Preface

From basic genetics and genomics to molecular mechanisms and management of human disease

The current volume of the *Advances in Genetics* (103, 2019) includes a combination of recent advances in basic and applied genetics. Most articles highlight applications in medicine and healthcare.

The intriguing question of biological adaptability and tolerance of environmental stresses is addressed by Muthamilarasan and Prasad (2019) employing model crops investigated using range of *omics* technologies. This article provides an overview on the role of *omics* facilitating crop improvement programs in developing climate-resilient varieties. Such a promising development could, to some extent, assist meeting the challenge of food shortages in drought hit regions and thus helping with the burden of under nutrition in developing and less developed nations.

The article of Dufner-Almeida, do Carmo, Masotti, and Haddad (2019) from São Paulo, Brazil provides insight to the role of next-generation genome sequencing variants on pre-mRNA splicing. Pre-mRNA splicing relies on recognition of short sequences on the primary transcript intron ends, and takes place along transcription by RNA polymerase II. Splicing DNA variants (SV) have been associated with human genetic diseases at canonical intron sites, as well as exonic substitutions putatively classified as nonsense, missense, or synonymous variants. The increasing use of next-generating sequencing targeting full genomic gene sequence has raised awareness of the relevance of deep intronic SV in genetic diseases and inclusion of pseudo-exons into mRNA. Authors explore the Catalog of Somatic Mutations in Cancer to describe the proportion of splice-site mutations in *cis* and *trans* regulatory elements. Genomic data from large cohorts of different cancer types are increasingly available. These advances enhance understanding the genetic control of alternative splicing by mapping splicing quantitative trait *loci* in tumors.

The article by McEneaney and Tee (2019) draws attention to the understanding the basic mechanism(s) of pathology that are caused through the presence of disease-causing mutations is a real hurdle for many rare genetic disorders. Authors describe amazing success story of targeted molecular treatment in Tuberous Sclerosis Complex (TSC), a rare clinically variable autosomal dominant disorder. Through the discovery of the *TSC1* and

TSC2 genes and the signaling pathways responsible for the pathology of TSC, a new drug target called mechanistic target of rapamycin complex 1 (mTORC1) was discovered. Rapamycin, an mTORC1 inhibitor, is now the only pharmacological therapy approved for the treatment of TSC. This chapter explores the future possibilities of finding a cure in rare human genetic diseases.

The article by Sivadas and Scaria (2019) is challenging as it takes the reader to the scope of precision public healthcare in the context of population genomics. The current excitement for affordable genomics technologies and global precision medicine initiatives marks a turning point in worldwide healthcare practices. The last decade of global population sequencing efforts has defined the enormous extent of genetic variation in the human population resulting in insights into differential disease burden and response to therapy within and between populations. Population-scale pharmacogenomics helps to provide insights into the choice of optimal therapies and an opportunity to estimate, predict, and minimize adverse events. Such an approach can potentially empower countries to formulate national selection and dosing policies for therapeutic agents thereby promoting public health with precision. We review the breadth and depth of worldwide population-scale sequencing efforts and their implications for the implementation of clinical pharmacogenetics toward making precision medicine a reality.

Hamilton and Suri (2019) describe association of cyclin-dependent kinase (CDK) in the pathogenesis of intellectual difficulties with brain and craniofacial malformations. Mutations in *CDK13* have recently been identified as a novel cause of syndromic intellectual disability. In this article, authors review *CDK13*-related disorder highlighting key clinical pointers including characteristic craniofacial features, feeding difficulties in infancy, and the presence of structural heart or brain malformations. Exploration of genotype–phenotype correlations suggests a trend toward milder phenotypes in patients with mutations predicted to cause haploinsufficiency of *CDK13*, while missense mutations affecting amino acid residue 842 appear most likely to be associated with structural malformations. The greater phenotypic impact of missense variants is hypothesized to occur due to a dominant-negative mechanism, by which the mutant protein acts to sequester cyclin K in inactive complexes. To assist other investigators, future directions for *CDK13* research are also discussed, including the need to resolve uncertainty regarding pathogenicity of *CDK13* haploinsufficiency, and to gather further longitudinal data from large cohorts in order to inform the clinical care of patients with the CDK 13 syndrome.

In the article by Short and Sampson (2019), recent genetic advances in colorectal cancer (CRC) are summarized. The CRC is the third most

common cancer in men and the second most common cancer in women across the world. Most CRCs occur sporadically, but in 15%–35% of cases, hereditary factors are important. Some patients with an inherited predisposition to CRC will be diagnosed with a "genetic polyposis syndrome" such as Familial Adenomatous Polyposis (FAP), *MUTYH*-Associated Polyposis (MAP), Polymerase Proofreading-Associated Polyposis, *NTHL1*-Associated Polyposis, *MSH3*-Associated Polyposis, or a hamartomatous polyposis syndrome. Individuals with $\geq$10 colorectal polyps have traditionally been referred for genetic diagnostic testing aiming to identify *APC* and *MUTYH* mutations which cause FAP and MAP, respectively. Mutations are found in most patients with >100 adenomas but in only a minority of those with 10–100 adenomas. The reasons that diagnostic laboratories are not identifying pathogenic variants include mutations occurring outside of the open reading frames of genes, individuals exhibiting generalized mosaicism, and the involvement of additional genes. It is important to identify patients with an inherited polyposis syndrome, and to define the mutations causing their polyposis, so that the individuals and their relatives can be managed appropriately.

It is anticipated that range of articles in the current volume would generate further discussion on the scope of basic genetic and gēnomic research in developing models of diseases mechanisms and thereby novel therapeutic applications.

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