Genomic Variations in Korean Patients with Inherited Cardiac Arrhythmia

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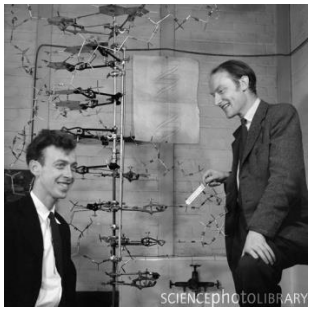
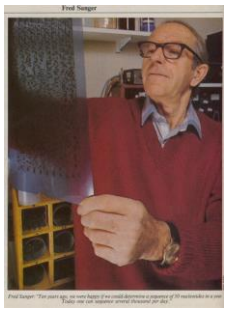
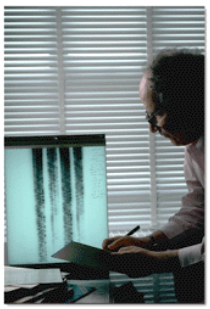
Timeline of Genetics/Genomics







1869, Discovery of DNA molecule

1941, First established medical genetics clinic

1944, DNA as genetic material

1953, DNA double helix structure

1961, Triplet codon

1967-1977, DNA sequencing

1977, Intervening sequences and RNA splicing

1983, PCR

1984, Mapping of the first eye disease locus

1986, Positional cloning of the first human disease gene

1990, The first RP gene discovery

1990, Begining of HGP

1995, First Bacterial genome sequenced

1995, DNA microarray

1996, First cloned animal

2000, First NGS report

2001, Draft of human genome

2002, HapMap project launched

2005, First AMD GWAS

2005-2008, NGS comes of age

2008, Begining of 1000 Genomes Project

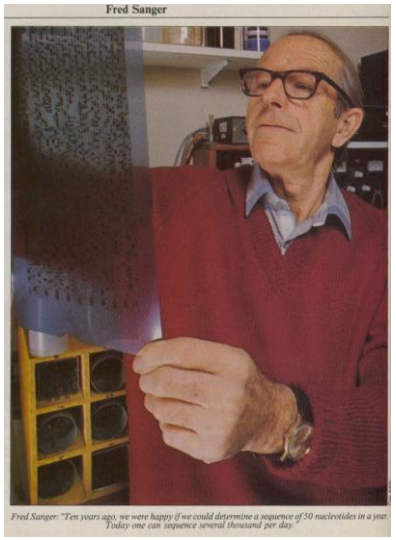
2015, Global reference for human genetic variation

2016, 34 novel AMD loci

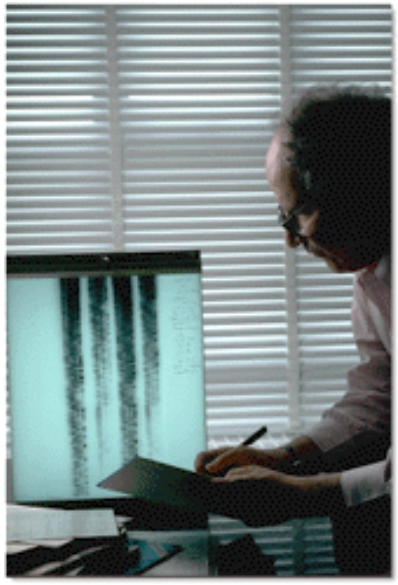
Prog Retin Eye Res 2016;55:1

Sequencing Revolution

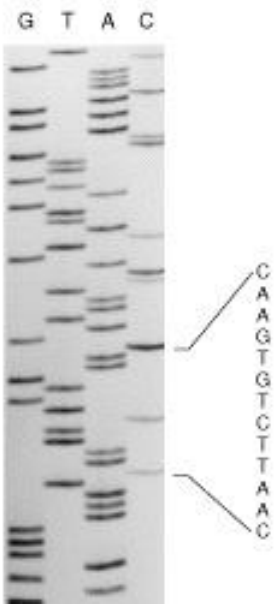
- Chain termination method
  - Frederick Sanger and Alan Coulson
  - J Mol Biol 1975;94:441-8

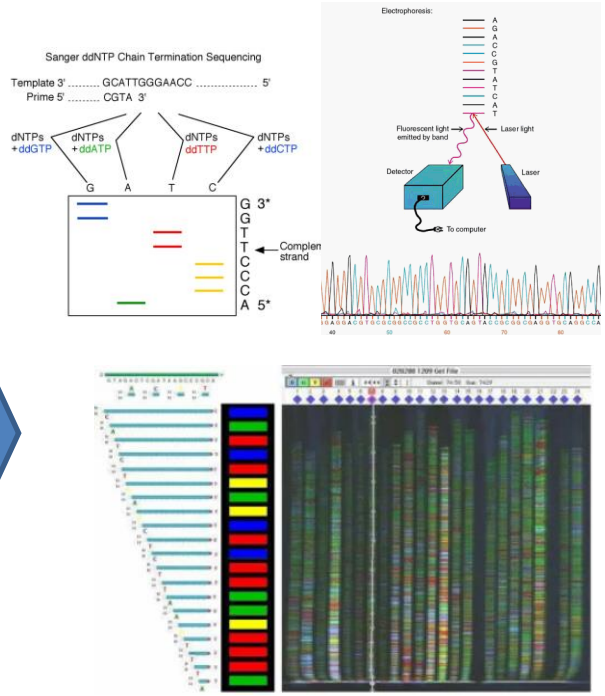


- Chemical degradation method
  - Allan Maxam and Walter Gilbert
  - Proc Natl Acad Sci 1977;74:560-4



Evolution of Sanger Sequencing





1977 1987 1998

Sequencing From Bench to Clinical Lab

실험(Experiment)

- Research fund
- For the purpose of understanding of a condition better
- No responsibilities to patients

~20 yrs

검사(Clinical Test)

- Payment by patients
- For prevention, diagnosis, treatment as part of patient care
- Responsibilities to patients

Sanger Monopoly on Sequencing

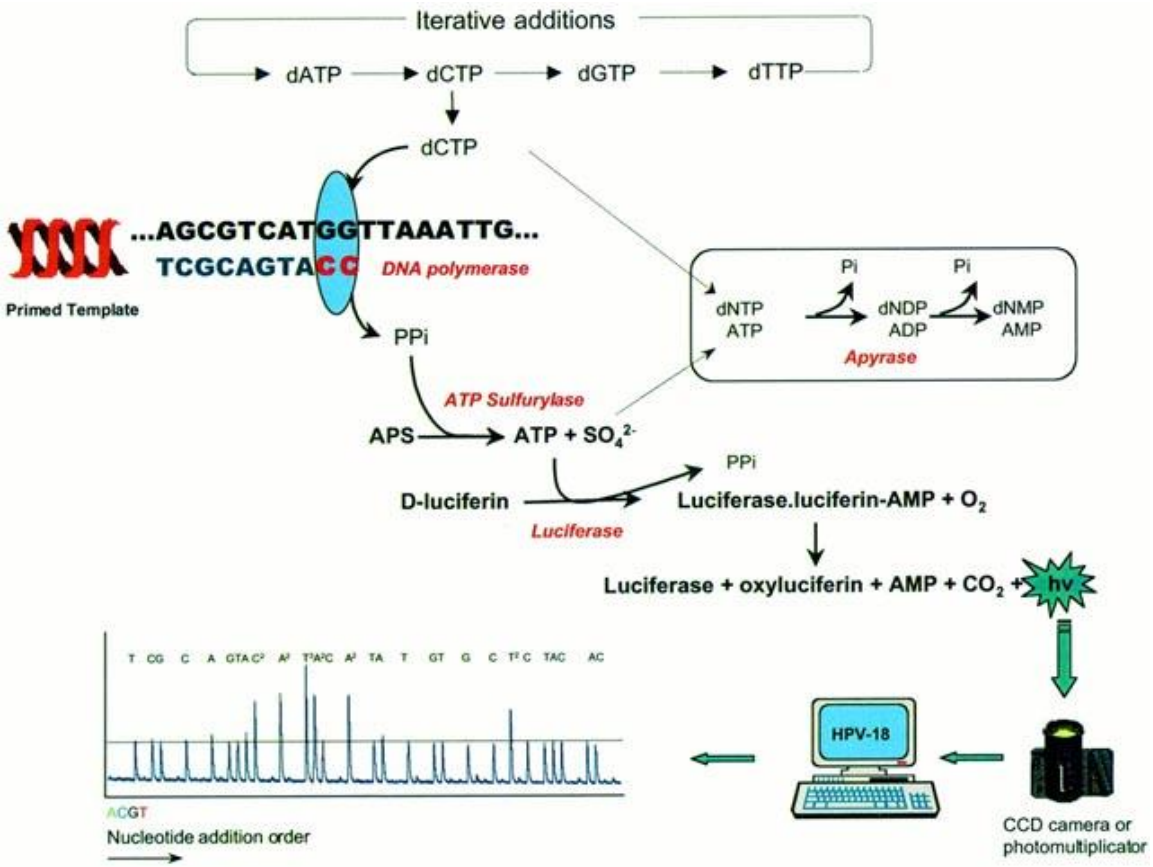
- Over more than 20 years

1990	BLAST — the key to comparative genomics (Milestone 15)
1992	BACs (Milestone 13)
1995	Microarray technology (Milestone 16) 
1998	RNAi (Milestone 17) Sequencing by synthesis (Milestone 18) Full-length cDNA technologies (Milestone 5)
2002	Launch of UCSC Genome Browser (Milestone 19)
2003	DNA assembly programs (Milestone 20) 
2004	ENSEMBL - an example of a gene annotation tool (Milestone 21)
2005	HapMap (Milestone 22)  Sequencing by ligation/polony sequencing (Milestone 18)

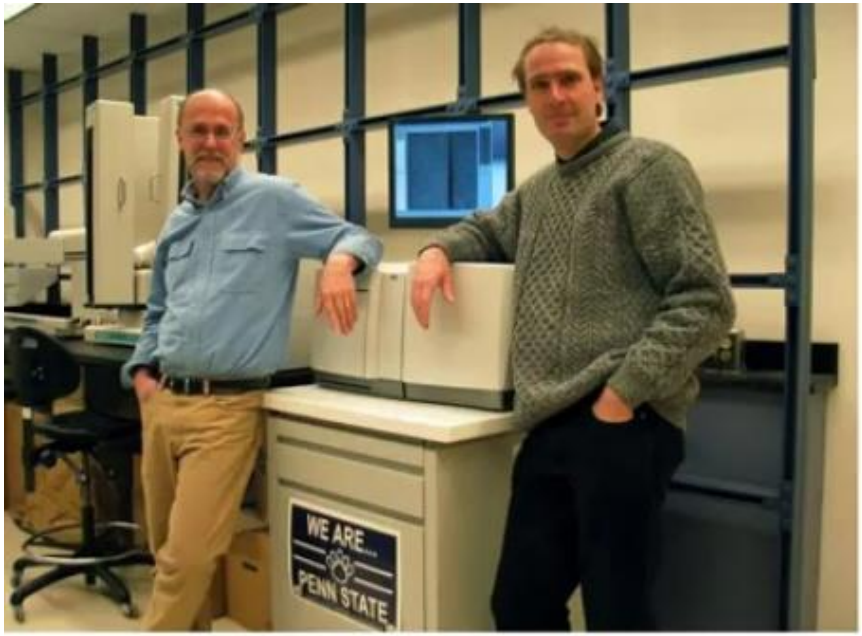
Nature.com

Novel Sequencing Techniques

- Pyrosequencing (sequencing by synthesis)



The First NGS Platform



The 454 GS has a capability of 1 billion bases/day.

Compared that to my 200 in 1995
or 3600 in 2001.

Yale Scientific

From Engineering to Entrepreneurship: Jonathan Rothberg, Ph.D. Biology '91

Joshua Ryu February 4, 2013 02:21 http://www.yalescientific.org/2013/02/from-engineering-to-entrepreneurship-jonathan-rothberg-ph-d-biology-91/

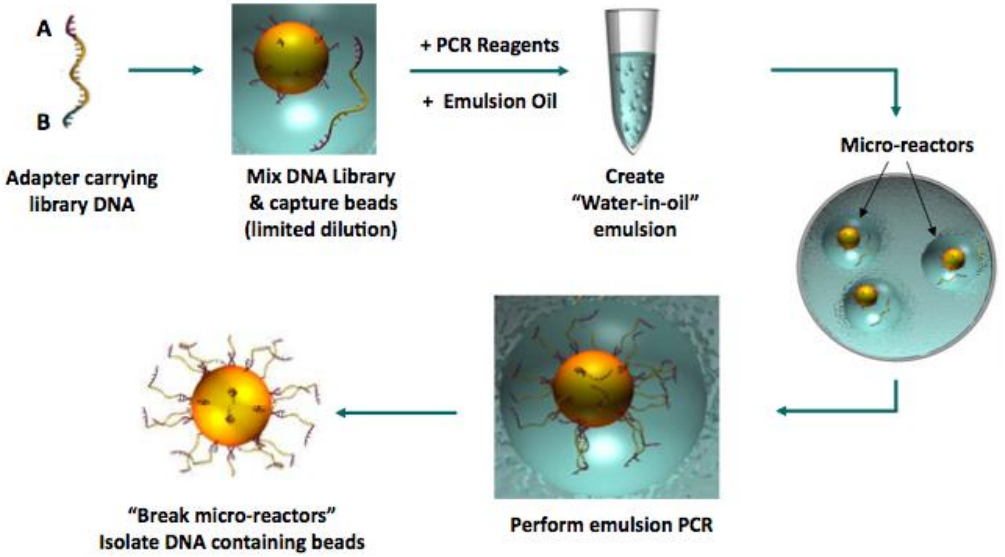
Related Articles

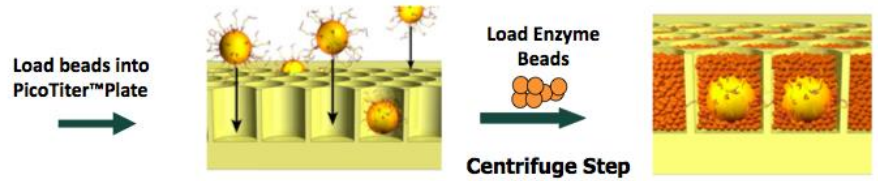
- Richard Conniff, B.A. '73
- Five Things You Didn't Know About Scientific Discoveries at Yale
- Q&A: Seasons Turned Upside Down. What is the El Niño Effect? 0 02.Apr

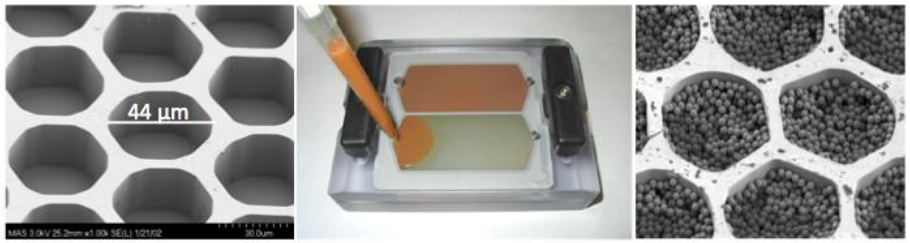
Dr. Rothberg has achieved technological advances in human genome sequencing as an entrepreneur and a scientist. His ideas have improved the efficiency of agriculture and fuel production, with widespread effects. Courtesy of Jonathan Rothberg.

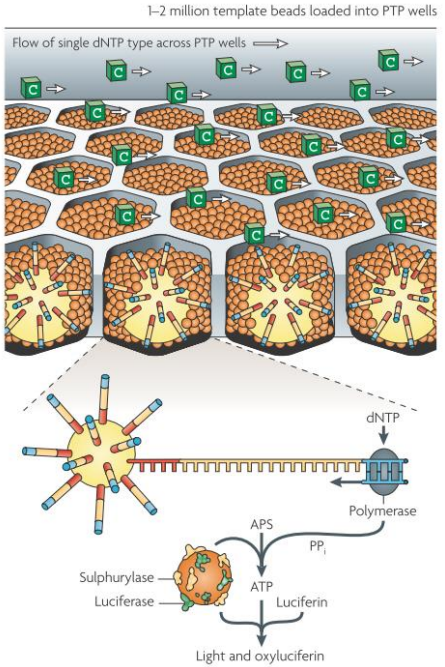
Dr. Jonathan Rothberg's journey in next-generation personal genome sequencing began in the neonatal intensive care unit. His newborn son Noah was completely blue from the inability to breathe properly, and Rothberg and the doctors did not know why. Noah would be okay, but little did Rothberg know that this heart-pounding experience, combined with his passion for engineering, would lead to one of the most widely used technologies for genomic sequencing and one of the most important recent inventions in medicine.

NGS Technologies: Roche 454









Individual Genome

nature Vol 452|17 April 2008|doi:10.1038/nature06884

LETTERS

May 31, 2007

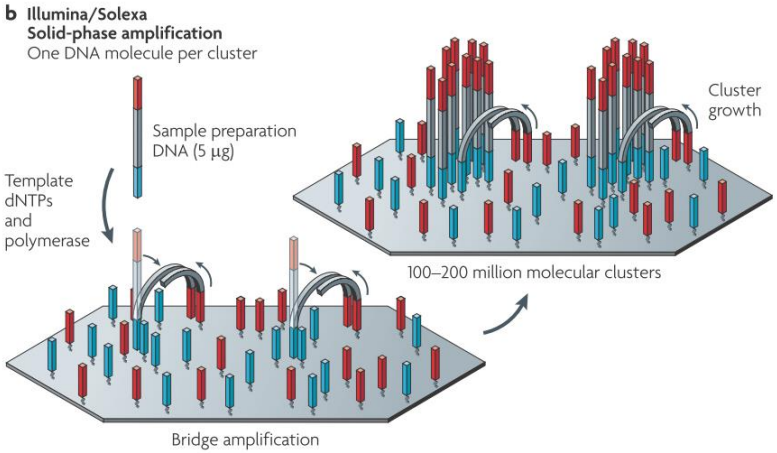
http://www.bcm.edu/news/packages/watson_genome.cfm

The complete genome of an individual by massively parallel DNA sequencing

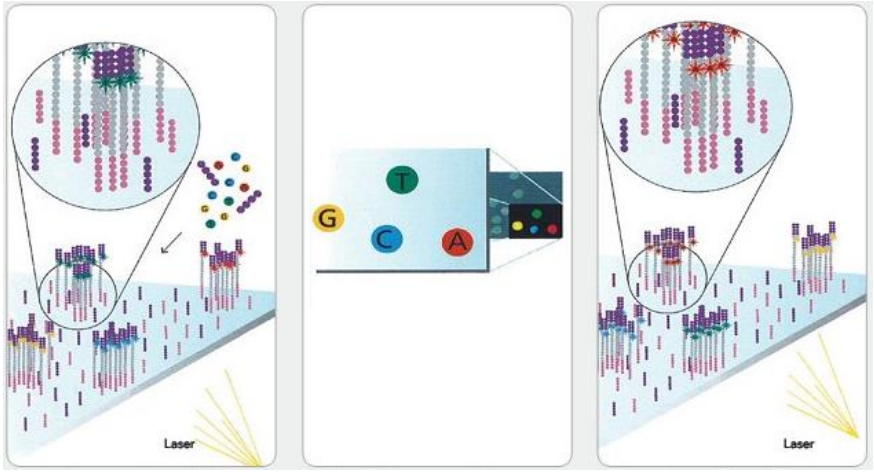
David A. Wheeler[1]*, Maithreyan Srinivasan[2]*, Michael Egholm[2]*, Yufeng Shen[1]*, Lei Chen[1], Amy McGuire[3], Wen He[2], Yi-Ju Chen[2], Vinod Makhijani[2], G. Thomas Roth[2], Xavier Gomes[2], Karrie Tartaro[2]†, Faheem Niazi[2], Cynthia L. Turcotte[2], Gerard P. Irzyk[2], James R. Lupski[4,5,6], Craig Chinault[4], Xing-zhi Song[1], Yue Liu[1], Ye Yuan[1], Lynne Nazareth[1], Xiang Qin[1], Donna M. Muzny[1], Marcel Margulies[2], George M. Weinstock[1,4], Richard A. Gibbs[1,4] & Jonathan M. Rothberg[2]†

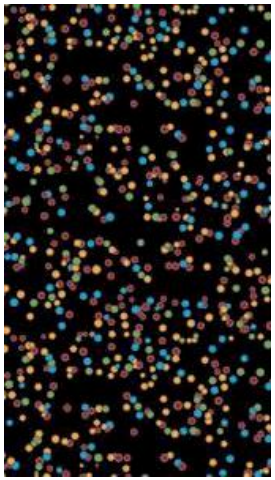
James Watson (left) receives a digital copy of his genome sequence from Jonathan Rothberg in May 2007. (Apr 16, 2008. Bio-IT World)

NGS Technologies: Illumina



Sequencing by Synthesis (SBS)





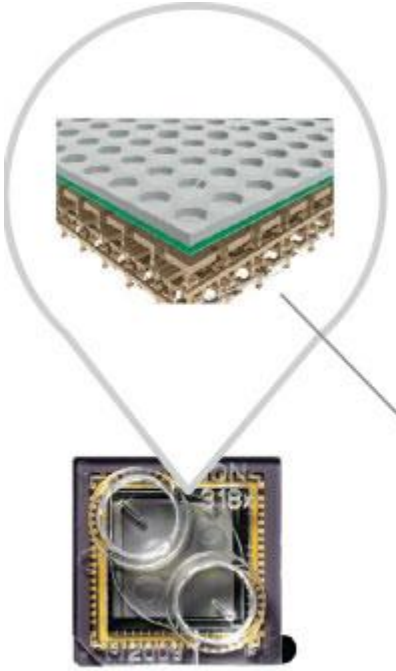
The Next-Generation

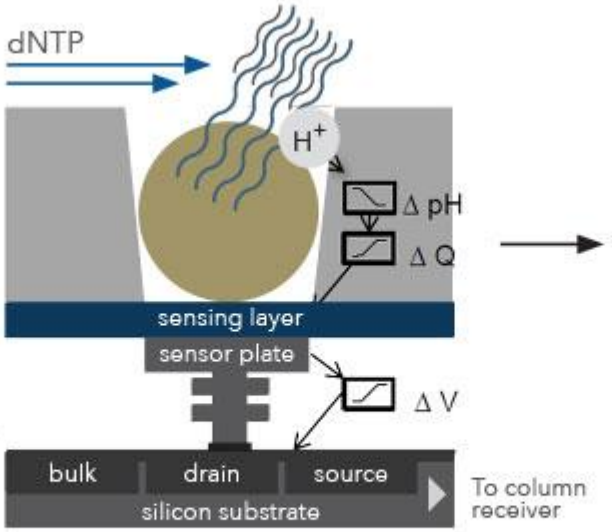
ABI SOLiD

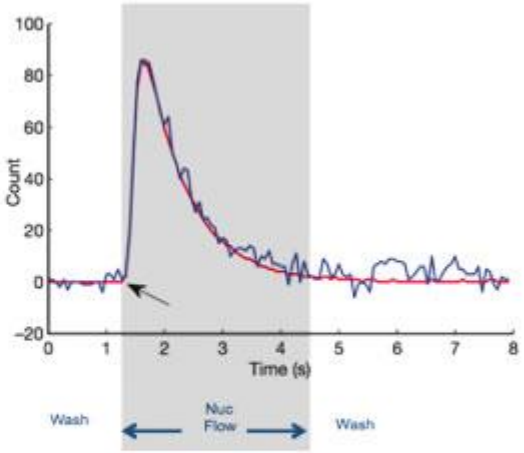
454 FLX

Ilumina Genome Analyzer

Semi-Conductor Sequencing







Rothberg J.M. *et al Nature doi:10/1038/nature10242*

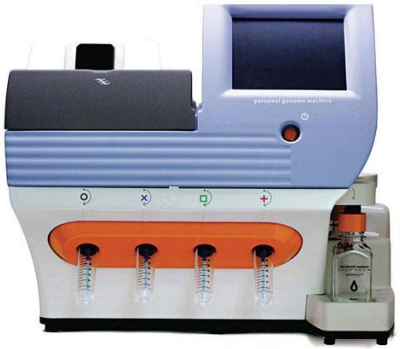
DNA ▶ Ions ▶ Sequence

The Next-Generation

ABI SOLiD

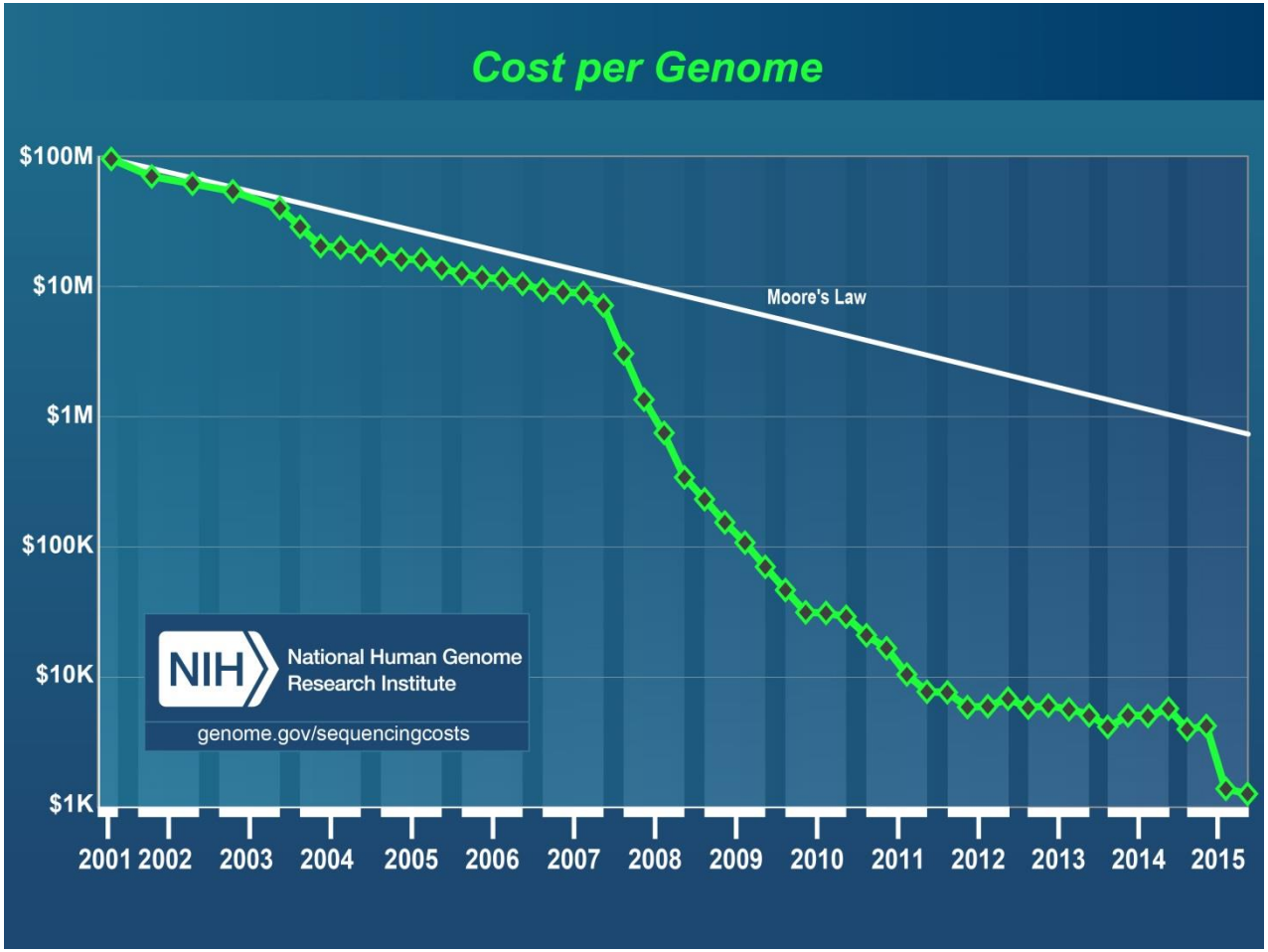
454 FLX

Ilumina Genome Analyzer



Ion Torrent

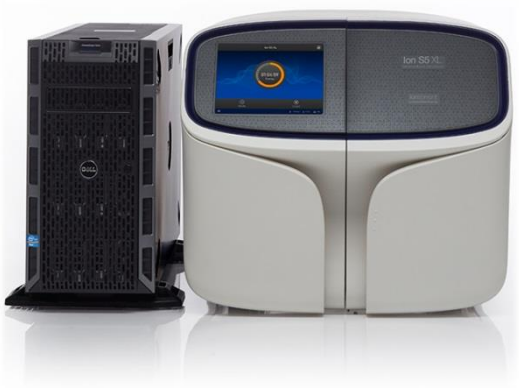
Sequencing Cost



NGS Systems

Ion PGM™ Dx System

Ion Proton™ System



Ion S5™ XL System

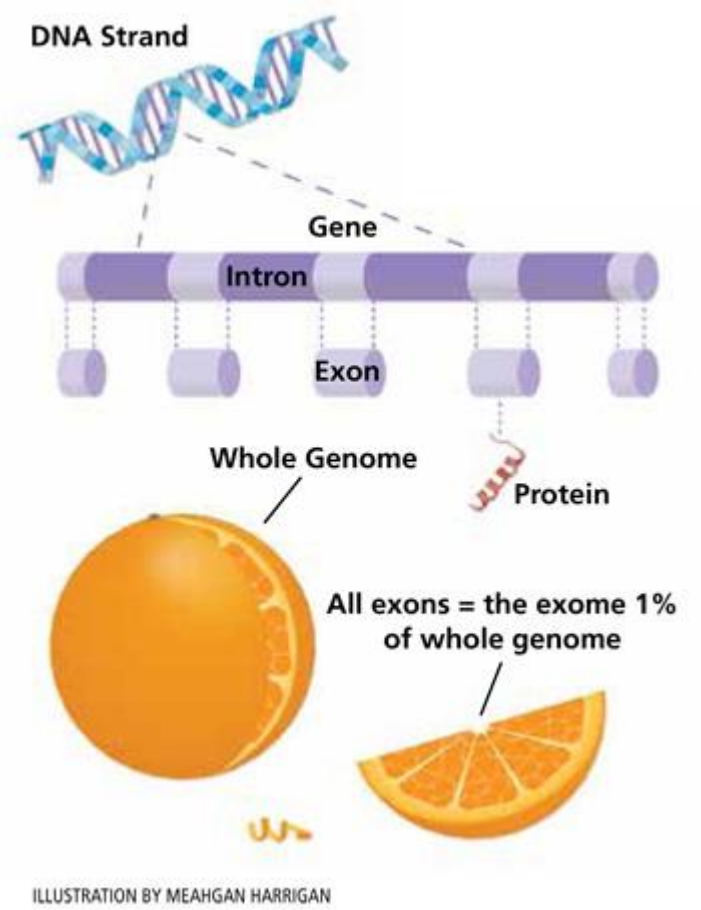
What Can We Do with NGS?

Gene Panel Testing

Exome Sequencing

Genome Sequencing

Exome Sequencing



http://www.dana-farber.org/newsroom/publications/paths-of-progress-spring-summer-2014/expanding-the-search/

ACMG POLICY STATEMENT | Genetics inMedicine

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

In clinical exome and genome sequencing, there is a potential for the recognition and reporting of incidental or secondary findings unrelated to the indication for ordering the sequencing but of medical value for patient care. The American College of Medical Genetics and Genomics (ACMG) recently published a policy statement on clinical sequencing that emphasized the importance of alerting the patient to the possibility of such results in pretest patient discussions, clinical testing, and reporting of results. The ACMG appointed a Working Group on Incidental Findings in Clinical Exome and Genome Sequencing to make recommendations about responsible management of incidental findings when patients undergo exome or genome sequencing. This Working Group conducted a year-long consensus process, including an open forum at the 2012 Annual Meeting and review by outside experts, and produced recommendations that have been approved by the ACMG Board. Specific and detailed recommendations, and the background and rationale for these recommendations, are described herein. The ACMG recommends that laboratories performing clinical sequencing seek and report mutations of the specified classes or types in the genes listed here. This evaluation and reporting should be performed for all clinical germline (constitutional) exome and genome sequencing, including the "normal" of tumor-normal subtractive analyses in all subjects, irrespective of age but excluding fetal samples. We recognize that there are insufficient data on penetrance and clinical utility to fully support these recommendations, and we encourage the creation of an ongoing process for updating these recommendations at least annually as further data are collected.

Genet Med 2013:15(7):565–574

Key Words: genome; genomic medicine; incidental findings; personalized medicine; secondary findings; sequencing; whole exome; whole genome

Incidental/Secondary Findings

- Hereditary Cancer Syndromes
  - Hereditary breast and ovarian cancer, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, Lynch syndrome, Familial adenomatous polyposis, MYH-associated polyposis, Von Hippel-Landau syndrome, Multiple endocrine neoplasia type 1, Multiple endocrine neoplasia type 2, Familial medullary thyroid cancer, PTEN harmartoma tumor syndrome, Retinoblastoma, Hereditary paraganglioma-pheochromocytoma syndrome, Tuberous sclerosis complex, WT1-related Wilms tumor, Neurofibromatosis type 2
- Hereditary Cardiovascular Syndromes
  - Ehlers-Danlos syndrome type IV, Marfan syndrome, Loeys-Dietz syndrome, Familial thoracic aortic aneurysms and dissections, Hypertrophic cardiomyopathy, Dilated cardiomyopathy, Catecholaminergic polymorphic ventricular tachycardia, Arrhythmogenic right-ventricular cardiomyopathy, Romano-Ward long QT syndrome types 1,2,3, Brugada syndrome, Familial hypercholesterolemia
- Other Syndromes
  - Malignant hyperthermia

56 genes

Table 1 Conditions, genes, and variants recommended for return of incidental findings in clinical sequencing

Phenotype	MIM-disorder	PMID-Gene Reviews entry	Typical age of onset	Gene	MIM-gene	Inheritance[a]	Variants to report[b]
Hereditary breast and ovarian cancer	604370 612555	20301425	Adult	*BRCA1* *BRCA2*	113705 600185	AD	KP and EP
Li–Fraumeni syndrome	151623	20301488	Child/adult	*TP53*	191170	AD	KP and EP
Peutz–Jeghers syndrome	175200	20301443	Child/adult	*STK11*	602216	AD	KP and EP
Lynch syndrome	120435	20301390	Adult	*MLH1* *MSH2* *MSH6* *PMS2*	120436 609309 600678 600259	AD	KP and EP
Familial adenomatous polyposis	175100	20301519	Child/adult	*APC*	611731	AD	KP and EP
MYH-associated polyposis; adenomas, multiple colorectal, *FAP* type 2; colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas	608456 132600	23035301	Adult	*MUTYH*	604933	AR[c]	KP and EP
Von Hippel–Lindau syndrome	193300	20301636	Child/adult	*VHL*	608537	AD	KP and EP
Multiple endocrine neoplasia type 1	131100	20301710	Child/adult	*MEN1*	613733	AD	KP and EP
Multiple endocrine neoplasia type 2	171400 162300	20301434	Child/adult	*RET*	164761	AD	KP
Familial medullary thyroid cancer[d]	1552401	20301434	Child/adult	*RET*	164761	AD	KP
PTEN hamartoma tumor syndrome	153480	20301661	Child/adult	*PTEN*	601728	AD	KP and EP
Retinoblastoma	180200	20301625	Child	*RB1*	614041	AD	KP and EP
Hereditary paraganglioma–pheochromocytoma syndrome	168000 (PGL1) 601650 (PGL2) 605373 (PGL3) 115310 (PGL4)	20301715	Child/adult	*SDHD* *SDHAF2* *SDHC* *SDHB*	602690 613019 602413 185470	AD	KP and EP KP KP and EP
Tuberous sclerosis complex	191100 613254	20301399	Child	*TSC1* *TSC2*	605284 191092	AD	KP and EP
WT1-related Wilms tumor	194070	20301471	Child	*WT1*	607102	AD	KP and EP
Neurofibromatosis type 2	101100	20301380	Child/adult	*NF2*	607379	AD	KP and EP
Ehlers–Danlos syndrome, vascular type	130050	20301667	Child/adult	*COL3A1*	120180	AD	KP and EP
Marfan syndrome, Loeys–Dietz syndromes, and familial thoracic aortic aneurysms and dissections	154700 609192 608967 610168 610380 613795 611788	20301510 20301312 20301299	Child/adult	*FBN1* *TGFBR1* *TGFBR2* *SMAD3* *ACTA2* *MYLK* *MYH11*	134797 190181 190182 603109 102620 600922 160745	AD	KP and EP
Hypertrophic cardiomyopathy, dilated cardiomyopathy	115197 192600 601494 613690 115196 608751 612098 600858 301500 608758 115200	20301725	Child/adult	*MYBPC3* *MYH7* *TNNT2* *TNNI3* *TPM1* *MYL3* *ACTC1* *PRKAG2* *GLA* *MYL2* *LMNA*	600958 160760 191045 191044 191010 160790 102540 602743 300644 160781 150330	AD XL AD 	KP and EP KP KP and EP KP KP and EP (hemi, het, hom) KP KP and EP
Catecholaminergic polymorphic ventricular tachycardia	604772			*RYR2*	180902	AD	KP
Arrhythmogenic right-ventricular cardiomyopathy	609040 604400 610476 607450 610193	20301310	Child/adult	*PKP2* *DSP* *DSC2* *TMEM43* *DSG2*	602861 125647 125645 612048 125671	AD 	KP and EP KP KP and EP
Romano–Ward long QT syndrome types 1, 2, and 3, Brugada syndrome	192500 613688 603830 601144	20301308	Child/adult	*KCNQ1* *KCNH2* *SCN5A*	607542 152427 600163	AD 	KP and EP
Familial hypercholesterolemia	143890 603776	No GeneReviews entry	Child/adult	*LDLR* *APOB* *PCSK9*	606945 107730 607786	SD SD AD	KP and EP KP
Malignant hyperthermia susceptibility	145600	20301325	Child/adult	*RYR1* *CACNA1S*	180901 114208	AD 	KP

[a]Some conditions that may demonstrate semidominant inheritance (SD) have been indicated as autosomal dominant (AD) for the sake of simplicity. Others have been labeled as X-linked (XL); [b]KP: known pathogenic, sequence variation is previously reported and is a recognized cause of the disorder; EP: expected pathogenic, sequence variation is previously unreported and is of the type that is expected to cause the disorder. Note: The recommendation to not report expected pathogenic variants for some genes is due to the recognition that truncating variants, the primary type of expected pathogenic variants, are not an established cause of some diseases on the list. [c]Although carriers may have modestly increased risk, we recommend searching only for individuals with biallelic mutations; [d]On the basis of evidence presented to the Working Group after the online posting of these Recommendations, the decision was made to remove one gene, NTRK1, from the recommended list.

ACMG STATEMENT | Genetics inMedicine

Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics

Sarah S. Kalia, ScM[1], Kathy Adelman[2], Sherri J. Bale, PhD[3], Wendy K. Chung, MD, PhD[4,5], Christine Eng, MD[6], James P. Evans, MD, PhD[7], Gail E. Herman, MD, PhD[8], Sophia B. Hufnagel, MD[9], Teri E. Klein, PhD[10], Bruce R. Korf, MD, PhD[11], Kent D. McKelvey, MD[12,13], Kelly E. Ormond, MS[10], C. Sue Richards, PhD[14], Christopher N. Vlangos, PhD[15], Michael Watson, PhD[16], Christa L. Martin, PhD[17], David T. Miller, MD, PhD[18]; on behalf of the ACMG Secondary Findings Maintenance Working Group

To promote standardized reporting of actionable information from clinical genomic sequencing, in 2013, the American College of Medical Genetics and Genomics (ACMG) published a minimum list of genes to be reported as incidental or secondary findings. The goal was to identify and manage risks for selected highly penetrant genetic disorders through established interventions aimed at preventing or significantly reducing morbidity and mortality. The ACMG subsequently established the Secondary Findings Maintenance Working Group to develop a process for curating and updating the list over time. We describe here the new process for accepting and evaluating nominations for updates to the secondary findings list. We also report outcomes from six nominations received in the initial 15 months after the process was implemented. Applying the new process while upholding the core principles of the original policy statement resulted in the addition of four genes and removal of one gene; one gene did not meet criteria for inclusion. The updated secondary findings minimum list includes 59 medically actionable genes recommended for return in clinical genomic sequencing. We discuss future areas of focus, encourage continued input from the medical community, and call for research on the impact of returning genomic secondary findings.

Genet Med advance online publication 17 November 2016

Key Words: exome sequencing; genetic testing; genome sequencing; incidental findings; secondary findings

Incidental/Secondary Findings

- Hereditary Cancer Syndromes
  - Hereditary breast and ovarian cancer, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, Lynch syndrome, Familial adenomatous polyposis, MYH-associated polyposis, Juvenile polyposis, Von Hippel-Landau syndrome, Multiple endocrine neoplasia type 1, Multiple endocrine neoplasia type 2, Familial medullary thyroid cancer, PTEN harmartoma tumor syndrome, Retinoblastoma, Hereditary paraganglioma-pheochromocytoma syndrome, Tuberous sclerosis complex, WT1-related Wilms tumor, Neurofibromatosis type 2
- Hereditary Cardiovascular Syndromes
  - Ehlers-Danlos syndrome type IV, Marfan syndrome, Loeys-Dietz syndrome, Familial thoracic aortic aneurysms and dissections, Hypertrophic cardiomyopathy, Dilated cardiomyopathy, Catecholaminergic polymorphic ventricular tachycardia, Arrhythmogenic right-ventricular cardiomyopathy, Romano-Ward long QT syndrome types 1,2,3, Brugada syndrome, Familial hypercholesterolemia
- Other Syndromes
  - Malignant hyperthermia, Wilson disease, Ornithine transcarbamylase deficiency

59 genes

Table 1 ACMG SF v2.0 genes and associated phenotypes recommended for return of secondary findings in clinical sequencing

Phenotype	MIM disorder	PMID Gene Reviews entry	Typical age of onset	Gene	MIM gene	Inheritance[a]	Variants to report[b]
Hereditary breast and ovarian cancer	604370 612555	20301425	Adult	*BRCA1* *BRCA2*	113705 600185	AD	KP and EP
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Lynch syndrome	120435	20301390	Adult	*MLH1* *MSH2* *MSH6* *PMS2*	120436 609309 600678 600259	AD	KP and EP
Familial adenomatous polyposis	175100	20301519	Child/adult	*APC*	611731	AD	KP and EP
MYH-associated polyposis; adenomas, multiple colorectal, *FAP* type 2; colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas	608456 132600	23035301	Adult	*MUTYH*	604933	AR[c]	KP and EP
Juvenile polyposis	174900	20301642	Child/adult	*BMPR1A* *SMAD4*	601299 600993	AD	KP and EP
Von Hippel–Lindau syndrome	193300	20301636	Child/adult	*VHL*	608537	AD	KP and EP
Multiple endocrine neoplasia type 1	131100	20301710	Child/adult	*MEN1*	613733	AD	KP and EP
Multiple endocrine neoplasia type 2	171400 162300	20301434	Child/adult	*RET*	164761	AD	KP
Familial medullary thyroid cancer[d]	1552401	20301434	Child/adult	*RET*	164761	AD	KP
PTEN hamartoma tumor syndrome	153480	20301661	Child/adult	*PTEN*	601728	AD	KP and EP
Retinoblastoma	180200	20301625	Child	*RB1*	614041	AD	KP and EP
Hereditary paraganglioma-pheochromocytoma syndrome	168000 (PGL1) 601650 (PGL2) 605373 (PGL3) 115310 (PGL4)	20301715	Child/adult	*SDHD* *SDHAF2* *SDHC* *SDHB*	602690 613019 602413 185470	AD	KP and EP KP KP and EP
Tuberous sclerosis complex	191100 613254	20301399	Child	*TSC1* *TSC2*	605284 191092	AD	KP and EP
WT1-related Wilms tumor	194070	20301471	Child	*WT1*	607102	AD	KP and EP
Neurofibromatosis type 2	101100	20301380	Child/adult	*NF2*	607379	AD	KP and EP
Ehlers-Danlos syndrome, vascular type	130050	20301667	Child/adult	*COL3A1*	120180	AD	KP and EP
Marfan syndrome, Loeys-Dietz syndromes, and familial thoracic aortic aneurysms and dissections	154700 609192 608967 610168 610380 613795 611788	20301510 20301312 20301299	Child/adult	*FBN1* *TGFBR1* *TGFBR2* *SMAD3* *ACTA2* *MYH11*	134797 190181 190182 603109 102620 160745	AD	KP and EP
Hypertrophic cardiomyopathy, dilated cardiomyopathy	115197 192600 601494 613690 115196 608751 612098 600858 301500 608758 115200	20301725	Child/adult	*MYBPC3* *MYH7* *TNNT2* *TNNI3* *TPM1* *MYL3* *ACTC1* *PRKAG2* *GLA* *MYL2* *LMNA*	600958 160760 191045 191044 191010 160790 102540 602743 300644 160781 150330	AD XL AD	KP and EP KP KP and EP KP KP and EP (hemi, het, hom) KP KP and EP
Catecholaminergic polymorphic ventricular tachycardia	604772			*RYR2*	180902	AD	KP
Arrhythmogenic right ventricular cardiomyopathy	609040 604400 610476 607450 610193	20301310	Child/adult	*PKP2* *DSP* *DSC2* *TMEM43* *DSG2*	602861 125647 125645 612048 125671	AD	KP and EP KP KP and EP
Romano-Ward long-QT syndrome types 1, 2, and 3, Brugada syndrome	192500 613688 603830 601144	20301308	Child/adult	*KCNQ1* *KCNH2* *SCN5A*	607542 152427 600163	AD	KP and EP
Familial hypercholesterolemia	143890 603776	No GeneReviews entry	Child/adult	*LDLR* *APOB* *PCSK9*	606945 107730 607786	SD SD AD	KP and EP KP
Wilson disease	277900	20301685	Child	*ATP7B*	606882	AR[c]	KP and EP
Ornithine transcarbamylase deficiency	311250	24006547	Newborn (male), child (female)	*OTC*	300461	XL	KP and EP (hemi, het, hom)
Malignant hyperthermia susceptibility	145600	20301325	Child/adult	*RYR1* *CACNA1S*	180901 114208	AD	KP

[a]Some conditions that may demonstrate semidominant inheritance have been indicated as autosomal-dominant (AD) for the sake of simplicity. Others have been labeled as X-linked (XL). [b]KP: known pathogenic, sequence variation is previously reported and is a recognized cause of the disorder; EP: expected pathogenic, sequence variation is previously unreported and is of the type that is expected to cause the disorder. Note: The recommendation to not report expected pathogenic variants for some genes is due to the recognition that truncating variants, the primary type of expected pathogenic variants, are not an established cause of some diseases on the list. [c]We recommend searching only for individuals with biallelic mutations.

BRIEF REPORT | Genetics inMedicine

Frequency and spectrum of actionable pathogenic secondary findings in 196 Korean exomes

Mi-Ae Jang, MD[1,4], Sang-Heon Lee, BS[2,3], Namshin Kim, PhD[2,3] and Chang-Seok Ki, MD, PhD[1]

Purpose: One of the biggest challenges of exome and genome sequencing in the era of genomic medicine is the identification and reporting of secondary findings. In this study we investigated the frequency and spectrum of actionable pathogenic secondary findings in Korean exomes.

Methods: Data from 196 Korean exomes were screened for variants from a list of 56 genes recommended by the American College of Medical Genetics and Genomics (ACMG) for return of secondary findings. Identified variants were classified according to the evidence-based guidelines reached by a joint consensus of the ACMG and the Association for Molecular Pathology.

Results: Among the 196 exomes, which were from 100 healthy controls and 96 patients with suspected genetic disorders, 11 variants in 13 individuals were found to be pathogenic or likely pathogenic. We estimated that the frequency of actionable pathogenic secondary findings was 7% for the control subjects (7/100) and 6% for the patients with disease (6/96). For one autosomal-recessive disease, four individuals exhibited either one pathogenic or one likely pathogenic variant of the *MUTYH* gene, leading to a carrier frequency of 2% (4/196).

Conclusion: Secondary findings are not uncommon in Korean exomes.

Genet Med advance online publication 9 April 2015

Key Words: exome; Korean; secondary finding; variant

Table 1 Filtering and classification of variants by study group

Classification	Group A (control)	Group B (disease)	Total
Variants (*n*)			
Total variants for 56 genes	2,309	2,100	4,409
After exclusion of nongenic or intronic variants	509	494	1,003
Variants listed as disease-causing in the HGMD	33	37	70
Any novel disruptive variants	2	4	6
After application of evidence guideline			
Pathogenic variants (A)	3[a]	2[a]	5[b]
Likely pathogenic variants (B)	4	4	8
Uncertain significance variants	28	35	63
Sum of pathogenic or likely pathogenic variants (A + B)	7	6	13[b]
Participants (*n*)			
Participants with pathogenic variants[c] (C)	1	1	2
Participants with likely pathogenic variants[c] (D)	6	5	11
Sum of participants with pathogenic or likely pathogenic variants (C + D)	7	6	13

Group A comprised 100 unrelated healthy individuals from the Korean Genome and Epidemiology Study. Group B consisted of 96 unrelated Korean patients with suspected Mendelian disorders who underwent exome sequencing.

HGMD, the Human Gene Mutation Database, professional version for release 2014.1.

Table 2 Pathogenic or likely pathogenic variants according to the evidence-based guidelines in ACMG reportable genes

Category	Gene	Variant	dbSNP	HGMD accession no.	Disease association per the ACMG	Frequency in A (control)	Frequency. in B (disease)
P	*BRCA2*	NM_000059.3:c.1399A>T NP_000050.2:p.Lys467*	rs80358427	CM021955	Hereditary breast and ovarian cancer	1/100	1/96
P	*MUTYH*	NM_001128425.1:c.799C>T NP_001121897.1:p.Gln267*	NA	CM077607	MYH-associated polyposis	1/100	0/96
P	*MUTYH*	NM_001128425.1:c.934-2A>G	rs77542170	CS04822	MYH-associated polyposis	2/100	1/96
LP	*BRCA1*	NM_007294.3:c.3629dupA NP_009225.1:p.Ser1211Valfs*8	NA	NA	Hereditary breast and ovarian cancer	1/100	0/96
LP	*DSP*	NM_004415.2:c.269A>G NP_004406.2:p.Gln90Arg	rs188516326	CM063959	Arrhythmogenic right ventricular cardiomyopathy	1/100	0/96
LP	*MYBPC3*	NM_000256.3:c.1000G>A NP_000247.2:p.Glu334Lys	NA	CM073211	Hypertrophic cardiomyopathy, dilated cardiomyopathy	0/100	1/96
LP	*MYL3*	NM_000258.2:c.170C>G NP_000249.1:p.Ala57Gly	rs139794067	CM14210	Hypertrophic cardiomyopathy, dilated cardiomyopathy	0/100	2/96
LP	*RYR1*	NM_000540.2:c.5701C>T NP_000531.2:p.Gln1901*	NA	NA	Malignant hyperthermia susceptibility	0/100	1/96
LP	*RYR2*	NM_001035.2:c.1217C>T NP_001026.2:p.Ser406Leu	NA	CM126236	Catecholaminergic polymorphic ventricular tachycardia	0/100	1/96
LP	*SCN5A*	NM_198056.2:c.3250G>A NP_932173.1:p.Gly1084Ser	rs199473190	CM085685	Long QT syndrome	1/100	0/96
LP	*TP53*	NM_000546.5:c.91G>A NP_000537.3:p.Val31Ile	rs201753350	CM074603	Li-Fraumeni syndrome	3/100	0/96

ACMG, the American College of Medical Genetics and Genomics; HGMD, the Human Gene Mutation Database, professional version for release 2014.1; LP, likely pathogenic variant; NA, not available; P, pathogenic variant; dbSNP, single-nucleotide polymorphism database.

OPEN

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ORIGINAL ARTICLE

Findings of a 1303 Korean whole-exome sequencing study

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Ethnically specific data on genetic variation are crucial for understanding human biology and for clinical interpretation of variant pathogenicity. We analyzed data obtained by deep sequencing 1303 Korean whole exomes; the data were generated by three independent whole exome sequencing projects (named the KOEX study). The primary focus of this study was to comprehensively analyze the variant statistics, investigate secondary findings that may have clinical actionability, and identify loci that should be cautiously interpreted for pathogenicity. A total of 495 729 unique variants were identified at exonic regions, including 169 380 nonsynonymous variants and 4356 frameshift insertion/deletions. Among these, 76 607 were novel coding variants. On average, each individual had 7136 nonsynonymous single-nucleotide variants and 74 frameshift insertion/deletions. We classified 13 pathogenic and 13 likely pathogenic variants in 56 genes that may have clinical actionability according to the guidelines of the American College of Medical Genetics and Genomics, and the Association for Molecular Pathology. The carrier frequency of these 26 variants was 2.46% (95% confidence interval 1.73–3.46). To identify loci that require cautious interpretation in clinical sequencing, we identified 18 genes that are prone to sequencing errors, and 671 genes that are highly polymorphic and carry excess nonsynonymous variants. The catalog of identified variants, its annotation and frequency information are publicly available (http://koex.snu.ac.kr). These findings should be useful resources for investigating ethnically specific characteristics in human health and disease.

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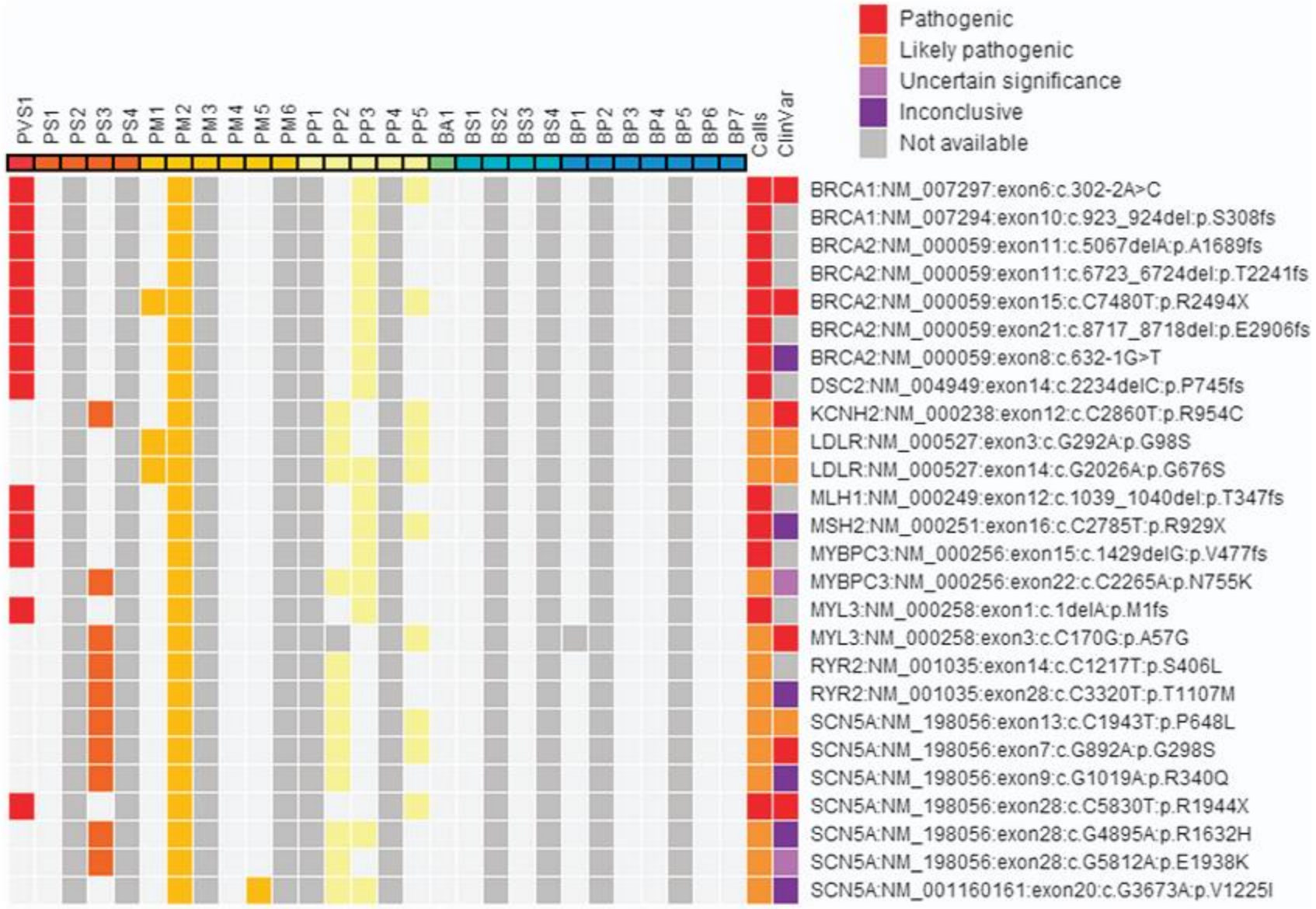
PVS1
PS1
PS2
PS3
PS4
PM1
PM2
PM3
PM4
PM5
PM6
PP1
PP2
PP3
PP4
PP5
BA1
BS1
BS2
BS3
BS4
BP1
BP2
BP3
BP4
BP5
BP6
BP7
Calls
ClinVar
Pathogenic
Likely pathogenic
Uncertain significance
Inconclusive
Not available
BRCA1:NM_007297:exon6:c.302-2A>C
BRCA1:NM_007294:exon10:c.923_924del:p.S308fs
BRCA2:NM_000059:exon11:c.5067delA:p.A1689fs
BRCA2:NM_000059:exon11:c.6723_6724del:p.T2241fs
BRCA2:NM_000059:exon15:c.C7480T:p.R2494X
BRCA2:NM_000059:exon21:c.8717_8718del:p.E2906fs
BRCA2:NM_000059:exon8:c.632-1G>T
DSC2:NM_004949:exon14:c.2234delC:p.P745fs
KCNH2:NM_000238:exon12:c.C2860T:p.R954C
LDLR:NM_000527:exon3:c.G292A:p.G98S
LDLR:NM_000527:exon14:c.G2026A:p.G676S
MLH1:NM_000249:exon12:c.1039_1040del:p.T347fs
MSH2:NM_000251:exon16:c.C2785T:p.R929X
MYBPC3:NM_000256:exon15:c.1429delG:p.V477fs
MYBPC3:NM_000256:exon22:c.C2265A:p.N755K
MYL3:NM_000258:exon1:c.1delA:p.M1fs
MYL3:NM_000258:exon3:c.C170G:p.A57G
RYR2:NM_001035:exon14:c.C1217T:p.S406L
RYR2:NM_001035:exon28:c.C3320T:p.T1107M
SCN5A:NM_198056:exon13:c.C1943T:p.P648L
SCN5A:NM_198056:exon7:c.G892A:p.G298S
SCN5A:NM_198056:exon9:c.G1019A:p.R340Q
SCN5A:NM_198056:exon28:c.C5830T:p.R1944X
SCN5A:NM_198056:exon28:c.G4895A:p.R1632H
SCN5A:NM_198056:exon28:c.G5812A:p.E1938K
SCN5A:NM_001160161:exon20:c.G3673A:p.V1225I

ORIGINAL ARTICLE
Cardiovascular Disorders

JKMS

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Genetic Mutation in Korean Patients of Sudden Cardiac Arrest as a Surrogating Marker of Idiopathic Ventricular Arrhythmia

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Mutation or common intronic variants in cardiac ion channel genes have been suggested to be associated with sudden cardiac death caused by idiopathic ventricular tachyarrhythmia. This study aimed to find mutations in cardiac ion channel genes of Korean sudden cardiac arrest patients with structurally normal heart and to verify association between common genetic variation in cardiac ion channel and sudden cardiac arrest by idiopathic ventricular tachyarrhythmia in Koreans. Study participants were Korean survivors of sudden cardiac arrest caused by idiopathic ventricular tachycardia or fibrillation. All coding exons of the *SCN5A*, *KCNQ1*, and *KCNH2* genes were analyzed by Sanger sequencing. Fifteen survivors of sudden cardiac arrest were included. Three male patients had mutations in *SCN5A* gene and none in *KCNQ1* and *KCNH2* genes. Intronic variant (rs2283222) in *KCNQ1* gene showed significant association with sudden cardiac arrest (OR 4.05). Four male sudden cardiac arrest survivors had intronic variant (rs11720524) in *SCN5A* gene. None of female survivors of sudden cardiac arrest had *SCN5A* gene mutations despite similar frequencies of intronic variants between males and females in 55 normal controls. Common intronic variant in *KCNQ1* gene is associated with sudden cardiac arrest caused by idiopathic ventricular tachyarrhythmia in Koreans.

Table 1. Clinical characteristics of patients who survived sudden cardiac arrest caused by idiopathic ventricular tachyarrhythmia

Patient No.	Sex	Age (yr)	*SCN5A* gene mutation	Family History of SCD	Rhythm at cardiac event	Rest ECG abnormality	TTE	CAG
1	M	35	No	Yes (uncle)	VT	NI	NI	NI
2	M	18	No	No	VF/VT	NI	NI	NI
3	M	50	c.3578G > A (p.R1193Q)	No	VF/VT	NI	NI	NI
4	M	35	No	No	VF	NI	NI	NI
5	M	38	c.5812G > A (p.E1938K)	No	VF	LAFB	NI	NI
6	M	66	No	No	VT	APC	NI	NI
7	M	18	No	No	VT	LAFB	NI	NI
8	M	39	No	No	VF	NI	NI	NI
9	F	50	No	No	VT	NI	NI	NI
10	M	35	No	No	VF	NI	NI	NI
11	M	37	No	No	VF	NI	NI	NI
12	F	50	No	No	VF	NI	NI	NI
13	F	34	No	No	VF	NI	NI	NI
14	M	45	c.3578G > A (p.R1193Q)	No	VF/VT	NI	NI	NI
15	F	46	No	No	VT	NI	NI	NP

APC, atrial premature complex; CAG, coronary angiography; ECG, electrocardiography; LAFB, left anterior fascicular block; NI, normal; NP, not performed; SCD, sudden cardiac death; TTE, transthoracic echocardiography; VF, ventricular fibrillation; VT, ventricular tachycardia.

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ORIGINAL ARTICLE

Identification of pathogenic variants in genes related to channelopathy and cardiomyopathy in Korean sudden cardiac arrest survivors

Ju Sun Song[1,7], Jong-Sun Kang[2,7], Young-Eun Kim[3], Seung-jung Park[4], Kyoung-Min Park[4], June Huh[5], June Soo Kim[4], Hana Cho[6], Chang-Seok Ki[1] and Young Keun On[4]

Pathogenic variants in genes related to channelopathy and cardiomyopathy are the most common cause of sudden unexplained cardiac death. However, few reports have investigated the frequency and/or spectrum of pathogenic variants in these genes in Korean sudden cardiac arrest survivors. This study aimed to investigate the causative genetic variants of cardiac-associated genes in Korean sudden cardiac arrest survivors. We performed exome sequencing followed by filtering and validation of variants in 100 genes related to channelopathy and cardiomyopathy in 19 Korean patients who survived sudden cardiac arrest. Five of the 19 patients (26.3%) had either a pathogenic variant or a likely pathogenic variant in *MYBPC3* ($n=1$), *MYH7* ($n=1$), *RYR2* ($n=2$), or *TNNT2* ($n=1$). All five variants were missense variants that have been reported previously in patients with channelopathies or cardiomyopathies. Furthermore, an additional 12 patients (63.2%) had more than one variant of uncertain significance. In conclusion, pathogenic or likely pathogenic variants in genes related to channelopathy and cardiomyopathy are not uncommon in Korean sudden cardiac arrest survivors and cardiomyopathy-related genes should be included in the molecular diagnosis of sudden cardiac arrest in Korea.
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Table 1 Demographic and clinical characteristics of the 19 sudden cardiac arrest survivors

Case no.	*Sex*	*Age at SCA, years*	*Smoking*	*Medical history*	*Diagnosis*	*Family history*
SCAS-1	M	66	Ex-smoker	CKD (Cr 1.8)	Idiopathic VF	CHF—daughter
SCAS-2	M	48	Current	NS	Brugada phenocopy	None
SCAS-3	M	60	No	Hypertension	Idiopathic VF	SCA—father
SCAS-4	M	35	No	NS	Idiopathic VF	No
SCAS-5	M	18	No	NS	Long QT syndrome	SCA—father
SCAS-6	M	35	Current	NS	Idiopathic VF	None
SCAS-7	M	18	No	NS	CPVT	None
SCAS-8	M	39	No	NS	Idiopathic VF	None
SCAS-9	F	50	No	Hypertension	Idiopathic VF	None
SCAS-10	M	37	Ex-smoker	NS	Idiopathic VF	None
SCAS-11	F	50	No	NS	Idiopathic VF	None
SCAS-12	F	34	No	NS	Idiopathic VF	None
SCAS-13	M	21	Current	NS	Idiopathic VF	None
SCAS-14	M	12	No	NS	HCMP	None
SCAS-15	M	22	Current	NS	Brugada syndrome	SCA—maternal side
SCAS-16	M	8	No	NS	CPVT	None
SCAS-17	M	34	No	NS	Complete AV block	None
SCAS-18	M	33	No	NS	Complete AV block	None
SCAS-19	M	34	Ex-smoker	Hypertension	Idiopathic VF	AMI—father

Abbreviations: AMI, acute myocardiac infarction; AV, atrioventricular; CHF, congestive heart failure; CKD, chronic kidney disease; CPVT, catecholaminergic polymorphic ventricular tachycardia; F, female; HCMP, hypertrophic cardiomyopathy; M, male; NS, not significant; SCA, sudden cardiac arrest; SCAS, sudden cardiac arrest survivor; VF, ventricular fibrillation.

Table 3 Variants in the 19 sudden cardiac arrest survivors classified according to the 2015 American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines

Case no.	Gene	Reference sequence	Nucleotide change	Protein change	HGMD phenotype	HGMD variant class	ACMG classification	MAF (ExAC)	MAF (KRGDB)
SCAS-1	***MYH7***	**NM_000257.2**	**c.4130C>T**	**p.Thr1377Met**	**HCM**	**DM**	**Likely pathogenic variant**	**0.00000**	**0.00000**
SCAS-2	***MYBPC3***	**NM_000256.3**	**c.1000G>A**	**p.Glu334Lys**	**HCM**	**DM**	**Likely pathogenic variant**	**0.00030**	**0.00400**
SCAS-3	*TTN*	NM_133378.4	c.60256G>C	p.Asp20086His	—	—	VUS	0.00004	0.00000
SCAS-4	*DSG2*	NM_001943.3	c.166G>A	p.Val56Met	ARVC	DM?	VUS	0.00187	0.00160
	PKP2	NM_004572.3	c.2150C>T	p.Pro717Leu	ARVC	DM?	VUS	0.00013	0.00720
	PKP2	NM_004572.3	c.1546_1584del	p.Lys516_Thr528del	—	—	VUS	0.00000	0.00000
SCAS-5				Not detected					
SCAS-6	*ANK2*	NM_001148.4	c.9689C>T	p.Thr3230Met	—	—	VUS	0.00001	0.00000
	CTNNA3	NM_013266.2	c.1853A>G	p.His618Arg	—	—	VUS	0.00002	0.00080
	SCN2B	NM_004588.4	c.250C>T	p.Arg84Cys	—	—	VUS	0.00005	0.00000
	TCAP	NM_003673.3	c.145G>A	p.Glu49Lys	DCM	DM?	VUS	0.00008	0.00160
SCAS-7	*DSP*	NM_004415.2	c.4943A>G	p.Gln1648Arg	—	—	VUS	0.00016	0.00000
	RYR2	**NM_001035.2**	**c.14311G>A**	**p.Val4771Ile**	**PVT**	**DM**	**Likely pathogenic variant**	**0.00000**	**0.00000**
	TTN	NM_133378.4	c.4874C>G	p.Ser1625Cys	—	—	VUS	0.00004	0.00080
	TTN	NM_133378.4	c.53585G>A	p.Cys17862Tyr	—	—	VUS	0.00006	0.00080
SCAS-8	*CTNNA3*	NM_013266.2	c.2260A>C	p.Asn754His	—	—	VUS	0.00000	0.00000
SCAS-9				Not detected					
SCAS-10	*CTNNA3*	NM_013266.2	c.1850T>C	p.Ile617Thr	—	—	VUS	0.00026	0.00560
	RBM20	NM_001134363.1	c.2089G>A	p.Gly697Arg	—	—	VUS	0.00066	0.00080
	TTN	NM_133378.4	c.84049T>G	p.Phe28017Val	—	—	VUS	0.00000	0.00000
SCAS-11	*MYBPC3*	NM_000256.3	c.1519G>A	p.Gly507Arg	HCM	DM?	VUS	0.00068	0.00400
	PRDM16	NM_022114.3	c.3461A>C	p.Glu1154Ala	—	—	VUS	0.00010	0.00560
	RYR2	NM_001035.2	c.12334G>A	p.Asp4112Asn	—	—	VUS	0.00000	0.00000
	TTN	NM_133378.4	c.43675G>C	p.Val14559Leu	—	—	VUS	0.00000	0.00080
SCAS-12	*TNNI3*	NM_000363.4	c.235C>T	p.Arg79Cys	—	—	VUS	0.00039	0.00400
	TTN	NM_133378.4	c.8069C>T	p.Thr2690Ile	—	—	VUS	0.00059	0.00480
	TTN	NM_133378.4	c.22100A>G	p.Asn7367Ser	—	—	VUS	0.00002	0.00000
SCAS-13	*RYR2*	NM_001035.2	c.4840C>T	p.Arg1614Cys	—	—	VUS	0.00005	0.00000
	TTN	NM_133378.4	c.27403G>A	p.Glu9135Lys	—	—	VUS	0.00000	0.00160
	TTN	NM_133378.4	c.89405C>A	p.Thr29802Asn	—	—	VUS	0.00005	0.00160
SCAS-14	***TNNT2***	**NM_001001430.2**	**c.274C>T**	**p.Arg92Trp**	**HCM**	**DM**	**Pathogenic variant**	**0.00001**	**0.00000**
SCAS-15	*TTN*	NM_133378.4	c.81041C>T	p.Ser27014Phe	—	—	VUS	0.00000	0.00000
SCAS-16	***RYR2***	**NM_001035.2**	**c.6737C>T**	**p.Ser2246Leu**	**PVT**	**DM**	**Pathogenic variant**	**0.00000**	**0.00000**
SCAS-17	*PKP2*	NM_004572.3	c.2150C>T	p.Pro717Leu	ARVC	DM?	VUS	0.00013	0.00720
	TTN	NM_133378.4	c.34052A>G	p.Asp11351Gly	—	—	VUS	0.00000	0.00000
	TTN	NM_133378.4	c.37246G>C	p.Gly12416Arg	—	—	VUS	0.00004	0.00000
	TTN	NM_133378.4	c.47690C>A	p.Ala15897Glu	—	—	VUS	0.00000	0.00000
	TNNI3K	NM_015978.2	c.2225_2227delCTT	p.Ser745del	—	—	VUS	0.00026	0.00400
SCAS-18	*TTN*	NM_133378.4	c.19712G>A	p.Arg6571Gln	—	—	VUS	0.00002	0.00080
	TTN	NM_133378.4	c.48691G>A	p.Ala16231Thr	—	—	VUS	0.00003	0.00080
SCAS-19	*SCN5A*	NM_198056.2	c.5851G>A	p.Val1951Met	AF	DM	VUS	0.00008	0.00800

Abbreviations: ACMG, American College of Medical Genetics and Genomics; AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; DM, disease-causing mutation; ExAC, Exome Aggregation Consortium; HCM, hypertrophic cardiomyopathy; HGMD, human gene mutation database; KRGDB, Korean Reference Genome Database; MAF, minor allele frequency; PVT, polymorphic ventricular tachycardia; VUS, variant of uncertain significance. Rows in bold are pathogenic or likely pathogenic variants.

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Ethnic Differences in Genetic Ion Channelopathies Associated with Sudden Cardiac Death: A Systematic Review and Meta-Analysis.

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⊕ Author information

Abstract

BACKGROUND AND AIMS: Reports of allele frequencies encoding ion channel, or their interacting proteins associated with sudden cardiac death among different ethnic groups have been inconsistent. Here, we aimed to characterize the distribution of these genes and their alleles among various ethnicities through meta-analysis.

METHODS: We conducted a systematic review and meta-analysis to assess the mean allele frequencies of channelopathy genes *SCN5A*, *NOS1AP*, *KCNH2*, *KCNE1*, and *KCNQ1* among the Black, Caucasian, Asian, and Hispanic ethnicities. Searches in PubMed, Google Scholar, and Web of Science resulted in 18 reports published before July 2015 that met the eligible criteria. Allele frequencies were averaged by weight, and pooled values were calculated by inverse variance. Fixed-effects and random-effects models were used to pool effect sizes within each study and across different studies, respectively. Moreover, to extend our findings, we used sequenced genomic data from the Exome Aggregation Consortium to compare allele frequencies between different ethnicities.

RESULTS: Meta-analysis of published studies supports that Asians had the highest overall mean allele frequencies of *NOS1AP* (0.36%, 95% CI: 0.30, 0.43; $P<0.001$), and *SCN5A* frequencies (0.17%, 95% CI: 0.07, 0.27, $P=0.001$), and whereas Caucasians had the highest *KCNH2* frequency (0.21%, 95% CI: 0.16, 0.25; $P<0.001$), and Hispanics the highest *KCNQ1* frequency (0.16%). Analysis of the Exome Aggregation Consortium also provided consistent data in agreement the meta-analysis.

CONCLUSION: Overall, Asians carried the most alleles of genes associated with sudden cardiac death. The meta-analysis reveals significant differences in allele distribution of channelopathy-associated genes among different ethnic groups.

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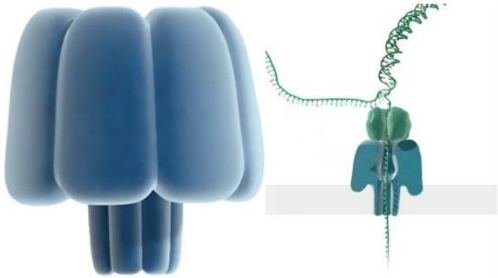

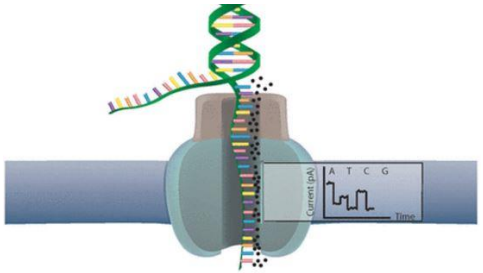


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