From mechanisms to therapy: RNA processing's impact on human genetics

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40 years ago, the laboratories of Philip Sharp and Richard Roberts reported the discovery of introns (Berget et al. 1977; Chow et al. 1977). Their seminal work revealed that protein-coding messenger RNAs (mRNA) are derived from much longer precursor transcripts (pre-mRNA) containing both exonic (coding) and intronic (non-coding) sequences. During the ensuing decades, the burgeoning field of pre-mRNA processing solved numerous molecular mechanisms underlying the catalysis of splicing, polyadenylation, RNA editing and translation.

Pre-mRNA processing has major impacts on gene expression. The human genome contains far fewer protein-coding genes than initially predicted. The final number, 19,215, was less than a third of what had been expected and indicated that other modes of gene regulation, rather than just gene number, contribute to organism complexity (Jalali et al. 2016; Wright et al. 2016). The first transcriptomic maps built with data from the EST project illuminated an important source of information- alternative splicing and polyadenylation (Mironov et al. 1999). Three decades ago, these processes were seen as exceptions to the rule, but current estimates suggest that more than 95% of the human genes give rise to multiple transcripts (Frankish et al. 2015).

Protein-coding genes defy the one gene-one enzyme paradigm, in part, through the process of alternative pre-mRNA splicing. This mode of gene regulation is critical for generating protein isoforms with specific functions in development and homeostasis (Kalsotra and Cooper 2011). Alternative pre-mRNA processing not only expands the protein coding capacity of our genes, but also influences the regulation of downstream mRNA processing events such as translation, mRNA decay and transport in unexpected ways (Hachet and Ephrussi 2004; Sanford et al. 2004; Lareau et al. 2007; Ni et al. 2007; Wang et al. 2012; Sterne-Weiler et al. 2013; Floor and Doudna 2016; Taliaferro et al. 2016). These highly integrated steps in post-transcriptional gene are governed in part, through the interplay of *trans*-acting RNA binding proteins with a diverse array of *cis*-regulatory elements scattered throughout the pre-mRNA (Fu and Ares 2014).

Human genes contain overlapping layers of information. For example, the genetic code is constrained by sequences that also regulate pre-mRNA splicing (Parmley et al. 2006; Warnecke and Hurst 2011). These overlapping codes complicate efforts to understand how genetic variation influences phenotype. Does a polymorphism within a codon affect transcript splicing or the protein structure and function? The impact of aberrant RNA processing on phenotype is now undeniable, as numerous human diseases, including cancer, arise from mutations in *cis*-acting RNA elements and *trans*-acting RNA binding proteins, as well as the creation of toxic repetitive RNA elements through nucleotide expansion (Faustino and Cooper 2003; Sterne-Weiler and Sanford 2014; Li et al. 2016).

Splicing alterations are a common topic among genetic disorders. In recent years, we have seen tremendous advance in respect to splicing and therapy. Currently, there are FDA approved modified anti-sense oligo-nucleotides that are capable to correct splicing alterations in SMN2, the key gene

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in Spinal Muscular Atrophy (Singh et al. 2017). This drug has been recently approved by the FDA and most patients are showing dramatic responses to treatment. Similar strategies could be used to treat a variety of Mendelian diseases.

The impact of RNA processing on cancer development is also well documented with long lists of genes implicated in all hallmarks of cancer, displaying wide-spread alterations in splicing and poly A site selection (Brooks et al. 2014; Wang et al. 2016). Genomic projects such as The Cancer Genome Atlas (TCGA) provided an additional and more powerful platform to identify global changes in the splicing profile of cancer cells and expression alterations of its regulators. These studies increased the catalogue of biomarkers, mapped novel tumor suppressors and oncogenes and established RNA processing as an import route towards malignancy (Sebestyen et al. 2015; Bjorklund et al. 2017).

This special issue on RNA processing is a tribute to this initial discovery that opened a new chapter of gene expression regulation. We assembled a collection of articles from expert labs, covering a variety of biomedical topics in data analysis, RNA processing mechanisms and aberrant RNA processing in inherited diseases and cancer. As editors of this special issue, it has been our goal to increase the awareness of the readership of *Human Genetics* of RNA processing as a mechanism that drives human phenotypic variation. We are grateful to the authors who have contributed such creative and scholarly work. Finally, we thank the senior editorial board and the production staff at *Human Genetics* for helping us to share this important corner of the RNA world with you.

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