

SPOTLIGHT

Challenges and opportunities at the interface of birth defects, human genetics and developmental biology

Mustafa K. Khokha^{1,*}, Karen J. Liu² and John B. Wallingford³

In November 2019, The Company of Biologists hosted a Workshop in the UK entitled ‘Understanding Human Birth Defects in the Genomic Age’ (<https://www.biologists.com/workshops/november-2019-2/>). This Workshop brought together a mix of pediatricians, human geneticists and developmental biologists to discuss how these groups might coordinate better in hopes of changing the course of prevention, treatment and management of the most impactful disease burden in children. Working as a group, the participants identified key hurdles in the field as well as priorities for overcoming them. A summary of the group’s conclusions is provided here:

Birth defects: the number one cause of infant mortality

The incidence of birth defects is underestimated by the general population. Indeed, birth defects are the number one cause of infant mortality in the US and Europe (for US data, see: <https://www.cdc.gov/nchs/data/databriefs/db328-h.pdf>; for UK data, see: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/childhoodinfantandperinatalmortalityinenglandandwales/2018>) and in non-lethal cases, the impact on child health is lifelong. As a consequence, the resources currently made available for discovering the causes and understanding the consequences of birth defects are not proportional to the overall impact on human health. Transforming society’s views on these fragile children is critical for improving their lives.

Individually rare, collectively common

Many families want cures. But they also desperately want answers as to why their child has a birth defect. Even the most common birth defects are genetically complex; therefore, the cause of any individual birth defect is ultra-rare. As a consequence, patient families often do not have access to the kind of community that can garner attention and resources. Thus, these families lack easy ways to find answers or solutions. This can leave patients and families feeling isolated. To combat this, we should push towards considering birth defects as a collective problem and identify areas where pooling of resources (research and societal support) can have the highest common impact.

From gene identification to disease causality

Until recently, the vast majority of birth defects generally had an unknown cause. Recent technical advances in genomics and genetics have greatly improved our chances of linking gene variants to birth defects. This is important, as it improves

diagnosis and genetic counseling. Patients and families also then have the possibility of pre-implantation genetic screening. However, despite this incredible technical advance, assigning disease causality remains difficult, in part because of the complex interplay between gene(s) and the environment. This challenge is further complicated by a lack of understanding of how gene variants drive disease etiology. To address this challenge, gene discovery must be coupled with mechanism discovery.

Genotype to phenotype: understanding molecular mechanisms of disease pathogenesis

Although novel sequencing approaches have made gene variant identification much easier, the identified genes are often of unknown function or, in cases with known function, do not provide a plausible mechanism for the observed tissue-specific developmental defects. Thus, we often have very little mechanistic understanding of the biological consequences of genetic variation or the impact of genetic variation and the environment. If we understood the molecular and cellular pathogenesis, we could improve treatment for patients and hope to identify preventative strategies. This is where developmental biology research, in model organisms and/or *in vitro* culture systems, becomes essential – helping us to link the genetic variant to the observed developmental pathology.

The impact of returning results to patients and families

Identification of gene-function interactions underlying congenital anomalies should be a primary goal of the biomedical community. Importantly, patients and families should be active participants in this process, rather than simply subjects of research. This is an opportunity to directly address the impact on one family, one patient and potentially transform their lives. The impact on families includes understanding the cause of the disorder, disease pathogenesis and treatment, as well as long-term genetic counseling and the potential for pre-implantation genomics. Given the collective significance of birth defects in society, we can multiply these impacts many times over. The overall goal is to prevent and treat birth defects to decrease the risk and impact on patients, families and society.

Perspective: seeking a collaborative understanding of patient phenotype, genetic variation and biological mechanisms

In order to fully realize the promise of the genomic age for preventing and managing human developmental disorders, we need to understand the relevance of any genetic variant to the disease phenotype. This presents a huge challenge to the community and will require far better communication between clinicians (such as clinical geneticists, dysmorphologists, pediatricians) and research biologists (such as epidemiologists, developmental, cellular and molecular biologists). In fact, we feel it crucial that birth defects research involves input from very disparate fields of biology that have often not associated themselves with developmental biology in the past. Strategies to

¹Pediatric Genomics Discovery Program, Department of Pediatrics and Genetics, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06520, USA. ²Centre for Craniofacial and Regenerative Biology, Faculty of Dentistry, Oral & Craniofacial Sciences, King’s College London, London SE1 9RT, UK. ³Department of Molecular Biosciences, University of Texas at Austin, Austin, TX 78712, USA.

*Author for correspondence (mustafa.khokha@yale.edu)

© M.K.K., 0000-0002-9846-7076; K.J.L., 0000-0002-2483-2165; J.B.W., 0000-0002-6280-8625

promote interdisciplinary synergy will accelerate discoveries, and the responsibility to develop such strategies lies with us.

Acknowledgements

We thank participants of The Company of Biologists Workshop for their contribution to the ideas formulated in this brief Spotlight, and for their continuing engagement in further discussions on the topic. In addition to M.K., K.L. and J.W., the full list of participants at the Workshop is as follows: Kate Ackerman (University of Rochester Medical Center, USA); Phil Beales (University College London, UK); Anahi Binagui-Casas (University of Edinburgh, UK); Katherine Brown (The Company of Biologists, UK); Samantha Brugmann (Cincinnati Children's Hospital Medical Center, USA); Megan Davey (University of Edinburgh, UK); Ashish Deswar (Hospital for Sick Children, Toronto, Canada); Nicole Edwards (Cincinnati Children's Hospital Medical Center, USA); Stefan Galander (The Company of Biologists, UK); Annie Godwin (University of Portsmouth, UK); Ryan Gray (University of Texas at Austin, USA); Nick Green (University College London, UK); John Griffin (University of East Anglia, UK); Jacinta Kalisch-Smith (University of Oxford, UK); Ian Krantz (Children's Hospital of Philadelphia, USA); Janina Kueper (Center for Regenerative Medicine, Massachusetts General Hospital, USA); Harry Leitch (MRC London Institute of

Medical Sciences, UK); Elizabeth Leslie (Emory University, USA); Soren Lienkamp (University of Zurich, Switzerland); Kate McDole (MRC Laboratory of Molecular Biology, Cambridge, UK); Sigolène Meilhac (Institut Imagine, Institut Pasteur, France); Nannette Nascone-Yoder (North Carolina State University, USA); Lee Niswander (University of Colorado, Boulder, USA); Mauricio Rocha-Martins (Max Planck Institute of Molecular Cell Biology and Genetics, Germany); Christiana Ruhrberg (University College London, UK); Jacqui Tabler (Max Planck Institute of Molecular Cell Biology and Genetics, Germany); Ludovic Vallier (Cambridge Stem Cell Institute, UK); Andrew Wilkie (University of Oxford, UK).

Competing interests

M.K.K. is a founder of Victory Genomics, Inc.

Funding

M.K.K. is supported by the National Institutes of Health (R01HD102186, R01HL149746, R01HL124402). K.J.L. is supported by a H2020 Marie Skłodowska-Curie Actions grant (NEUCREST 860635) and the Biotechnology and Biological Sciences Research Council (BB/R015953/1). J.B.W. is supported by the National Institutes of Health (R01HD085901, R01HD099191, R01HD090163, and R01HL117164).