screened in a population of patients in which a disease-causing mutation has not been identified in known disease-genes.

However, many studies using a candidate gene approach are not so robust:

1. **Lack of genotype-phenotype correlation data (identification in one or two sporadic cases)**

2. **Lack of adequate number of controls (100-200 controls!)**

3. **Functional studies performed in heterologous expression system, creating condition that may be different from those encountered in vivo**

With NGS new approaches for gene-discovery have been proven to be possible:

- Target screening of huge genes or of great number of genes simultaneously
- In large families a preliminary linkage analysis could be skipped
- Parent-child trios whole-exome sequencing analysis: de novo mutations in unknown disease-genes
- Exome-sequencing may identify the disease-causing gene even in families with small number of affected individuals

Molecular Genetics & Genomic Medicine

Open Access

ORIGINAL ARTICLE

Concordance between whole-exome sequencing and clinical Sanger sequencing: implications for patient care

Alison Hamilton[1], Martine Tétreault[2,3], David A. Dyment[1,4], Ruobing Zou[1], Kristin Kernohan[1], Michael T. Geraghty[1,5], FORGE Canada Consortium, Care4Rare Canada Consortium, Taila Hartley[1,*] & Kym M. Boycott[1,4,*]

[1]Children's Hospital of Eastern Ontario Research Institute, University of Ottawa, Ottawa, Ontario, Canada
[2]Department of Human Genetics McGill University, Montréal, Québec, Canada
[3]McGill University and Genome Québec Innovation Center, Montréal, Québec, Canada
[4]Department of Genetics, Children's Hospital of Eastern Ontario Research, Ottawa, Ontario, Canada
[5]Division of Metabolics and Newborn Screening, Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

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