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Personalized Psychiatry and Neurology

Review

Unstable Genomes in the Human Brain: What Does It Mean for Personalized Psychiatry and Neurology

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Abstract: Despite efforts to uncover genome variability confined to the human brain, genome composition of neurons remains a matter of conjecture in health and disease. Still, somatic neurogenomics continuously gives further insights into understanding of mechanisms for devastative psychiatric and neurological disorders. For instance, since somatic genetic mosaicism and genome instability affecting the brain dynamically change during the ontogeny, these phenomena are able to shape individual features of disease manifestation, course, and outcome. This review is dedicated to the involvement of genome instability in the pathogenesis of brain diseases. Genome/chromosome instability and somatic mosaicism mediating brain dysfunction may produce specific (personalized) manifestations and course of a brain disorder via genetic-environmental interactions. Consequently, genome instability in the brain has to be taken into account during the development of personalized therapeutic interventions in a wide spectrum of psychiatric and neurological disorders. Among the latters, the most striking are schizophrenia, Alzheimer's diseases, and chromosome instability syndromes. Still, neurodevelopmental diseases (e.g., autism and intellectual disability) are to be investigated in the context of brain-specific genome instability.

Keywords: *brain, chromosome instability, genome instability, neurodegenerative diseases, personalized medicine, psychiatric disorders*

1. INTRODUCTION

During the last two decades, the human brain was shown to demonstrate somatic genomic mosaicism and genome/chromosome instability, the rates of which significantly increase in a number of psychiatric and neuroglial diseases [1-3]. Genomic instability and somatic mosaicism including chromosome imbalances (aneuploidy) and gene mutations have been systematically associated with brain dysfunction in early- and late-onset neurodegenerative diseases as well as in neurodevelopmental and late-onset mental disorders [3-6]. Moreover, proportions of cells with unstable/abnormal genomes vary with age tending to increase in the late life and to cause age-related brain diseases (for an overview, see [7]). An interplay between genome instability, cell senescence and brain aging is a likely mechanism for late-onset brain dysfunction [8, 9]. Generally, mechanisms for somatic mosaicism and genome/chromosome instability in the human brain seem to be sophisticated and involve numerous molecular and cellular pathways. For instance, brain-specific genome instability may result from alterations to pathways regulating cell cycle, mitotic division, chromosome segregation, DNA reparation/replication, chromatin remodeling, and programmed cell death (i.e., pathways involved in genome stability maintenance) [10]. Additionally, errors resulted from non-specific genome changes are able to cause

susceptibility to genome and chromosome instability [11,12]. The interaction between such susceptibility and alterations to genome stability maintenance pathways produces genome instability, which is able to result in genomic chaotization mediating devastative processes in the human brain [12]. Alternatively, it has long been suggested that brain-specific somatic mosaicism and genomic instability originate from early ontogeny inasmuch as the developing human demonstrate astronomical rates of cell divisions (including erroneous cell divisions) whereas the postnatal human brain is mostly composed of post-mitotic (non-dividing) cells [1,13,14]. Accordingly, it is proposed that postnatal somatic genome changes are likely to result from failures in managing/clearing abnormal cell lineages during early prenatal development [13-15]. In total, brain-specific genome instability and safeguarding neuronal genome integrity are involved in normal and pathological functioning of the human brain throughout the lifespan [16]. Still, the intrinsic role of the aforementioned processes and phenomena in the etiology of numerous psychiatric and neurological diseases remains questionable. To this end, tissue-specific genome instability appears to be an additional source for individual (personalized) features of disease manifestation, course, and outcome.

Here, we have addressed the contribution of studies in the field of somatic genomics of the brain to personalized psychiatry and neurology. Analyzing peer-reviewed articles from the available biomedical literature, we focused on how genome instability may shape the pathogenesis in the personal way. In addition, perspectives of studying unstable genomes in the diseased human brain for personalized psychiatry and neurology are discussed.

2. RESULTS

Analyzing the available literature, we have retrieved relevant data on genome/chromosome instability and somatic mosaicism confined to the diseased human brain. Figure 1 demonstrates the spectrum of genomic and chromosomal instability in the diseased human brain according to [3-7, 10, 17-24].

It should be noted that despite numerous attempts to determine the mechanisms of brain-specific genome instability and somatic genetic mosaicism, i.e., complex genetic-environmental interactions [25], origins of these genetic causes for brain diseases are to be identified. A wide range of possible environmental, intracellular and molecular factors are likely to influence pathogenic increase of mosaicism/instability levels in the brain [26] (e.g., oxidative stress [27]). However, according to the available data, the most relevant mechanism of the formation is the occurrence of unstable genomes of ontogenetic origin or, in other words, the persistence of developmental chromosomal instability in the postnatal brain of individuals suffering from neurological and psychiatric diseases [1, 13 ,14 ,28]. Additionally, alterations to more specific pathways (e.g., PI3K, PTEN, Akt, mTOR etc.) are also shown to be involved [10]. Thus, the combination of environmental effects [25], individual genetic background (combination of genomic variations) and pathway alterations [12, 17, 26] shape the somatic genetic landscape of the human brain and, consequently, the manifestation of brain disorders.

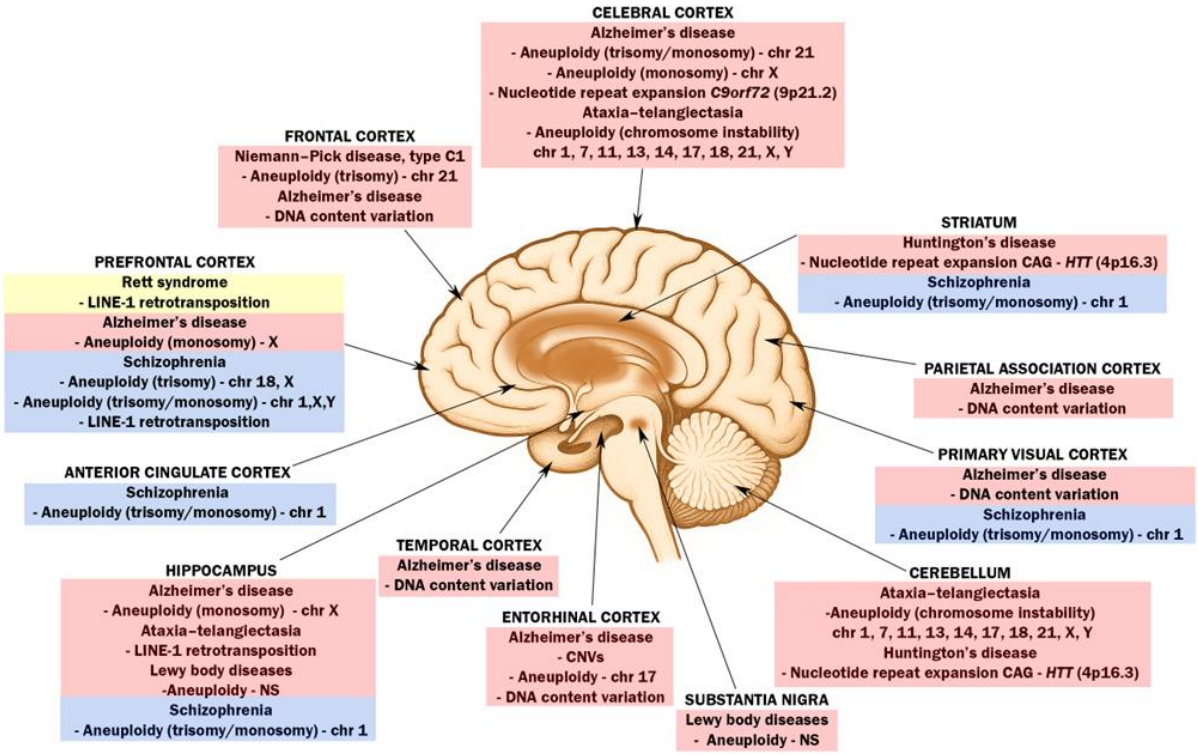

Figure 1. Spectrum of genomic/chromosomal instability in the diseased human brain (for more details, see [3-7, 10, 17-24]).
Note: chr = chromosome; NS = non-specified.

Somatic mosaicism in neurodevelopmental diseases has been repeatedly noted. In the neurogenomic context, it is to mention data on mutations (gene mutations and copy number variants) confined to specific brain areas in epilepsy (epileptic foci) or aneuploidy [28-31]. In the remainder (i.e., intellectual disability and autism), mosaic genomic changes are generally unrecognized as a common genetic cause, probably due to difficulties in the definition of the pathogenic value. On the other hand, single-cell multi-omics analyzes demonstrate that these genomic changes are likely to have a pathogenic effect [32]. In addition, X chromosome changes, which are repeatedly associated with a variety of brain diseases (for an overview, see [3, 14]), possess appreciable effects on brain functioning in neurological and psychiatric diseases [33]. Interestingly, these issues have been previously uncovered in mitotic cells (blood cells) during the molecular cytogenetic analyses of neurodevelopmental cohorts [1, 35-37]. As a result, neurogenomic pathways of autism spectrum disorders linking germline/somatic mutations to genetic-environmental interactions have been described [34]. It is also noticeable that genome and chromosome instability is associated with idiopathic and syndromic neurodevelopmental disorders [37,38]. Prototypic examples of syndromic neurodevelopmental disorders associated with unstable genomes are chromosome instability syndromes, e.g., ataxia-telangiectasia (for an overview, see [7, 39, 40]).

The rates of chromosome/genome instability in the brain are dynamically changing during the human life [1, 7, 41]. These changes are likely to mediate brain aging and aging-associated diseases of the brain [7, 42-44]. The Alzheimer's disease brain seems to be the most susceptible to brain-specific genomic instability [45]. The susceptibility is hypothesized to result from cell cycle re-entry and abnormal regulation of mitotic cell division occurring in neurons of the neurodegenerating brain [5, 9, 22, 25, 46]. Here, it is important to note, that alterations to these molecular and cellular pathways causing genome instability in the affected brain are not the sole cause of Alzheimer's disease [47].

Finally, the involvement of chromosome and genome instability (e.g., aneuploidy) in the immune response and inflammation (neuroinflammation) appears to be noteworthy inasmuch as both plays an important role in individual course and manifestation of brain diseases [48-50]. In this context, crosstalk between chromosome/genome instability and neuroinflammation represent a valuable target for developing personalized therapeutic interventions.

3. DISCUSSION

The discussion surrounding the meaning of brain-specific genome instability for personalized psychiatry and neurology is related to diagnostic opportunities required to be found on the basis of the aforementioned data. Identification of somatic mosaicism and genomic instability is a solved problem in current medical and personalized genomics [28, 37, 51, 52]. However, since genetic analysis of brain tissue is generally impossible to perform premortem, there is a need to develop indirect approaches of predicting genomic instability in the diseased brain [53]. Currently, there are several models for contribution of somatic mosaicism to neurological and psychiatric phenotypes, which might be used for diagnostic purposes [53-56]. Still, all these models have apparent limitations referred to the impossibility of testing premortem [3,14,57]. An alternative probably applicable for the aforementioned purposes is molecular cytogenetic analysis of exfoliated buccal cells, which are ectodermal in origin (brain cells are also ectodermal in origin) [53,58]. Nonetheless, correlation between intercellular and interindividual genomic/genetic heterogeneity remains to be established [14, 59]. This knowledge seems to be extremely valuable for personalized medicine, as a whole.

Another problem existing in current somatic neurogenomics (genomic studies of the brain) is the lack of widespread application of technologies for detecting somatic mosaicism (aneuploidy). Regardless of a wide panel of molecular genetic and molecular cytogenetic approaches to analyze somatic human cells, there is still a low growth rate of data on somatic genetic mosaicism and genomic instability in brain diseases [3, 14, 60, 61]. The technological solution is the combination of molecular genetic analysis of individual genomes, molecular cytogenetic detection of unstable genomes in single cells and bioinformatic evaluation of these two data sets (for details, see [62]). Technologically, genomic approaches to successful mapping genomic variations in the unaffected and diseased human brains are relatively easy to apply [3,63]. Nonetheless, the identification of genomic uniqueness of single neurons seems to be an intention for forthcoming research [10, 17, 64]. This appears particularly important for understanding autism spectrum disorders, which are challenging to treat and investigate using common neuroscientific theories of the pathogenesis [65]. In total, we conclude that current medical genomics provides technological opportunities for diagnosis and interpretation of genomic instability in the paradigm of personalized psychiatry and neurology.

Last but not least, there is an important issue concerning mosaic genomic variability as a key element of pathogenetic cascades of brain diseases referred to the dynamics of instability in light of environmental and endogenous factors. The dynamics determines individual features of disease manifestation, course and outcome of the associated brain diseases [3, 7, 17, 25]. Accordingly, it is to mention genome chaotization as a process intimately linked to genome instability and somatic genome variations. It is suggested that genome chaos is the molecular/cellular consequence of chromosomal and genomic instabilities critically affecting cellular homeostasis [66-68]. Genome chaotization is hypothesized to be involved in pathogenesis of brain disorders mediated by genomic (chromosomal) instability. However, there are no direct evidence for the involvement [62]. We suggest that uncovering the contribution of genome chaotization in neuronal cell populations is able to bring new insights into mechanisms of neurological and psychiatric diseases.

4. CONCLUSIONS

Personalized genomics generally operates with individual genomes according to an unproven idea that all the cells of a human organism are genomically identical. However, it is now clear that intercellular genomic variations are found in each individual. Moreover, somatic genomic mosaicism and genome/chromosome instability confined to the brain are mechanisms for brain diseases. Some disorders — autism spectrum disorders — require to become the focus of neurogenomic studies (analyses of somatic mosaicism and genomic instability in the brain). Since proportions of abnormal cells are not only individual, but also dynamical changing during ontogeny, genomic instability determines personalized features of manifestation, course and outcome of the associated brain diseases. Currently, the pathogenic meaning of genome/chromosome instability in the diseases brain is certainly underestimated. Therefore, this overlooked type of (somatic) genomic individualization occurring in the diseased brain is an important challenge for personalized psychiatry and neurology.

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