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Retrotransposons and Complex Diseases: Is it Time for a Retrotransposon-Based "Omics" Profiling approach to Elucidate the Origins of Pathogenesis?

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When Human Genome Project was completed, some unthinkable issues came to the fore. In contrast to the anticipations, the genic counterpart made up a mere ~2% of the genome. More surprisingly, it became evident the extent of the repetitive DNA, and we now know that it consists the most part of human genome [1,2].

Retrotransposons are discrete genetic entities, capable of moving their own sequences into new genomic locations, representing the vast majority of repetitive DNA. They are fixed and co-evolved in the ever-changing human genome during evolution, resulting in major fashioners of its landscape. Nowadays, it is widely accepted that retrotransposons can determine genome architecture and plasticity in a variety of modes, having a profound contribution to genomic variation (GV). Specifically, they are able to mobilize into new genomic sites (retrotransposition) or participate in genomic rearrangements leading to copy number variations (CNVs) or larger structural variations. From the aforementioned, one can easily deduce that the key to the genomic complexity does not lie into the genic, but the repetitive counterpart of our DNA. Moreover, retrotransposons represent an abundant and natural source of regulatory sequences for the host genome, having a great impact on a vast repertoire of cellular processes mainly through regulation of gene expression [3,4]. Retrotransposons, looking alike the double-faced Roman god Janus, have a dual impact on the genome. Controlled retrotransposon activity might be beneficial for the cell in terms of genetic and/or epigenetic regulation of gene expression, adaptation and homeostasis upon environmental challenges [3]. On the flip side, in some cases, their deregulated state may be noxious causing monogenic or complex (multifactorial) genetic diseases [5-7].

Disorders originating from the combinatorial effect of genetic, environmental and lifestyle factors in most cases unidentified yet are referred to as complex diseases. We now know that complex diseases probably represent the collection of GV in any of a large subset of loci, associated with disease and not obeying the standard Mendelian patterns of inheritance [8]. To get insights into the unusual inheritance patterns, genome-wide association studies (GWAS) have been widely used to define the genomic architecture of complex diseases. GWAS have revealed numerous genetic loci variants statistically associated with human complex diseases. Nevertheless, the results have not fulfilled the promise and gave rise to strenuous debate in the scientific community.

Congenital anomalies of the kidney and urinary tract (CAKUT), a well-known example of multifactorial/complex syndrome, are genetically heterogeneous anomalies of developmental origin with a wide spectrum of clinical phenotypes, constituting the major cause of chronic renal failure in childhood. The etiology of the majority of CAKUT phenotypes remains unknown. Mutations in *HNF1B* gene are common in CAKUT and the genomic imbalance, such as CNVs, genomic or *de novo* mutations, can only explain up to one third of all CAKUT cases. Siomou et al. have recently reported a novel aspect on the mechanism underlying the GV (genomic imbalance) leading to a complex disease, such as CAKUT. Using array-CGH, they have provided evidence for the causative role of a retrotransposon-associated genomic rearrangement - a 1.4 Mb deletion of chromosome 17q12 spanning *HNF1B* gene on a CAKUT phenotype (ureterovesical junction obstruction), uncovering retrotransposons activity as a possible source of pathogenic variants [9].

The multifactorial nature of complex diseases renders challenging the investigation of the cause(s) of such disorders. Interestingly, GV associated with complex disease often appears in non-coding parts of the genome, denoting that "cryptic variation" consists a major source of disease susceptibility. The advances of high-throughput genomics approaches have provided functional information about the human genome, emerging the central role of retrotransposons in GV between individuals [10-12]. Knowing that retrotransposons activity is affected by: (i) genetic, (ii) environmental and (iii) lifestyle factors [3], all three also "inducers" of complex diseases traits, an unequivocally reasonable number of questions is raised. Which factors are critical for complex diseases pathogenesis? Do GV matter in complex diseases and, if yes, to which extent? What is the role, if any, of retrotransposons in complex diseases? In practice, we must still await enlightening responses to such questions. Considering that: (a) a typical genome differs 82% from the reference human genome, counting in the variants single nucleotide polymorphisms (SNPs), short indels, large structural variants and CNVs [13], (b) retrotransposons constitute an important agent for generation of GV, being responsible for 20.5% of the structural variation in humans [14], (c) retrotransposons influence gene expression, as 31% of total protein-coding genes transcription start sites in humans are located within retrotransposon sequences and 14,546 retrotransposon-derived regions are identified as enhancers [15,16] and (d) 1.04% of the retrotransposon-generated variants lie within already known risk loci for common and rare human diseases [14], it seems straightforward a demand to determine the genomic landscape of individuals with complex diseases using advanced "omics" approaches. In this manner, it can be determined each individual's "mobilome" the sum of retrotransposon counterpart of the genome further representing a pathogenic "genomic identity card" (GID). GID data resulting from whole-genome sequencing (WGS) coupled with RNA sequencing (RNA-Seq) and Proteomic analyses will be exploitable to decipher both the genomic architecture and the pathogenic variants. To this direction, it would be of great help the existing approaches for identification of the

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LINE-1 and Alu mobilome designed and executed until now [17-19]. Nevertheless, the development of novel experimental methodologies, which can support and supplement the existing ones is necessary, in order to determine the whole human mobilome. Taken together, the above will likely contribute to the definition of the causative factors of complex diseases.

Definitely, it will take a lot of effort to understand and elucidate complex diseases susceptibility. However, the progress made in the post-genomic era will enable the development and application of a holistic retrotransposon-based "omics" genome profiling approach. Such an approach can be applicable to unravel the genomic architecture of complex diseases and elucidate the origins of pathogenesis. Barbara McClintock stated "one must await the right time for conceptual change". To our opinion, retrotransposons matter in complex diseases and it is the right time to be taken into consideration.

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