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Opinion

Runs of Homozygosity and Epigenetic Deregulation of Genomic Imprinting

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Abstract:

Runs of homozygosity (ROH) are uninterrupted contiguous regions within the genome exhibiting allelic homozygosity (alleles are inherited from the same parent). Genome-wide analyses consistently demonstrate that megabase-scale ROH are ubiquitous in humans, reflecting individual demographic history. The number and length of ROH correlate increasingly with the degree of consanguinity and can be associated with genetic diseases in both inbred and outbred individuals. Genomic imprinting and uniparental disomy (UPD) are two additional phenomena dependent on parental-origin-specific inheritance that should be noted. Here, we propose genomic imprinting is dysregulated by ROH (functional analogs of segmental UPD or those partially affecting chromosomes) spanning imprinted loci resulting in a phenotype of an imprinting disorder. Interestingly, it has recently been shown that ROH in genomic/chromosomal regions harboring imprinted disease genes are likely to be associated with brain diseases phenotypically resembling imprinting disorders (Angelman, Beckwith–Wiedemann and Prader–Willi syndromes). Therefore, ROH spanning the imprinted genes seem to be

a feasible focus of basic and diagnostic research into epigenomic regulation. Understanding the interplay between ROH and genomic imprinting is likely to illuminate a new epigenetic disease mechanism.

Keywords
Runs of homozygosity; genomic imprinting; brain diseases; epigenetic deregulation

1. Introduction

Runs of homozygosity (ROH) (long contiguous stretches of homozygosity or regions of homozygosity or losses of heterozygosity) result from the combination of ancestral haplotypes in a genomic (chromosomal) locus of an individual genome. The loci affected by ROH are always detectable in a genome and represent a relatively new focus in studies of molecular signatures of population/demographic histories, single gene recessive mutations and genetic architecture of complex diseases [1]. Although ROH are generally considered to be genomic signatures for inbreeding depression or parental consanguinity [2], ROH have been implicated in quantitative and disease phenotypes [1, 3]. However, since such (epi) genomic studies are relatively new, the contribution of ROH to human morbidity remains poorly understood.

Recently, we have observed phenotypic resemblance to imprinting disorders (Beckwith–Wiedemann, Silver–Russell, and Prader–Willi/Angelman syndromes) in individuals with brain conditions (neurobehavioral disorders, epilepsy) and congenital malformations exhibiting ROH at imprinted loci [3]. Taking into account the etiologic variability of imprinting disorders (structural chromosome abnormalities, copy number variations, uniparental disomies, and single gene mutations) and heterogeneity of genomic imprinting deregulation pathways [4-6], it is highly likely that ROH spanning the imprinted genes play a causative role in these cases [3]. Moreover, ROH in some imprinted loci have been identified as the unique relevant (diagnostic) finding in some cases of Prader–Willi and Angelman syndromes [7]. Finally, ROH seem to be functionally analogous to segmental uniparental disomy (UPD; a uniparental disomy affecting only a part of a chromosome) [3, 6]. Here, we suggest the existence of a link between ROH, UPD and dysregulation of genomic imprinting. If proven, this link will elucidate a new epigenetic mechanism in brain diseases.

2. ROH and Genetic Diseases

In the most recent review, a variety of quantitative and disease phenotypes associated with ROH was presented [1]. The majority of pathologic conditions are associated with increased ROH burden, ROH number variations and individual or locus-specific ROH. Although these epigenomic associations are rarely replicated, increasing evidence suggests that brain disorders (Alzheimer's disease, autism, depression, intellectual disability, schizophrenia) and cancers are linked to ROH burden/individual ROH. Interestingly, imprinting disorders of the brain are attributed to (epi) genetic mechanisms, whereas genomic imprinting deregulation is frequently observed in cancer [8]. However, the interplay between ROH and epigenetic changes (for instance, UPD or genomic imprinting) remains to be fully elucidated. Nonetheless, ROH at chromosomal regions containing imprinted genes have been previously detected in >5% of children with brain disorders

phenotypically resembling the Beckwith–Wiedemann, Silver-–Russell, and Prader–Willi/Angelman syndromes [3]. Based on the concept of functional similarity between short/long ROH and segmental uniparental disomies, the involvement of ROH in the pathogenesis of epigenetic diseases is probable. Thus, current views on these epigenomic variations provide a strong theoretical background for a role of a ROH-mediated "segmental-uniparental-disomy-like effect" in brain disorders.

3. Imprinting Disorders and Uniparental Disomies: Is there a Place for ROH?

During recent decades, numerous outstanding reviews have been dedicated to highlighting imprinting disorders and epigenetic deregulation of genomic imprinting [5, 6, 8, 9]. To avoid repetition and provide new insights, we have focused on epigenetic deregulation in imprinting disorders mediated by UPD, inasmuch as these aspects are the most relevant to our hypothesis. Currently, at least 12 imprinting diseases have been identified [6], nine of which are the result of a UPD. Additionally, the Beckwith–Wiedemann, Silver–Russell, and Prader–Willi/Angelman syndromes are commonly associated with epigenetic defects presenting as losses of heterozygosity affecting specific chromosomal loci [6, 9]. Our previous study showed that ROH are located within specific chromosomal loci (7q21.3, 7q31.2, 11p15.5, and 15p11.2); thus, these cases can be attributed to segmental uniparental disomies affecting imprinting centers (imprint control regions) in contrast to uniparental disomies of whole chromosomes [3]. Since epigenetic alterations in imprinting centers or imprint control regions are repeatedly reported to underlie imprinting disorders [8], it can be speculated that ROH simulate a UPD that is causative for Beckwith–Wiedemann, Silver–Russell, and Prader–Willi/Angelman syndromes. It is also probable that these ROH activate recessive mutations within the stretch.

Since ROH can affect a proportion of imprinted genes leading, thereby leading to milder phenotypes of the aforementioned imprinting disorders, it is important to mention somatic ROH leading to acquired UPD (i.e. "somatic epigenomic changes"), which produce neuropsychiatric phenotypes and milder forms of imprinting disorders [10-14]. Such epigenetic changes lead to almost exactly the same phenotypic effect as that observed in cases of somatic genomic variations or somatic mosaicism (i.e. number of cells with a causative genomic pathology is proportional to the severity of neurobehavioral or neurodevelopmental phenotype) [15, 16]. Summarizing these observations suggests that an increase in the overlap between genetic changes in imprinting disorder genes and neuropsychiatric (neurobehavioral) phenotypes. The phenotypic consequences of both somatic/acquired and regular/non-mosaic epigenomic changes are likely to result from a partial dysregulation of genes in an imprinted locus (i.e. some imprinted genes are dysregulated whereas some are not), which produces milder phenotypes of imprinting disorders. Similar explanations seem to be applicable for phenotypic differences between cases of whole-chromosome UPD and ROH at an imprinted locus.

4. Implications

ROH at chromosomal loci containing disease-associated imprinted genes are present in approximately 5% of children with intellectual disabilities, autism and/or epilepsy [3]. If these epigenetic changes are causative for cases presenting with typical/atypical phenotypes of imprinting disorders, ROH spanning the imprinted loci will become one of the commonest types of

epigenetic (epigenomic) variations associated with neurodevelopmental diseases. Furthermore, these pathogenic epigenomic changes are likely to have a frequency comparable to that of the chromosomal abnormalities, copy number variations or single gene mutations causing these devastating early-onset conditions [17, 18]. Therefore, it can be speculated that a proportion of imprinting disorders associated with these ROH is overlooked during molecular diagnosis. Furthermore, illuminating new epigenetic mechanisms for brain diseases appears to provide new opportunities for uncovering altered pathways that are feasible targets for personalized drug design and/or exogenous correction of processes that are modified by epigenomic variations [19, 20].

Globally, in accordance with the concepts of systems biology and systems medicine (or even "systems pharmacology"), full implementation of systems science in healthcare provision and drug development requires extended studies of all the components of a system and all their interactions at different hierarchical levels of organization [16, 21]. An almost identical is used for studying the (epi) genetic causes of brain diseases. Accordingly, ROH analysis in the epigenetic context may lead to the incorporation of epigenomic variations into an orchestrated view of molecular and cellular mechanisms of brain dysfunction.

5. Conclusions

The intrinsic contribution of ROH to brain diseases remains unknown. In addition, ROH are rarely addressed in the clinical epigenetic context. Our hypothesis concerning the possible interplay between ROH and genomic imprinting may illuminate a new epigenetic mechanism underlying neurobehavioral and neurodevelopmental diseases associated with imprinting defects. Consequently, new opportunities for molecular diagnosis and personalized therapies for brain diseases associated with ROH at imprinted genomic loci are likely to become available. To this end, the elucidation of the role of ROH in imprinting disorders requires further studies involving larger clinical cohorts.

Author Contributions

IYI wrote the manuscript; IYI, SGV and YBY conceived the ideas.

Competing Interests

The authors have declared that no competing interests exist.

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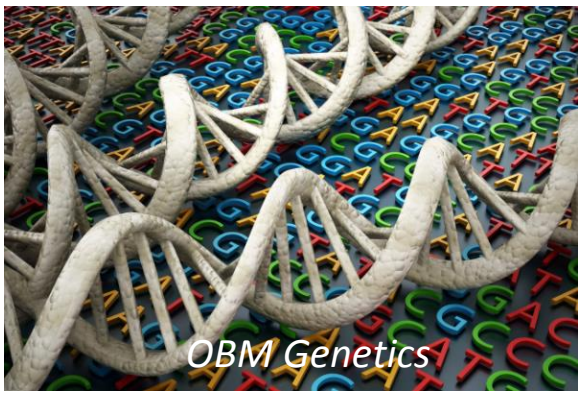

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