Personalized Medicine in the Genomics Era: highlights from an international symposium on childhood heart disease

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Personalized Medicine in the Genomics Era: an international symposium on childhood heart disease

Toronto, Ontario, Canada, 17–18 October 2011

As the population of childhood heart disease survivors grows, a better understanding of the genetic underpinnings of heart disease is needed to improve diagnostics, therapeutics and outcomes. The Trans-Atlantic Research Network, GenomeHeart and The SickKids Heart Centre Biobank hosted an international symposium on childhood heart disease titled 'Personalized Medicine in the Genomics Era'. Experts in cardiology, developmental biology, genomics, pharmacology, bioinformatics, stem cell biology, ethics and biobanking shared their knowledge and expertise. The 2-day symposium hosted participants from North America, Europe and Asia including scientists, physicians, nurses, trainees and representatives from industry partners, federal and provincial funding agencies, and patient and community groups. The symposium focused on international research partnerships and application of current state-of-the-art in genomics and stem cell medicine towards personalized healthcare for childhood onset heart disease.

Genomics of complex disorders: new approaches

Advances in the diagnosis and management of childhood heart disease have dramatically improved survival in the current era. Nevertheless, significant gaps in knowledge about the etiology of congenital heart disease (CHD) persist. In his opening address, Matthew Hurles (Wellcome Trust Sanger Institute, London, UK) highlighted the quantum leaps in our understanding of the genomic architecture of humans through high-resolution genomic sequencing, which has resulted in the successful annotation of 99% of variation in the human genome [1]. This is yielding new knowledge about the genetic etiology of human disease. Large cohort studies have identified common variants associated with tetralogy of Fallot as reported by Bernard Keavney (Newcastle University, Newcastle, UK), as well as rare copy number variants (CNVs) as reported by Steven Greenway (Hospital for Sick Children, Toronto, Canada) [2]. Common variation, however, only accounts for a small fraction of CHD heritability. Next-generation sequencing approaches are beginning to identify novel rare variants associated with complex disorders [3,4]. An example is a novel deletion in *NRXN3* and a novel 64-kb deletion in *SHANK1*, which is associated with autism spectrum disorder as reported by Stephen Scherer (University of Toronto, Toronto, Canada) [5]. The development of new sequencing technologies has been paralleled by the emergence of high-throughput bioinformatic approaches to analyze large volumes of genomic data. New bioinformatic approaches were discussed by Michael Brudno (University of Toronto, Toronto, Canada) who described 'Savant Genome browser' [6] for desktop visualization of genomic data and shared glimpses of a new software platform 'MedSavant' for accelerating the identification of disease-causing genetic variants found in population sequencing studies. Derek Chiang (University of North Carolina, NC, USA) described programming tools that characterize transcript diversity with RNA sequencing, and methods and algorithms to identify novel splicing events [7]. The ability to functionally validate novel variants will be

Keywords
■ biobanking ■ congenital heart disease ■ genomics ■ pediatrics ■ personalized medicine ■ stem cell

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a key determinant of the success of large-scale sequencing efforts. While validation methods have traditionally used animal models, human pluripotent stem cell-derived cardiac lineages provide an attractive alternative as human relevant models without the confounding effect of species differences. The next decade is, therefore, poised to generate significant new knowledge about the genetic etiology of complex disorders.

Designing genomic studies in CHD populations

Genomics studies in complex disorders like CHD have to overcome the challenges of heterogeneity of anatomic diagnoses and outcomes. The large sample sizes needed to overcome this challenge requires harmonization of cardiac and extracardiac phenotyping, in addition to genotyping and bioinformatics platforms. At a round table discussion, panelists emphasized the need to standardize imaging in order to permit uniformity in diagnosis and the inclusion of functional characterization to identify genetic associations with outcomes across cohorts. As the pace of genomic discovery increases, greater emphasis on translation of new findings to the bedside is needed. This will require a serious investment by federal agencies to ensure that children with heart disease are able to reap the full benefits of genomic discovery. Klaus Fiebig (Ontario Genomics Institute, Ontario, Canada) identified exciting funding opportunities for personalized medicine that are soon to be launched in Canada, with an emphasis on translation of genomics towards personalized healthcare.

Cardiac pharmacogenomics: personalized approaches

Besides diagnostics, the application of genomics to improve the safety and efficacy of drugs remains central to the practice of personalized medicine. Even as a growing number of drugs are beginning to include pharmacogenetic labeling [8], these studies are almost exclusively derived from adult populations. The impact of pharmacogenetic variants may differ considerably between children and adults due to the developmental immaturity of drug-metabolizing enzymes in children as was discussed by Michael Phillips (Université de Montréal, Montréal, Canada) and Shinya Ito (University of Toronto) [9]. Seema Mital (University of Toronto) discussed the importance and strategies for designing pediatric pharmacogenetic trials that incorporate age-related variations in the genetics of drug-metabolizing enzymes [10,11]. Niteesh Choudhry (Harvard University, MA, USA) presented cost–effectiveness assessment strategies for the incorporation of genetic information and companion diagnostics into medical therapies [12]. Overall, the session drew attention to the need for pediatric pharmacogenetic studies and a requirement for pharmacokinetic, pharmacogenetic and cost–effectiveness data as part of pediatric drug trials.

The ethical, legal & social challenges

An increase in population-based genomics projects brings with it a need to ensure responsible and ethical participation of research subjects. Bartha Knoppers (McGill University, Montréal, Quebec, Canada) discussed ethical, legal and social issues surrounding genomics and stem cell biobanks, and strategies for ethically responsible conduct of biobank-based research. Tanya Daljevic conducted a workshop on biobanking (Hospital for Sick Children) and provided guidelines for the nature of informed consents, policies on reconsenting minors and strategies for community engagement, maintaining quality and data integrity, and financial sustainability of biobanks. This session highlighted the need to standardize the ethical and regulatory framework surrounding genomics research, particularly in children.

Cardiac disease modeling using personalized stem cells

Human-induced pluripotent stem (iPS) cells can efficiently generate a renewable resource of differentiated cardiac cells that can be used to model disease *in vitro*. In a captivating keynote presentation, Joseph Wu (Stanford University, CA, USA) identified the clinical hurdles pluripotent stem cell therapy must overcome to be compatible with successful, safe transplantation into patients [13]. Although defined clear safety and efficacy obstacles need to be addressed, he stressed that patient-specific iPS cells continue to provide a valuable platform to perform *in vitro* clinical trials. Modeling cardiac disease *in vitro* enables screening of drug candidates or small molecules at the cellular level. To this end, he described their recent efforts using pharmacological arrays of iPS cell-derived beating cardiac cells from dilated cardiomyopathy patients with *TNNT2* mutations. James Ellis (University of Toronto) discussed the potential for modeling neuronal and cardiac diseases including Rett syndrome and Williams–Beuren syndrome using patient-specific iPS cells [14]. Peter Gruber (University of Utah, UT, USA) addressed the longstanding problem in predicting

patient responses to intervention in CHD and individualizing interventions based on prediction of response. Gruber provided evidence that iPS cells generated from amniocentesis-derived fetal fibroblasts provide an avenue for generating patient-derived cells to test for drug responses or hypoxia tolerance. This approach can recapitulate developmental processes that lead to childhood heart disease, and ultimately iPS cells derived from fetal fibroblasts may allow production of functional autologous cardiac tissue for repair after birth of the same child. Proteomics approaches to identify cardiac disease biomarkers using human cardiac stem cells were presented by Anthony Gramolini (University of Toronto).

Generating functional cardiac tissue reproducibly & efficiently

In describing improved methods for optimizing cardiovascular differentiation from human pluripotent stem cells, Nicole Dubois from Gordon Keller's group (McEwen Center for Regenerative Medicine, Toronto, Canada) took the audience back to early embryonic development as she addressed the issue of generating cardiac tissue. By identifying the cell surface marker, SIRPA, as a means to enrich for cardiomyocyte production and by taking lessons from the signaling gradients that govern early embryonic development, they have made remarkable progress in differentiating stem cells in a controllable, reproducible and efficient way [15]. Concerns about the genomic instability of iPS cells were discussed by Samer Hussein who described CNV alterations that accompany reprogramming [16]. Systems biology was discussed by Bill Stanford (Ottawa Hospital Research Institute, Ottawa, Canada) who introduced the concept of integrating systems genetics approaches to dissect the disease process using patient iPS cells [17]. Michael Tyers (Institute for Research in Immunology and Cancer, Université of Montréal) stressed the need for systematic biocuration, highlighting that better computation of biological information in the form of networks rather than pathways, coupled to novel chemistries and ultra-high-throughput screening approaches, is necessary to propel discovery of novel drugs. Rapid throughput would require industrial generation of iPS cell-derived cardiomyocytes, an endeavor presented by Steven Kattman from Cellular Dynamics International (Madison, WI, USA) [18]. Cellular Dynamics International's ready-to-use iCell cardiomyocytes are the product of large-scale manufacturing efforts that yield high-purity differentiated cells for disease modeling or drug screening purposes. This was echoed by Robert Passier (Leiden University Medical School, Leiden, Netherlands), who stressed the importance of stem cells for cardiotoxicity drug testing [19]. To wrap up the symposium and further emphasize the importance of generating functional tissue types, Milica Radisic (University of Toronto) described her biomaterial engineering technologies for generating healthy, functional heart tissues for cardiovascular regeneration following myocardial infarction. Her vision has led to the development of a system that can test the ability of different cell populations to survive and integrate in a cardiac environment [20].

Conclusion

In conclusion, the symposium provided exciting opportunities for international research collaborations. Standardizing genotyping, phenotyping, and biocomputing platforms across patient cohorts emerged as a critical need to combine large population cohorts for genomic studies. Collaboration between genomics, bioinformatics, systems biologists and stem cell researchers emerged as a key strategy to facilitate functional application of genomic discoveries towards development of new diagnostics and novel therapies.

Future perspective

High-throughput genomic and stem cell platforms have revolutionized the pace of biomedical discovery in human disease. Evolving bioinformatics and systems biology approaches are providing novel ways to synthesize new knowledge into 'actionable' results. Stem cell technologies will bring new insights into disease modeling, drug discovery and cardiotoxicity testing, and have the potential for regenerative medicine approaches. Ultimately, the convergence of these disciplines will enable discovery and development of new therapeutic strategies for childhood heart disease. Greater participation of the community including practitioners, community groups, regulatory agencies and funding agencies is needed to facilitate the translation of scientific discovery to improve the health of survivors of childhood heart disease.

Acknowledgements

The event was funded by the Ontario Ministry of Research and Innovation, the Ontario Genomics Institute, Mitacs, the SickKids Labatt Family Heart Centre, SickKids Research Institute, Artificial Intelligence in Medicine, and Cellular Dynamics

International. The event was supported by the American Heart Association Council on Cardiovascular Disease in the Young (in name only).

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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