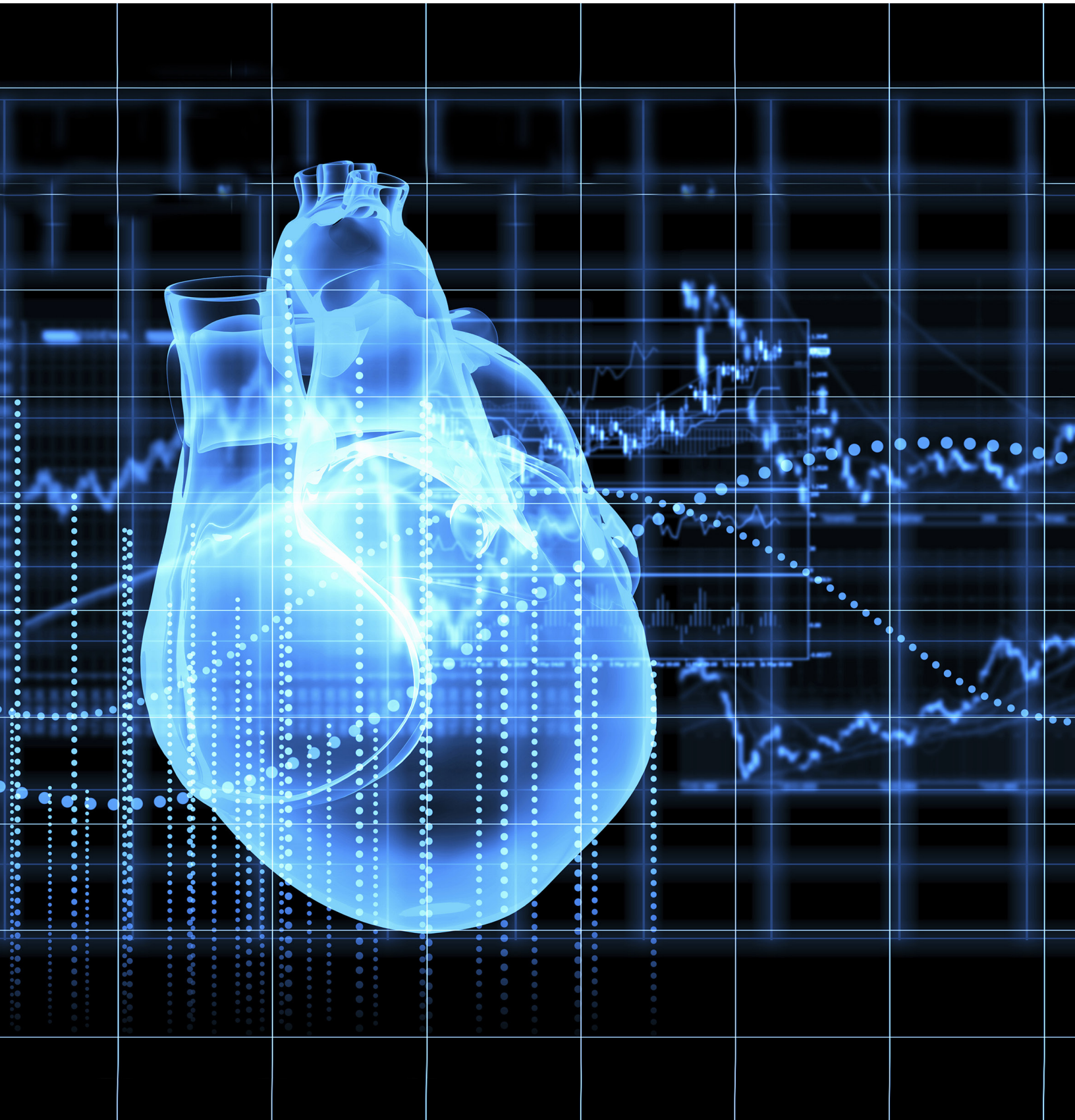
Cardiology Research Review

An Overview of Recent Publications Featuring Illumina® Technology



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INTRODUCTION

The increased information obtained from next-generating sequencing (NGS) is providing remarkable insight into the genomic and environmental components that underlie cardiac diseases. This improved understanding could ultimately translate into improved screening for risk factors and treating diseases based on their underlying molecular mechanisms.[1] Because the utility of genomic studies is now clearly established, it provides the impetus for larger and more expansive approaches. For example, molecular autopsies for all sudden cardiac deaths are now actively being pursued in New York City.[2] With that large effort, the hope is that targeted or whole-genome sequencing for inherited heart rhythm disorders can potentially offer grief-stricken family members an explanation for the loss of their loved ones and provide actionable diagnostic information to help them avoid the same fate. The information from this study, combined with other large studies, has the potential to substantially improve the detection, risk assessment, and treatment of cardiac diseases.

1. Topol E. J. (2014) Individualized medicine from prewomb to tomb. Cell 157: 241-253
2. Erdmann J. (2013) Telltale hearts. Nat Med 19: 1361-1364

Reviews

Fatica A. and Bozzoni I. (2014) Long non-coding RNAs: new players in cell differentiation and development. Nat Rev Genet 15: 7-21

The pervasive expression of different types of non-coding RNAs (ncRNAs) is a characteristic of the genomes of multicellular organisms. Long ncRNAs (lncRNAs) are involved in gene expression control, and the number of lncRNAs correlates to the developmental complexity of the species. This review describes the functions of lncRNAs in developmental processes and describes the current methodologies for lncRNA identification, including tiling arrays, serial analysis of gene expression (SAGE), cap analysis of gene expression (CAGE), RNA sequencing (RNA-Seq), and chromatin-immunoprecipitation sequencing (ChIP-Seq). The authors discuss dosage compensation, genomic imprinting, and cell differentiation, with a particular emphasis on mammalian development.

Mestroni L., Begay R. L., Graw S. L. and Taylor M. R. (2014) Pharmacogenetics of heart failure. Curr Opin Cardiol 29: 227-234

This review describes the role that polymorphic variants play in drug response in cardiovascular disease. A future challenge is the development of strategies to use this information in conjunction with a patient's genetic profile to personalize and optimize cardiovascular therapy.

Rabbani B., Tekin M. and Mahdieh N. (2014) The promise of whole-exome sequencing in medical genetics. J Hum Genet 59: 5-15

Topol E. J. (2014) Individualized medicine from prewomb to tomb. Cell 157: 241-253

CARDIAC RESEARCH TECHNIQUES

Expression Analysis

Expression analysis provides an insight into cellular activity. Array-based expression analysis is well established, but is being supplanted by expression analysis through RNA-Seq.[3] RNA-Seq provides an extended linear range and the ability to detect RNA expression down to single-cell levels.[4] In addition, it can detect splice variants,[5] RNA editing,[6] and allele-specific expression.[7]

References

Kivela R., Bry M., Robciuc M. R., Rasanen M., Taavitsainen M., et al. (2014) VEGF-B-induced vascular growth leads to metabolic reprogramming and ischemia resistance in the heart. EMBO Mol Med 6: 307-321

The authors use rat expression arrays to demonstrate that vascular endothelial growth factor-β (VEGF-β) can increase the coronary vasculature and reprogram myocardial metabolism to improve cardiac function in ischemic heart disease.

Illumina Technology: RatRef-12 Expression BeadChip

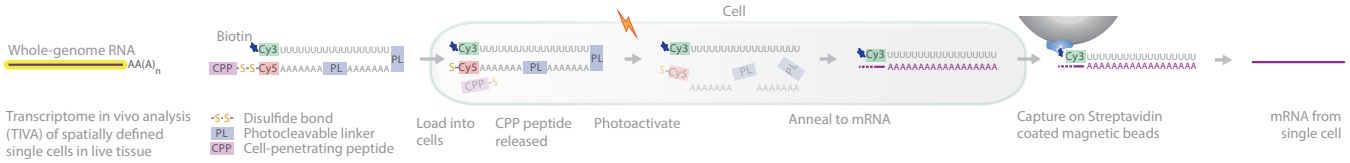
Lovatt D., Ruble B. K., Lee J., Dueck H., Kim T. K., et al. (2014) Transcriptome *in vivo* analysis (TIVA) of spatially defined single cells in live tissue. Nat Methods 11: 190-196

RNA-Seq methods rely on RNA extracted from cell mixtures and do not convey the individual variability in expression among cells of the same tissue. In this paper the authors present transcriptome *in vivo* analysis (TIVA), a technique that is applicable to single-cell studies. In combination with Illumina sequencing technology, the authors captured and analyzed the transcriptome variance across single neurons, both in culture and *in vivo*. This method is non-invasive and can be applied to intact tissues. It will enable detailed studies of cell heterogeneity in complex tissues, which have been intractable previously, and it opens up the possibility of *in vivo*, live functional mapping.

Illumina Technology: HiSeq 1000 for RNA-Seq

3. Mortazavi A., Williams B. A., McCue K., Schaeffer L. and Wold B. (2008) Mapping and quantifying mammalian transcriptomes by RNA-Seq. Nat Methods 5: 621-628
4. Marinov G. K., Williams B. A., McCue K., Schroth G. P., Gertz J., et al. (2014) From single-cell to cell-pool transcriptomes: stochasticity in gene expression and RNA splicing. Genome Res 24: 496-510
5. Ames E. G., Lawson M. J., Mackey A. J. and Holmes J. W. (2013) Sequencing of mRNA identifies re-expression of fetal splice variants in cardiac hypertrophy. J Mol Cell Cardiol 62: 99-107
6. Bazak L., Haviv A., Barak M., Jacob-Hirsch J., Deng P., et al. (2014) A-to-I RNA editing occurs at over a hundred million genomic sites, located in a majority of human genes. Genome Res 24: 365-376
7. Zhang S., Wang F., Wang H., Zhang F., Xu B., et al. (2014) Genome-wide identification of allele-specific effects on gene expression for single and multiple individuals. Gene 533: 366-373

TIVA



Transcriptome *in vivo* analysis (TIVA) of spatially defined single cells in live tissue.

Tong X., Zu Y., Li Z., Li W., Ying L., et al. (2014) Kctd10 regulates heart morphogenesis by repressing the transcriptional activity of Tbx5a in zebrafish. Nat Commun 5: 3153
The T-box transcription factor Tbx5 plays a dose-dependent role in the formation of cardiac chambers. The authors use a zebrafish model to show that Kctd10 binds directly to Tbx5 (Tbx5a in zebrafish) to repress its transcriptional activity. This observation implies that KCTD10 may be a new causative gene of congenital heart disease.

Illumina Technology: HiSeq 2000 with TruSeq total RNA preparation kit and 50 bp single-end reads

Jiang Z., Zhu L., Hu L., Slesnick T. C., Pautler R. G., et al. (2013) Zic3 is required in the extra-cardiac perinodal region of the lateral plate mesoderm for left-right patterning and heart development. Hum Mol Genet 22: 879-889
The authors use a mouse model with targeted deletion of Zic3, a member of the Zinc finger of the cerebellum (ZIC) protein family, to demonstrate an early role for Zic3 in gastrulation, central nervous system (CNS), cardiac, and left–right axial development. They used mouse expression arrays to show that Zic3 is required in epiblast for proper transcriptional control of embryonic heart development.

Illumina Technology: MouseWG-6 v2.0 Expression BeadChips

Ames E. G., Lawson M. J., Mackey A. J. and Holmes J. W. (2013) Sequencing of mRNA identifies re-expression of fetal splice variants in cardiac hypertrophy. J Mol Cell Cardiol 62: 99-107

Kim C., Wong J., Wen J., Wang S., Wang C., et al. (2013) Studying arrhythmogenic right ventricular dysplasia with patient-specific iPSCs. Nature 494: 105-110

MicroRNA

MicroRNAs (miRNAs) are highly cell-specific and could potentially improve the diagnostic potential of currently used biomarkers. Troponin assays offer high sensitivity as a marker of general myocardial damage, but more specific biomarkers may detect other cardiac diseases that accompany myocardial damage, such as Takotsubo cardiomyopathy or various forms of myocarditis.[8,9]

The highly specific cellular expression of miRNAs should be taken into account when cell populations change due to natural or pathological processes. For example, the observed increase in miR-150 in the plasma of patients undergoing cardiac remodeling after cardiac infarction[10] can also be explained by migration of inflammatory cells into the infarct zone.[11]

Reviews

Kent O. A., McCall M. N., Cornish T. C. and Halushka M. K. (2014) Lessons from miR-143/145: the importance of cell-type localization of miRNAs. Nucleic Acids Res 42: 7528-7538

Rayner K., Dimmeler S., Calin G. A., Thum T., Raizman J. E., et al. (2014) Novel biomarkers for acute myocardial infarction: is MicroRNA the new kid on the block? Clin Chem 60: 812-817

8. Rayner K., Dimmeler S., Calin G. A., Thum T., Raizman J. E., et al. (2014) Novel biomarkers for acute myocardial infarction: is MicroRNA the new kid on the block? Clin Chem 60: 812-817
9. Hu Y., Matkovich S. J., Hecker P. A., Zhang Y., Edwards J. R., et al. (2012) Epitranscriptional orchestration of genetic reprogramming is an emergent property of stress-regulated cardiac microRNAs. Proc Natl Acad Sci U S A 109: 19864-19869
10. Devaux Y., Vausort M., McCann G. P., Zangrando J., Kelly D., et al. (2013) MicroRNA-150: a novel marker of left ventricular remodeling after acute myocardial infarction. Circ Cardiovasc Genet 6: 290-298
11. Kent O. A., McCall M. N., Cornish T. C. and Halushka M. K. (2014) Lessons from miR-143/145: the importance of cell-type localization of miRNAs. Nucleic Acids Res 42: 7528-7538

References

Grunert M., Dorn C., Schueler M., Dunkel I., Schlesinger J., et al. (2014) Rare and private variations in neural crest, apoptosis and sarcomere genes define the polygenic background of isolated Tetralogy of Fallot. Hum Mol Genet 23: 3115-3128

The authors resequenced 167 miRNAs of known or potential interest for cardiac development and function. No relevant mutations were observed in mature miRNA sequences.

Illumina Technology: Genome Analyzer$_{IIx}$ with 26 bp paired-end reads for DNA targeted resequencing and mRNA sequencing

Long Non-coding RNAs

LncRNAs are defined as RNA transcripts that are longer than 200 bases and devoid of open reading frames.[12] At least two lncRNAs are known to be involved in mouse cardiac development[13]—braveheart (Bvht)[14] and Foxf1-adjacent non-coding developmental regulatory RNA (Fendrr).[15]

Reviews

Fatica A. and Bozzoni I. (2014) Long non-coding RNAs: new players in cell differentiation and development. Nat Rev Genet 15: 7-21

DNA-Protein Interactions

References

Stefanovic S., Barnett P., van Duijvenboden K., Weber D., Gessler M., et al. (2014) GATA-dependent regulatory switches establish atrioventricular canal specificity during heart development. Nat Commun 5: 3680

The embryonic vertebrate heart tube develops into an atrioventricular canal, which further develops into the ventricular chambers and valves. The authors used ChIP-Seq to determine the complex control of embryonic atrioventricular canal-specific gene activity to form these structures.

Illumina Technology: Genome Analyzer$_{IIx}$ for ChIP-Seq

Wolchinsky Z., Shivtiel S., Kouwenhoven E. N., Putin D., Sprecher E., et al. (2014) Angiomodulin is required for cardiogenesis of embryonic stem cells and is maintained by a feedback loop network of p63 and Activin-A. Stem Cell Res 12: 49-59

The authors used ChIP-Seq analysis to identify angiomodulin (AGM) as a cardiogenic secreted factor that is regulated by TAp63. They showed that AGM is necessary for cardiac commitment of embryonic stem cells (ESCs), and its regulation depends on the TAp63 isoform.

Illumina Technology: Genome Analyzer for ChIP-Seq

12. Rinn J. L. and Chang H. Y. (2012) Genome regulation by long noncoding RNAs. Annu Rev Biochem 81: 145-166
13. Fatica A. and Bozzoni I. (2014) Long non-coding RNAs: new players in cell differentiation and development. Nat Rev Genet 15: 7-21
14. Klattenhoff C. A., Scheuermann J. C., Surface L. E., Bradley R. K., Fields P. A., et al. (2013) Braveheart, a long noncoding RNA required for cardiovascular lineage commitment. Cell 152: 570-583
15. Grote P., Wittler L., Hendrix D., Koch F., Wahrisch S., et al. (2013) The tissue-specific lncRNA Fendrr is an essential regulator of heart and body wall development in the mouse. Dev Cell 24: 206-214

Stem Cells and Cardiomyocytes

Stem cells and cardiomyocytes are useful model systems to elucidate how cells respond to lineage specification, as well as pathologies and treatment. During division and differentiation, cells acquire somatic mutations, which may lead to a specific phenotype.[16] Cells not only differ at the genome level, but also differ at the epigenome level, which controls RNA expression and cellular phenotype. Measuring the RNA expression profiles of specific single-cell types at various stages of development has made it possible to reverse-engineer tissues.[17] RNA-Seq profiling of single cells during development can provide insights as to the changes in gene expression that dictate lineage specification.[18] The utilization of DNA and RNA sequencing in these model systems is enhancing research in development, tissue differentiation, diseases, and drug discovery.

16. Han A., Glanville J., Hansmann L. and Davis M. M. (2014) Linking T-cell receptor sequence to functional phenotype at the single-cell level. Nat Biotechnol 32: 684-692
17. Quo C. F., Kaddi C., Phan J. H., Zollanvari A., Xu M., et al. (2012) Reverse engineering biomolecular systems using -omic data: challenges, progress and opportunities. Brief Bioinform 13: 430-445
18. Treutlein B., Brownfield D. G., Wu A. R., Neff N. F., Mantalas G. L., et al. (2014) Reconstructing lineage hierarchies of the distal lung epithelium using single-cell RNA-seq. Nature

References

Marchant D. J., Bellac C. L., Moraes T. J., Wadsworth S. J., Dufour A., et al. (2014) A new transcriptional role for matrix metalloproteinase-12 in antiviral immunity. Nat Med 20: 493-502
The authors demonstrate that the nuclei of cardiomyocytes take up macrophage-secreted MMP-12 after viral infection.

Illumina Technology: Genome Analyzer for ChIP-Seq

Stefanovic S., Barnett P., van Duijvenboden K., Weber D., Gessler M., et al. (2014) GATA-dependent regulatory switches establish atrioventricular canal specificity during heart development. Nat Commun 5: 3680
The embryonic vertebrate heart tube develops into an atrioventricular canal, which further develops into the ventricular chambers and valves. The authors used ChIP-Seq to determine the complex control of embryonic atrioventricular canal-specific gene activity to form these structures.

Illumina Technology: Genome Analyzer$_{IIx}$ for ChIP-Seq

Tse H. F., Ho J. C., Choi S. W., Lee Y. K., Butler A. W., et al. (2013) Patient-specific induced-pluripotent stem cells-derived cardiomyocytes recapitulate the pathogenic phenotypes of dilated cardiomyopathy due to a novel DES mutation identified by whole exome sequencing. Hum Mol Genet 22: 1395-1403
This paper is a case study of a patient with documented dilated cardiomyopathy (DCM) and a familial history of sudden heart failure. To determine the potential underlying genetic variation causing DCM, the authors performed whole-exome sequencing using the Illumina Genome Analyzer. They found a novel heterozygous mutation on exon 4 of the desmin (DES) gene. To confirm the finding, the authors created induced pluripotent stem (iPS) cell cardiomyocytes with the DES mutation and showed that the cardiomyocytes exhibited functional abnormalities *in vitro*.

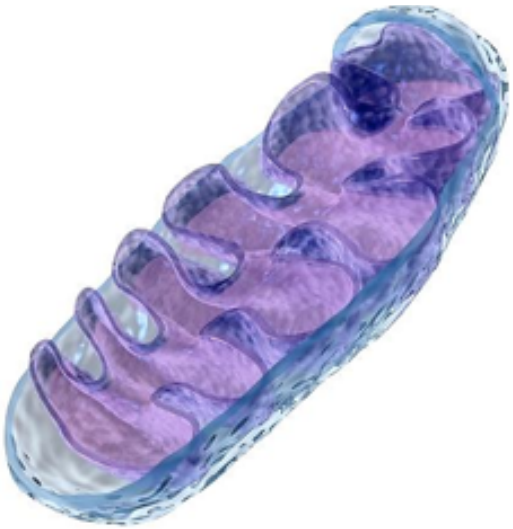
Illumina Technology: Genome Analyzer$_{IIx}$ with 76 bp paired-end reads for exon sequencing

Wang Q., Chen J., Ko C. I., Fan Y., Carreira V., et al. (2013) Disruption of aryl hydrocarbon receptor homeostatic levels during embryonic stem cell differentiation alters expression of homeobox transcription factors that control cardiomyogenesis. Environ Health Perspect 121: 1334-1343

Kim C., Wong J., Wen J., Wang S., Wang C., et al. (2013) Studying arrhythmogenic right ventricular dysplasia with patient-specific iPSCs. Nature 494: 105-110

Mitochondria

The human mitochondrial genome encodes RNA components of its own translational machinery to produce the 13 mitochondrial-encoded subunits of the respiratory chain. Nuclear-encoded gene products are essential for all processes within the organelle, including RNA processing.



Mitochondrion

Reviews

Rabbani B., Tekin M. and Mahdieh N. (2014) The promise of whole-exome sequencing in medical genetics. J Hum Genet 59: 5-15

References

Kivela R., Bry M., Robciuc M. R., Rasanen M., Taavitsainen M., et al. (2014) VEGF-B-induced vascular growth leads to metabolic reprogramming and ischemia resistance in the heart. EMBO Mol Med 6: 307-321

The authors use rat expression arrays to demonstrate that vascular endothelial growth factor-β (VEGF-β) can increase the coronary vasculature and reprogram myocardial metabolism to improve cardiac function in ischemic heart disease. Interestingly, VEGF-β and mitochondrial gene expression are coordinately regulated.

Illumina Technology: RatRef-12 Expression BeadChip

Seppala I., Kleber M. E., Lyytikainen L. P., Hernesniemi J. A., Makela K. M., et al. (2014) Genome-wide association study on dimethylarginines reveals novel AGXT2 variants associated with heart rate variability but not with overall mortality. Eur Heart J 35: 524-531

Heart diseases are usually complex, with multiple factors influencing the outcome. This study examines the genetic variants that influence circulating asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA). It also investigates their association with cardiovascular mortality. The authors performed a meta-analysis of ~5,000 individuals genotyped in previous genome-wide association studies (GWAS). They evaluated the correlation with ADMA, SDMA levels, heart rate variability, and sudden cardiac death. The authors identified two single-nucleotide variants (SNVs) in coding regions in the AGXT2 gene associated with circulating SDMA levels, suggesting a regulatory role for AGXT2. They also observed a genome-wide significant association for SDMA with SLC25A45, a mitochondrial inner-membrane transporter protein that has the same intracellular localization than AGXT2.

Illumina Technology: 670k BeadChip

Haack T. B., Kopajtich R., Freisinger P., Wieland T., Rorbach J., et al. (2013) ELAC2 mutations cause a mitochondrial RNA processing defect associated with hypertrophic cardiomyopathy. Am J Hum Genet 93: 211-223

The authors report mutations in the endoribonuclease ELAC2 gene in five individuals with infantile hypertrophic cardiomyopathy and complex I deficiency. ELAC2 encodes a long RNase Z, which is restricted to eukaryotes. Alternative translation of ELAC2 generates two products, of which only the longer form localizes to mitochondria. Mitochondrial RNA (mtRNA) precursors accumulated in affected individuals muscle and fibroblasts. The results were confirmed in mutant cell lines where complementation restored RNA processing.

Illumina Technology: HiSeq 2000 for exome sequencing and RNA-Seq of the mitochondrial transcriptome

Chen Y., Sparks M., Bhandari P., Matkovich S. J. and Dorn G. W., 2nd (2013) Mitochondrial Genome Linearization Is a Causative Factor for Cardiomyopathy in Mice and Drosophila. Antioxid Redox Signal.

CARDIAC DISEASES

Mutation detection through exome sequencing or targeted sequencing allows simultaneous analysis of selected regions of the genome. This study examined whether the sensitivity and specificity of targeted NGS is equal to that of Sanger sequencing (SS). Using the Illumina MiSeq sequencer, the authors constructed a targeted enrichment kit that included 48 genes associated with hereditary cardiomyopathies. The authors demonstrated a reproducibility of near 100% with excellent sensitivity and specificity compared to SS, demonstrating that targeted NGS of a disease-specific subset of genes can be readily implemented as a stand-alone diagnostic test.[19]

19. Sikkema-Raddatz B., Johansson L. F., de Boer E. N., Almomani R., Boven L. G., et al. (2013) Targeted next-generation sequencing can replace Sanger sequencing in clinical diagnostics. Hum Mutat 34: 1035-1042
20. Rehm H. L. (2013) Disease-targeted sequencing: a cornerstone in the clinic. Nat Rev Genet 14: 295-300

Clinically available disease-targeted tests[20]

Cardiac Disease Type	Genes
Cardiomyopathies	50-70
Arrhythmias (e.g., long QT syndrome)	10-30
Aortopathies (e.g., Marfan's syndrome)	10

Reviews

Mestroni L., Begay R. L., Graw S. L. and Taylor M. R. (2014) Pharmacogenetics of heart failure. Curr Opin Cardiol 29: 227-234

This review describes the role that polymorphic variants play in drug response in cardiovascular disease. A future challenge is the development of strategies to use this information in conjunction with a patient's genetic profile to personalize and optimize cardiovascular therapy.

References

Atanur S. S., Diaz A. G., Maratou K., Sarkis A., Rotival M., et al. (2013) Genome sequencing reveals loci under artificial selection that underlie disease phenotypes in the laboratory rat. Cell 154: 691-703

The authors sequenced the genomes of 25 new rat strains, with a focus on strains with well-characterized cardiovascular and metabolic phenotypes. Based on genome comparisons, genes and pathways involved in cation transport, angiotensin production, and regulators of oxidative stress are implicated in the development of cardiovascular disease.

Illumina Technology: HiSeq 2000

Sequencing the genomes of 25 new rat strains showed that pathways involved in cation transport, angiotensin production, and regulators of oxidative stress are implicated in the development of cardiovascular disease.

Tetralogy of Fallot

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease. An increased risk of recurrence in siblings and familial cases demonstrates that this disease has a genetic basis.

References

Grunert M., Dorn C., Schueler M., Dunkel I., Schlesinger J., et al. (2014) Rare and private variations in neural crest, apoptosis and sarcomere genes define the polygenic background of isolated Tetralogy of Fallot. Hum Mol Genet 23: 3115-3128

The authors show that a combination of deleterious private and rare mutations cause isolated TOF. The affected genes are essential for apoptosis and cell growth, the assembly of the sarcomere and neural crest, the secondary heart field, and the cellular basis of the right ventricle and its outflow tract. In cases with a mutually affected TOF gene, these genes share significant disturbances in expression.

Illumina Technology: Genome Analyzer$_{IIx}$ with 26 bp paired-end reads for DNA targeted resequencing and mRNA sequencing

Cordell H. J., Topf A., Mamasoula C., Postma A. V., Bentham J., et al. (2013) Genome-wide association study identifies loci on 12q24 and 13q32 associated with tetralogy of Fallot. Hum Mol Genet 22: 1473-1481

Cardiomyopathies

In cardiomyopathy, the heart muscle becomes enlarged, thickened, or rigid. In rare cases, the muscle tissue in the heart is replaced with scar tissue.[21,22]

References

Chauveau C., Bonnemann C. G., Julien C., Kho A. L., Marks H., et al. (2014) Recessive TTN truncating mutations define novel forms of core myopathy with heart disease. Hum Mol Genet 23: 980-991

Myopathies are a heterogeneous group of conditions affecting muscle function. Core myopathies (CM) remain genetically unexplained in many cases. This study analyzed a series of 23 families with congenital CM and primary heart disease using whole-exome sequencing, transcriptome sequencing, and targeted sequencing of the titin (TTN) gene, which codes for a giant protein of striated muscle. The authors identified seven novel homozygous or compound heterozygous TTN mutations associated with both known and novel titinopathies, including cardiac septal defects, implicating titin kinase in cardiac morphogenesis.

Illumina Technology: HiSeq 2000 with 100 bp paired-end reads

21. Rapezzi C., Arbustini E., Caforio A. L., Charron P., Gimeno-Blanes J., et al. (2013) Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J 34: 1448-1458
22. http://www.nhlbi.nih.gov/health/health-topics/topics/cm/

Ellims A. H., Iles L. M., Ling L. H., Chong B., Macciocca I., et al. (2014) A comprehensive evaluation of myocardial fibrosis in hypertrophic cardiomyopathy with cardiac magnetic resonance imaging: linking genotype with fibrotic phenotype. Eur Heart J Cardiovasc Imaging

Hypertrophic cardiomyopathy (HCM) has diverse clinical manifestations, but the underlying mechanism for this diversity is unknown. This study examined the association between genotype and phenotype in HCM by applying cardiac magnetic resonance (CMR) imaging for phenotyping and whole-exome sequencing for genotyping. Although each assay was highly sensitive and specific, the study did not comprise enough statistical power to identify significant associations between genotype and phenotype.

Illumina Technology: HiSeq targeted resequencing

Hicks D., Farsani G. T., Laval S., Collins J., Sarkozy A., et al. (2014) Mutations in the collagen XII gene define a new form of extracellular matrix-related myopathy. Hum Mol Genet 23: 2353-2363

Bethlem myopathy (BM) [MIM 158810] is a slow, progressive muscle disease characterized by contractures and proximal weakness. It is frequently caused by mutations in one of the collagen VI genes (COL6A1, COL6A2, and COL6A3). The authors first sequenced 12 candidate genes based on their function and then performed whole-exome sequencing. They identified mutations in the COL12A1 gene, a member of the fibril-associated collagens with interrupted triple helices (FACIT), in five individuals from two families.

Illumina Technology: Genome Analyzer$_{IIx}$ and HiSeq 2000

Swaggart K. A., Demonbreun A. R., Vo A. H., Swanson K. E., Kim E. Y., et al. (2014) Annexin A6 modifies muscular dystrophy by mediating sarcolemmal repair. Proc Natl Acad Sci U S A 111: 6004-6009

Many monogenic disorders, including the muscular dystrophies, display phenotypic variability despite the same disease-causing mutation. This study examined the genetic modifiers of muscular dystrophy (MD) and associated cardiomyopathy in a mouse model of MD. The authors used Illumina genotyping arrays along with whole-genome and transcriptome sequencing on Illumina HiSeq2000 to characterize the associations between genetic variants and the MD phenotype. The analysis identified a splice variant in the annexin A6 gene, ANXA6. The truncated A6 protein was found to inhibit membrane repair indicating ANXA6 as a modifier of muscle repair in MD.

Illumina Technology: HiSeq 2000 with 100 bp paired-end reads for DNA and RNA sequencing; GoldenGate custom panel and Infinium Mouse Universal Genotyping Array

To identify genetic modifiers of muscular dystrophy and its associated cardiomyopathy, the authors used quantitative trait locus mapping and whole-genome sequencing in a mouse model.

van Spaendonck-Zwarts K. Y., Posafalvi A., van den Berg M. P., Hilfiker-Kleiner D., Bollen I. A., et al. (2014) Titin gene mutations are common in families with both peripartum cardiomyopathy and dilated cardiomyopathy. Eur Heart J

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy with heart failure toward the end of pregnancy or in the first months following delivery.[23] The authors sequenced 48 genes involved in inherited cardiomyopathies, in 18 families with PPCM and familial dilated cardiomyopathy (DCM). They identified three pathogenic mutations in the TTN gene and one in the BAG3 gene. In six other families, they identified six potentially pathogenic variants of unknown clinical significance: four in TTN, one in TNNC1, and one in MYH7.

Illumina Technology: MiSeq with 151 bp paired-end reads of targeted DNA

Ames E. G., Lawson M. J., Mackey A. J. and Holmes J. W. (2013) Sequencing of mRNA identifies re-expression of fetal splice variants in cardiac hypertrophy. J Mol Cell Cardiol 62: 99-107

The authors examined mRNA isoforms shared between hypertrophy and fetal heart development. The genes were significantly enriched for genes involved in cytoskeletal organization, RNA processing, developmental processes, and metabolic enzymes. Their data strongly support the concept that mRNA splicing patterns normally associated with heart development recur as part of the hypertrophic response to pressure overload.

Illumina Technology: Genome Analyzer$_{IIx}$ for RNA-Seq with 42 or 63 bp paired-end reads

Lopes L. R., Zekavati A., Syrris P., Hubank M., Giambartolomei C., et al. (2013) Genetic complexity in hypertrophic cardiomyopathy revealed by high-throughput sequencing. J Med Genet 50: 228-239

The authors analyzed coding, intronic, and regulatory regions of 41 cardiovascular genes. They detected an additional 94 candidate variants (73 novel) in desmosomal and ion-channel genes in 96 patients (43%).

Illumina Technology: Genome Analyzer$_{IIx}$

Sikkema-Raddatz B., Johansson L. F., de Boer E. N., Almomani R., Boven L. G., et al. (2013) Targeted next-generation sequencing can replace Sanger sequencing in clinical diagnostics. Hum Mutat 34: 1035-1042

Mutation detection through exome sequencing or targeted sequencing allows simultaneous analysis of the selected regions of the genome. This study examined whether the sensitivity and specificity of targeted NGS is equal to those of Sanger sequencing. Using the Illumina MiSeq sequencer, the authors constructed a targeted enrichment kit that included 48 genes associated with hereditary cardiomyopathies. The authors demonstrated a reproducibility of near 100% with excellent sensitivity and specificity compared to Sanger sequencing. This demonstrates that targeted NGS of a disease-specific subset of genes can be implemented as a stand-alone diagnostic test.

Illumina Technology: MiSeq

Arndt A. K., Schafer S., Drenckhahn J. D., Sabeh M. K., Plovie E. R., et al. (2013) Fine mapping of the 1p36 deletion syndrome identifies mutation of PRDM16 as a cause of cardiomyopathy. Am J Hum Genet 93: 67-77

Chen Y., Sparks M., Bhandari P., Matkovich S. J. and Dorn G. W., 2nd (2013) Mitochondrial Genome Linearization Is a Causative Factor for Cardiomyopathy in Mice and Drosophila. Antioxid Redox Signal

Haack T. B., Kopajtich R., Freisinger P., Wieland T., Rorbach J., et al. (2013) ELAC2 mutations cause a mitochondrial RNA processing defect associated with hypertrophic cardiomyopathy. Am J Hum Genet 93: 211-223

Roncarati R., Viviani Anselmi C., Krawitz P., Lattanzi G., von Kodolitsch Y., et al. (2013) Doubly heterozygous LMNA and TTN mutations revealed by exome sequencing in a severe form of dilated cardiomyopathy. Eur J Hum Genet 21: 1105-1111

23. Sliwa K., Hilfiker-Kleiner D., Petrie M. C., Mebazaa A., Pieske B., et al. (2010) Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. Eur J Heart Fail 12: 767-778

Long QT Syndrome (LQTS)

The QT interval is an electrocardiographic measure reflecting myocardial repolarization. It is a heritable trait, and a risk factor for ventricular arrhythmias and sudden cardiac death.

References

Arking D. E., Pulit S. L., Crotti L., van der Harst P., Munroe P. B., et al. (2014) Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization. Nat Genet

The QT interval, an electrocardiographic measure reflecting myocardial repolarization, is a heritable trait. In order to investigate the genomic association of the potentially lethal Mendelian long-QT syndrome (LQTS) this GWAS measured the QT interval and performed array-based genotyping of close to 100,000 individuals. The authors identified 35 common variant loci, collectively explaining up to 10% of QT-interval variation. Gene expression and protein-protein interaction were used to characterize the loci.

Illumina Technology: Human Cardio-MetaboChip and ExomeChip

Lundby A., Rossin E. J., Steffensen A. B., Acha M. R., Newton-Cheh C., et al. (2014) Annotation of loci from genome-wide association studies using tissue-specific quantitative interaction proteomics. Nat Methods

Lieve K. V., Williams L., Daly A., Richard G., Bale S., et al. (2013) Results of genetic testing in 855 consecutive unrelated patients referred for long QT syndrome in a clinical laboratory. Genet Test Mol Biomarkers 17: 553-561

GENETIC ANALYSIS

Cardiac genetics have yielded an increasingly nuanced understanding of the pathophysiological basis of inherited cardiac diseases. However, the large number of environmental factors, variable penetrance, and the difficulty of assessing the functional and clinical effects of novel mutations remains an ongoing challenge.[24]

24. Wilde A. A. and Behr E. R. (2013) Genetic testing for inherited cardiac disease. Nat Rev Cardiol 10: 571-583

The large number of environmental factors that contribute to cardiac disease.

Reviews

Hall S. S. (2013) Genetics: a gene of rare effect. Nature 496: 152-155

Wilde A. A. and Behr E. R. (2013) Genetic testing for inherited cardiac disease. Nat Rev Cardiol 10: 571-583

Genome-Wide Association Studies

GWAS are designed to detect associations between SNVs in common, complex diseases such as heart disease, diabetes, autoimmune diseases, and psychiatric disorders.[25] GWAS have led to many scientific and biological discoveries but have failed to explain the bulk of heritability.[26,27] The sequencing of entire genomes in large cohorts at affordable prices is likely to generate additional genes, pathways, and biological insights, as well as the potential to identify causal mutations.[28,29]

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Holmen O. L., Zhang H., Zhou W., Schmidt E., Hovelson D. H., et al. (2014) No large-effect low-frequency coding variation found for myocardial infarction. Hum Mol Genet

Coronary artery disease (CAD) and myocardial infarction (MI) are associated with a number of common variants in the genome. This study set out to explore the association of previously untested low-frequency variants with CAD and MI. Using Illumina HumanExome BeadChip and whole-exome sequencing on Illumina HiSeq, the authors genotyped 2,906 MI cases and 6,738 controls. They produced successful genotyping for 66.2% of Norwegian loss-of-function or missense variants with low frequency (< 1%). However, no novel genes or novel single low-frequency variants reached significant association for MI.

Illumina Technology: HiSeq DNA sequencing of 75 cases and 75 controls

Seppala I., Kleber M. E., Lyytikainen L. P., Hernesniemi J. A., Makela K. M., et al. (2014) Genome-wide association study on dimethylarginines reveals novel AGXT2 variants associated with heart rate variability but not with overall mortality. Eur Heart J 35: 524-531

Heart diseases are usually complex, with multiple factors influencing the outcome. This study set out to examine the genetic variants influencing circulating asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA), and investigate their association with cardiovascular mortality. The authors performed a meta-analysis of ~5,000 individuals genotyped in previous GWAS. They evaluated the correlation with ADMA, SDMA levels, heart rate variability, and sudden cardiac death. The authors identified two SNVs in coding regions in the AGXT2 gene associated with circulating SDMA levels, suggesting a regulatory role for AGXT2.

Illumina Technology: 670k BeadChip

Swaggart K. A., Demonbreun A. R., Vo A. H., Swanson K. E., Kim E. Y., et al. (2014) Annexin A6 modifies muscular dystrophy by mediating sarcolemmal repair. Proc Natl Acad Sci U S A 111: 6004-6009

Many monogenic disorders, including the muscular dystrophies, display phenotypic variability despite the same disease-causing mutation. This study examined the genetic modifiers of muscular dystrophy (MD) and associated cardiomyopathy in a mouse model of MD. The authors used Illumina genotyping arrays along with whole-genome and transcriptome sequencing on Illumina HiSeq2000 to characterize the associations between genetic variants and the MD phenotype. The analysis identified a splice variant in the annexin A6 gene, ANXA6. The truncated A6 protein inhibited membrane repair indicating annexin A6 as a modifier of muscle repair in MD.

Illumina Technology: HiSeq 2000 with 100 bp paired-end reads for DNA and RNA sequencing; GoldenGate custom panel and Infinium Mouse Universal Genotyping Array

Versmissen J., Oosterveer D. M., Yazdanpanah M., Dehghan A., Holm H., et al. (2014) Identifying genetic risk variants for coronary heart disease in familial hypercholesterolemia: an extreme genetics approach. Eur J Hum Genet

Mutations in the low-density lipoprotein receptor (LDLR) gene cause familial hypercholesterolemia (FH), a disorder characterized by coronary heart disease (CHD) at young age. From 17,000 FH patients from the Netherlands, whose functional LDLR mutation was unequivocally established, the authors selected cases and controls with an extreme contrast in CHD risk. The GWAS was performed on 249 very young FH patients with CHD, and 217 older (above 65 years for males and 70 years of age for females) FH control patients without CHD. Even applying an “extreme genetics” approach, the authors did not identify new genetic risk variants.

Illumina Technology: HumanHap550K chip

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26. McClellan J. and King M. C. (2010) Genetic heterogeneity in human disease. Cell 141: 210-217
27. Manolio T. A., Collins F. S., Cox N. J., Goldstein D. B., Hindorff L. A., et al. (2009) Finding the missing heritability of complex diseases. Nature 461: 747-753
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Bezzina C. R., Barc J., Mizusawa Y., Remme C. A., Gourraud J. B., et al. (2013) Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. Nat Genet 45: 1044-1049

Cordell H. J., Bentham J., Topf A., Zelenika D., Heath S., et al. (2013) Genome-wide association study of multiple congenital heart disease phenotypes identifies a susceptibility locus for atrial septal defect at chromosome 4p16. Nat Genet 45: 822-824

den Hoed M., Eijgelsheim M., Esko T., Brundel B. J., Peal D. S., et al. (2013) Identification of heart rate-associated loci and their effects on cardiac conduction and rhythm disorders. Nat Genet 45: 621-631

Hu Z., Shi Y., Mo X., Xu J., Zhao B., et al. (2013) A genome-wide association study identifies two risk loci for congenital heart malformations in Han Chinese populations. Nat Genet 45: 818-821

Leonard D., Svenungsson E., Sandling J. K., Berggren O., Jonsen A., et al. (2013) Coronary heart disease in systemic lupus erythematosus is associated with interferon regulatory factor-8 gene variants. Circ Cardiovasc Genet 6: 255-263

Sailani M. R., Makrythanasis P., Valsesia A., Santoni F. A., Deutsch S., et al. (2013) The complex SNP and CNV genetic architecture of the increased risk of congenital heart defects in Down syndrome. Genome Res 23: 1410-1421

Zaidi S., Choi M., Wakimoto H., Ma L., Jiang J., et al. (2013) De novo mutations in histone-modifying genes in congenital heart disease. Nature 498: 220-223

Rare Variants

Large, multigenerational families with congenital heart defects are uncommon, but analyses of these families have led to the identification of a number of variants for congenital heart defects. However, the variants discovered to date explain only a small proportion of cases of congenital heart defects, due to the high level of genetic heterogeneity in the disease. NGS provides an opportunity to identify more genes in the future, with the analysis of multiple individuals in small families and improved algorithms to distinguish between driver and passenger mutations.[30]

30. Arrington C. B., Bleyl S. B., Brunelli L. and Bowles N. E. (2013) Family-based studies to identify genetic variants that cause congenital heart defects. Future Cardiol 9: 507-518

Large, multigenerational families with congenital heart defects are relatively rare, but analyses of these families have led to the identification of a number of variants for congenital heart defects.

Reviews

Arrington C. B., Bleyl S. B., Brunelli L. and Bowles N. E. (2013) Family-based studies to identify genetic variants that cause congenital heart defects. Future Cardiol 9: 507-518

Genes associated with nonsyndromic forms of congenital heart defects.[31]

Congenital Heart Defect	Genes
Tetralogy of Fallot	NKX2–5, NOTCH1, GATA4, ZFMP2, TBX1, GATA6, JAG1, LPP
Ventricular septal defect	GATA4, NKX2–5, TBX20
Atrial septal defect	GATA4, MYH6, TBX20, NKX2–5
Truncus arteriosus	GATA6
Transposition of the great arteries	CFC1, MED13L (THRAP2), GDF1
Hypoplastic left heart syndrome	NOTCH1
Bicuspid aortic valve	NOTCH1
Aortic stenosis	NOTCH1
Atrioventricular septal defect	GATA4, ACVR1
Double outlet right ventricle	CFC1, GDF1

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Izumi R., Niihori T., Aoki Y., Suzuki N., Kato M., et al. (2013) Exome sequencing identifies a novel TTN mutation in a family with hereditary myopathy with early respiratory failure. J Hum Genet 58: 259-266

Myofibrillar myopathy (MFM) is a group of chronic muscular disorders that show the focal dissolution of myofibrils and accumulation of degradation products. The major genetic basis of MFMs is unknown. The authors performed linkage analysis and exome sequencing on these patients and identified a novel c.90263G4T mutation in the TTN gene (NM_001256850).

Illumina Technology: HiSeq 2000 for exome sequencing

Tegtmeyer L. C., Rust S., van Scherpenzeel M., Ng B. G., Losfeld M. E., et al. (2014) Multiple phenotypes in phosphoglucomutase 1 deficiency. N Engl J Med 370: 533-542
Protein glycosylation is an essential process in transforming proteins to their fully functional forms. This study examined a novel recessive glycosylation disorder with a range of clinical manifestations. The authors performed homozygosity mapping by genotyping two affected siblings using Illumina Human1M-Duo BeadChips. Exome sequencing of the identified regions revealed that both siblings harbor mutations in the gene for phosphoglucomutase 1 (PGM1). Genetic testing of an additional 17 patients and found 21 different mutations influencing PGM1 activity.

Illumina Technology: Human1M-Duo BeadChips

Carroll C. J., Isohanni P., Poyhonen R., Euro L., Richter U., et al. (2013) Whole-exome sequencing identifies a mutation in the mitochondrial ribosome protein MRPL44 to underlie mitochondrial infantile cardiomyopathy. J Med Genet 50: 151-159

Li Mura I. E., Bauce B., Nava A., Fanciulli M., Vazza G., et al. (2013) Identification of a PKP2 gene deletion in a family with arrhythmogenic right ventricular cardiomyopathy. Eur J Hum Genet 21: 1226-1231

Epigenetics

Epigenetics refers to changes in gene expression that are not explained by changes in DNA sequence. These changes are usually controlled through DNA methylation, histone modifications, and RNA iwnterference. Epigenetics has gained substantial scientific interest in recent years, and initial studies show that epigenetics may play an important role in cardiovascular disease.[32]

Reviews

Rivera C. M. and Ren B. (2013) Mapping human epigenomes. Cell 155: 39-55

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32. Zawada A. M., Rogacev K. S. and Heine G. H. (2013) Clinical relevance of epigenetic dysregulation in chronic kidney disease-associated cardiovascular disease. Nephrol Dial Transplant 28: 1663-1671

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Pub. No. 1070-2014-003 Current as of 01 August 2014

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