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CYTOGENETICS (T LIEHR, SECTION EDITOR)

Human Molecular Neurocytogenetics

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Abstract

Purpose of Review During the last decade, genomics has delivered basic insight into somatic genome variations contributing to human neuronal diversity in health and disease. Here, we review research on somatic chromosomal mosaicism and chromosome instability in the developing and adult (normal and diseased) human brain, representing the emerging field of molecular neurocytogenetics.

Recent Findings Chromosome instability and somatic chromosomal mosaicism were found to be involved in human brain development. Additionally, recent studies have highlighted the impact of neuronal aneuploidy and brain-specific chromosome instability on normal and pathological neurodevelopment and brain aging.

Summary Neurocytogenomic variations are nowadays thought to play a critical role in human brain development and aging. Chromosome instability is likely to be an element of pathogenetic cascades in a variety of brain diseases. Future studies are likely to reveal new neurocytogenetic/neurocytogenomic mechanisms for formation of human neuronal diversity and mental illness. Finally, human molecular neurocytogenetics may be recognized as an integral component of current biomedical science.

Keywords Brain · Chromosome instability · Aneuploidy · Somatic mosaicism · Molecular cytogenetics

Introduction

Molecular neurocytogenetics encompasses all studies of chromosomes within the central nervous system. The underlying idea of this emerging biomedical field is based on the logical assumption that all the cells of the human brain (no less than 80–100 billion neurons) cannot share identical genomes. Surprisingly, this idea was quite sensational at the time of the first molecular neurocytogenetic studies [1•, 2•, 3]. Presently, somatic mosaicism is accepted to be involved in human neuronal diversity and is suggested to be a possible causative mechanism for a wide spectrum of brain diseases [4–6]. Moreover, the results of neurocytogenomic research are found applicable for somatic genomics, in general [7, 8]. Although genetic mosaicism is hypothesized to have a specific effect on brain functioning (each neuron is able to form several thousand connections with other neurons; consequently, a genetically abnormal neuron might alter functions of several thousands of other neurons) [1•, 2•, 3–9], numerous neurocytogenetic studies have contributed to somatic cell genomics as a whole [10, 11]. In other words, cells of other tissues also exhibit variable rates of somatic mosaicism, which is likely to be both as a contributor to tissue development and maturation as a genetic causes of a disease. Furthermore, neurocytogenetic studies have given a new role of ontogenetic genome variations in human early development and aging [12, 13]. As a result, molecular neurocytogenetic findings may be generally relevant for genetic medicine.

Technological issues are an important starting point for understanding nuances of molecular neurocytogenetics. The first success of molecular neurocytogenetic analyses has become possible due to the development of interphase molecular cytogenetic techniques, which allowed the visualization of specific chromosomal regions or whole interphase chromosomes in their integrity during all stages of the cell cycle

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[14–17]. The next major technological step in studying intercellular genome variability was the development of single-cell whole-genome analysis by next-generation sequencing [3, 14, 17, 18]. Since each technological platform used for molecular neurocytogenetic studies is able to reveal specific types of chromosomal mosaicism and/or chromosome instability, there is a need for accurate comparative analysis of molecular neurocytogenetic data with special technical considerations. Accordingly, neurocytogenetic findings are to be reviewed taking into account cell scoring potential as well as direct/indirect nature of single-cell techniques for analyzing chromosomes in human brain cells (i.e., direct visualization of genomic loci or analyses of amplified DNA isolated from a single cell).

Overall, here, we review achievements in the field of human molecular neurocytogenetics. Ontogenetic changes of chromosome abnormality/instability rates in the developing and postnatal brain are addressed in the light of their potential roles in human neurodevelopment. Brain-specific somatic genomic variations are evaluated in the context of neuropsychiatric disorders and neurodegenerative diseases. The contribution of chromosomal mosaicism and instability to brain disease mechanisms is evaluated, and molecular neurocytogenetic analyses of brain aging are discussed, as well.

Developmental Neurocytogenetics and Neurocytogenetic Studies of the Adult Human Brain

The overwhelming majority of human neuronal cells are generated prenatally. During early brain development, neural cell numbers are dramatically increased and then extended clearance of neural cells by the programed cell death occurs. At this ontogenetic stage, significant decrease in neural cell population is suggested to be a mechanism that determines size, shape, and vulnerability of the mammalian central nervous system [19, 20]. Since high rates of somatic genome variations (mosaic aneuploidy and chromosome instability) are observed in the human developing brain [1•, 12, 14, 21–23], it has been proposed that chromosomal mosaicism and/or chromosome instability are likely to be intimately linked to neural cell number variations at early development [12, 24•].

The first molecular cytogenetic study of the developing human brain has been performed by fluorescence in situ hybridization (FISH) with 2–3 differently labeled chromosome-specific DNA probes (multiprobe FISH or mFISH). It has been shown that somatic (sporadic) aneuploidy ubiquitously affects the human fetal brain [25]. However, since mFISH technique does not discriminate between chromosome abnormalities and spatial nuclear organization of interphase chromosomes, these molecular cytogenetic analyses have evolved to a more sophisticated study. To solve technical problems, quantitative FISH (QFISH) [26, 27] and interphase chromosome-specific multicolor banding (ICS-MCB) have been developed [28]. The former offers an opportunity to differentiate between chromosome losses (monosomy) and FISH signal associations, which are frequent in brain cells, whereas the latter is the unique technique depicting interphase chromosomes in their integrity in single cells, at any cell cycle stage, and at molecular resolution. These original molecular cytogenetic techniques have revealed that the developing human brain is the embryonic tissue frequently demonstrating confined chromosomal mosaicism. Mosaic aneuploidy of chromosomes 15, 18, X, and Y has been found in fetal brain tissues in contrast to fetal skin and chorionic villi. Moreover, the developing human brain has sensationally demonstrated chromosome instability (sporadic aneuploidy) in >30% of cells [24•] (Table 1). The amount of cells with chromosome instability is comparable to the proportion of cells cleared by programmed cell death throughout human prenatal neurodevelopment [19, 45]. Bearing in mind the proven pathogenic effect of aneuploidy on cellular physiology [46–48], chromosome instability may be involved in neural cell number regulation executed by clearing genetically abnormal (aneuploid) cells through apoptosis or mitotic catastrophe [24•, 49]. Additionally, aneuploidy is the most common type of chromosome instability associated with a variety of cancer cell properties [50–52]. Consequently, neurodevelopmental chromosome instability has been hypothesized to be potential cause of pediatric brain cancers, the second most common cancer type in childhood [53].

Chromosome instability and somatic chromosomal mosaicism hallmark early brain development. It has been proposed that high rates of aneuploidy in particular and chromosome instability in general are likely to have a detrimental effect on neural cell populations [54•, 55–57]. Therefore, normal development of the central nervous system should be accompanied by a decrease (clearance) of genetically abnormal cells. If that is the case, then the unaffected adult brain has to exhibit lower rates of aneuploidy/chromosome instability in contrast to the diseased brain, which is likely to be affected by brain-specific somatic chromosomal mosaicism and/or chromosome instability.

Data on natural somatic genome variations in the human central nervous system are usually acquired from studying control samples in molecular neurocytogenetic analyses of disease. Direct evaluations of somatic chromosomal mosaicism and chromosome instability in the healthy human brain are exclusive [7, 58]. In Table 1, we summarize relevant molecular neurocytogenetic data on natural somatic genome variations at chromosomal level in the developing and adult human brain including results of studies focused on associations between chromosome instability (mosaicism) and brain diseases.

Table 1 Neurocytogenetic studies of the developing and adult human brain

Age	Chromosomes	Neurocytogenetic findings[a]	Methods	Cell scoring potential	Refs
Developing brain					
9–11 weeks of gestation	1, 13/21, 18, X, Y	0.6–3%/~28%	mFISH	High	[25]
8–15 weeks of gestation	1, 9, 15–18, X, Y	1.25–1.45%/30–35%	mFISH/QFISH/ICS-MCB	High	[24•]
Adult brain					
8–47 years	1, 7–9, 11, 16–18, X, Y	Cerebrum: 0.2–0.7%/12% Cerebellum: 0.3–1.2%/4.8%	mFISH/QFISH/ICS-MCB	High	[29•, 30•]
22–77 years	1, 9, 13/21, 16, 18, X, Y	0.1–1.7%/~10%	mFISH	High	[25, 31]
22–77 years	1, 9, 16, 18, X	0.2–2%/> 10%	ICS-MCB	High	[31]
~50–70 years	1, 9, 16, 18, X, Y	0.2–0.9%/~17%	mFISH/QFISH/ICS-MCB	High	[32]
~50–70 years	Gonosomes	0.57–1.13%/20.2% Two mosaic cases (> 2%)	mFISH/QFISH	High	[33, 34]
72–84 years	1, 7–9, 11, 16–18, X, Y	0.6–2.6% / 10–12%	mFISH/QFISH/ICS-MCB	High	[30•]
72–84 years (females)	1, 7, 11, 16, 17, 18, X	Autosomes: 0.5–0.8%/14.5% Chromosome X 1.3% Estimated for the entire genome: 15.8%	mFISH/QFISH/ICS-MCB	High	[35]
33–88 years	–	Hyperploidy: ~10–11.5%	Slide-based cytometry	Low	[36, 37•, 38]
35–95 years	–	Average intercellular genome content diversification: ~250 Mb	DNA content variation [b]	None	[39]
~60–90 years	4q22.1	Locus-specific CNV (*SNCA*): ~68%	Array CGH[b]/FISH	Low	[40]
62–97 years	All	Extensive clonal mosaicism of CNV	Array CGH	None	[41]
20–26 years	All	2.7%	Single-cell sequencing	Very low	[42•]
48–70 years	All	2.2%	Single-cell sequencing	Very low	[43•]
69–93 years	All	0.7%	Single-cell sequencing	Very low	[44•]

[a] Aneuploidy frequencies revealed by FISH-based approaches are given as follows: chromosome-specific frequencies/totally estimated frequencies (i.e., in terms of the entire genome); [b] Analysis of the total DNA extracted from a cellular population of the adult brain;

Aneuploidy is the main type of somatic genome variations detected in the adult human brain at chromosomal level [1•, 2•, 5, 6, 9, 14, 58]. To take a look at available neurocytogenetic data on chromosome instability (mosaicism) in the adult human brain, we have arranged the results of molecular neurocytogenetic studies according to techniques used for analyzing genomic variants and age (Table 1). Using mFISH, QFISH, and ICS-MCB, it has been shown that aneuploidy is likely to affect 5–12% of normal brain cells at the age of 8–47 years [29•, 30•]. The human cerebellum seems to be less affected by neural aneuploidy as to the human cerebrum [29•]. In the elder group of patients, post-mortem brain specimens demonstrated ~10% of aneuploid cells (data extrapolated to the entire genome) [25, 31]. FISH-based analysis of post-mortem cerebrum of individuals aged > 50 years have demonstrated the rates of neural aneuploidy to range from 17% to 20% (data extrapolated to the entire genome) [32–34]. In the eldest individuals, neural aneuploidy rates have been estimated as 10–16% [30•, 35]. In summary, aging has an unobvious effect on variations of neural aneuploidy rate addressed by mFISH, QFISH, and ICS-MCB. Alternative methods used for evaluating copy number variations (CNV) based on slide-based cytometry or array comparative genomic hybridization (CHG) yielded similar results [25–36, 37•, 38–41, 45–50, 51•, 52–58]. However, it is to note that these techniques are a weak alternative to FISH-based methods for analysis of human interphase chromosomes [16]. Neurons and non-neuronal cells of the normal adult brain have been found to have similar rates of aneuploidy [6, 9, 29•, 30•]. Single-cell next-generation sequencing is probably the best alternative to FISH-based evaluation of brain-specific unbalanced chromosome abnormalities. The rates of neural aneuploidy evaluated using next-generation sequencing of single cells isolated from the normal adult human brain have been found to vary between 0.7% and 3% [42•, 43•, 44•]. Thus, data on neural aneuploidy obtained by molecular cytogenetic techniques is significantly different from the data obtained by single-cell molecular genetic methods.

FISH-based approaches to single-cell detection of aneuploidy in post-mitotic brain cells appear to be very efficient because of having high cell scoring potential (> 10,000 cells can be analyzed per patient/probe set). The striking disadvantage of interphase FISH cytogenetic platforms is the impossibility of adequate analysis of all chromosomes in a single nucleus [15, 16, 59]. Intriguingly, single-cell next-generation

sequencing has almost exactly opposite advantage/disadvantage pair. The disadvantage is very low cell scoring potential; 100 cells is generally the upper limit for single-cell next-generation sequencing analysis. The advantage is the simultaneous evaluation of the whole single-cell genome [18, 43•, 44•]. It is important to underline that high cell scoring potential is critical for the efficiency of molecular neurocytogenetic studies inasmuch as uncovering such rare events as aneuploid brain cells requires large cell populations to be analyzed (>>100 cells per sample) [1•, 3, 60]. Another disadvantage of single-cell sequencing is the need for whole-genome amplification [18], which is able either to produce false-positive CNV or to "normalize" true-positive signals corresponding to deviation from the normal (diploid) profiling. This is certainly not a problem for molecular cytogenetic single-cell FISH-based methods [60, 61]. In conclusion, it is to stress that neglecting either data acquired through FISH-based techniques or data on single-cell next-generation sequencing absolutely hinders reliable analysis of intrinsic rates of neural aneuploidy in the normal adult human brain.

Summarizing the results of neurocytogenetic studies of the postnatal human brain, one can conclude that aneuploid cells do populate the central nervous system. However, the developing human brain exhibits significantly higher rates of somatic aneuploidy as compared to the postnatal human brain. Apparently, aneuploid brain cell populations in adulthood are the result of developmental chromosome instability, the levels of which are diminished through clearance of abnormal cells during late intrauterine development. On the other hand, this clearance may be altered; the result of the alterations is the presence of chromosome instability (chromosomal mosaicism) in the central nervous system after birth, which is a potential mechanism for brain diseases.

Neurocytogenetics of Disease

Somatic chromosomal variability has been repeatedly proposed as a mechanism for brain diseases [1•, 2•, 3, 4, 62, 63]. Actually, human molecular neurocytogenetics evolved from a successful study of the schizophrenia brain which supported the original hypothesis suggesting brain-specific chromosome abnormalities to cause mental illness [64•]. In parallel, neurodegenerative diseases (Alzheimer's disease) have been systematically studied in the light of a theoretical model suggesting that abnormal (abortive) cell cycle in neurons leads to genetic changes at chromosomal level (reviewed in [65]). Nowadays, it has been shown that a number of neuropsychiatric disorders and neurodegenerative diseases are associated with the characteristic neurocytogenetic findings. Table 2 reviews the results of molecular neurocytogenetic studies of the diseased brain.

Neuropsychiatric Disorders

Autism and schizophrenia are psychiatric disorders with a strong genetic background [81, 82]. Somatic genomic variations manifesting as mosaic (sub)chromosome abnormalities have been repeatedly reported in autistic individuals [66–69]. More precisely, mosaic aneuploidy of chromosome X (extra X chromosome in males; X chromosome loss and gain in females) appears to be one of the most common types of genetic variation in children with autism, and co-segregates with mental illnesses in families of affected children [66–68]. The male-to-female ratio in autism spectrum disorders (approximately 3:1 [83]) may be explained by a higher occurrence of mosaic extra X chromosome in autistic males [84, 85]. Preliminary studies have indicated the presence of chromosome instability and X chromosome aneuploidy in the autistic brain [70]. Additional molecular neurocytogenetic research has to be undertaken to determine the intrinsic rates of brain-specific chromosome instability and somatic chromosomal mosaicism in autism.

The first molecular neurocytogenetic study has found that two cases out of six with schizophrenia exhibited low-level mosaic trisomy of chromosome 18 (one case) and level mosaic trisomy of X chromosome (another case) in the brain [64•]. More detailed study of the schizophrenia brain has discovered chromosome 1-specific instability (aneuploidy) as a feature of the diseased brain. In addition, two cases out of 12 exhibited brain-specific low-level mosaic aneuploidy of chromosome 1: (i) 3.6% of cells with chromosome 1 loss (monosomy); (ii) 4.7% of cells with chromosome 1 gain (trisomy) [32]. There is also evidence that the schizophrenia brain exhibits increased rates of sex chromosome gains and losses (gonosomal aneuploidy) [33]. Molecular neurocytogenetic analyses of schizophrenia have shown an association of low-level mosaic aneuploidy with common and, probably, overlapping psychiatric disorders [34]. A number of studies have reported the presence of specific somatic CNV in the schizophrenia brain [71, 72]. The body of neurocytogenetic schizophrenia research allows concluding that at least a small proportion of this devastating neuropsychiatric disorder may be associated with somatic chromosomal mosaicism and chromosome instability in the diseased brain.

Neurodegenerative Diseases

Alzheimer's disease has been extensively studied in the neurocytogenetic context. This is mainly due to observations on cell cycle-mediated events in the Alzheimer's disease brain, which are suggested to result in changes of the cellular genome at chromosomal level [38, 65]. It has been shown that an increase of neuronal aneuploidy at preclinical stages of

Table 2 Summary of neurocytogenetic findings in the diseased brain

Disease	Neurocytogenetic findings	Refs
Neuropsychiatric disorders		
Autism	Suggested high-levels of chromosome instability and X chromosome aneuploidy in the diseased brain	[66–70]
Schizophrenia	Low-level mosaic trisomy of chromosome 18 (one case) and level mosaic trisomy of chromosome X (one case) in the diseased brain	[64•]
	Increase of sporadic chromosome 1-specific aneuploidy/instability plus 2 cases out of 12 exhibited low-level mosaic aneuploidy (monosomy and trisomy) of chromosome 1 in the diseased brain	[32]
	Increased rates of gonosomal aneuploidy in brain samples of patients with schizophrenia and comorbid psychiatric disorders	[33, 34]
	Somatic CNV suggested to be specific for the schizophrenia brain	[71, 72]
Neurodegenerative diseases		
Alzheimer's disease	An increase of aneuploidy confined to brain tissues at preclinical stages of the disease; aneuploidy mediates abnormal neuronal cell death	[36, 38, 73, 74•]
	Chromosome missegregation and aneuploidy probably resulted from mutations in the *APP* gene and presenelin 1	[75, 76]
	Chromosome 21-specific aneuploidy/instability dramatically increased in the diseased brain; aneuploidy/chromosome instability probably mediating neurodegeneration	[30•]
	An increase of X chromosome aneuploidy (a marker for aging of somatic mitotic tissues)	[35]
	Somatic CNV of the *APP* gene in the diseased brain	[77]
Ataxia-telangiectasia	Aneuploidy of all chromosomes in different brain areas; chromosome 14-specific instability confined to the degenerated cerebellum affecting ~40% of cells; brain-specific genome instability mediates neurodegeneration	[29•]
Frontotemporal dementia	Mitotic defects leading to neuronal aneuploidy and apoptosis due to *MAPT* mutations	[78]
Lewy body disease	Neuronal aneuploidy in multiple brain regions	[79•, 80]
Parkinson's disease	Increased levels of somatic *SNCA* gains in nigral dopaminergic neurons of the Parkinson's disease brain	[40]

Alzheimer's disease in the diseased brain as well as local mosaic genomic heterogeneity in affected central nervous system correlated with neuronal vulnerability [36, 38, 73]. Aneuploidy seems to mediate abnormal neuronal cell death underlying the progressive neurodegenerative process featuring Alzheimer's disease [74•].

There is a popular hypothesis that a extra copy of chromosome 21 (trisomy 21) containing the amyloid precursor protein (*APP*) gene leads to increased beta-amyloid (Aβ) peptide production contributing thereby to the development of Alzheimer's disease pathology and to higher risks of dementia in Down syndrome [75]. Research testing this hypothesis has demonstrated chromosome missegregation associated with aneuploidization resulted from mutations in the *APP* gene and presenilin 1. Both are well-known, albeit rare, genetic causes of Alzheimer's disease [75, 76]. The hypothesis has been recently supported by an association of somatic CNV of the *APP* gene in the Alzheimer's disease brain [77]. Alternatively, direct molecular neurocytogenetic studies of the Alzheimer's disease brain have provided partial support for this hypothesis demonstrating dramatically increased rates of chromosome 21-specific aneuploidy. These findings suggest that chromosome instability in general and aneuploidy in particular mediate neurodegeneration [30•]. X chromosome aneuploidy has been found to have higher rates in the Alzheimer's disease brain [35]. It is to note that X chromosome aneuploidy features aging of tissues composed of mitotic cells [10, 12, 86]. Neurocytogenetic data on Alzheimer's disease strongly indicate that aneuploidy (chromosome instability) is likely to mediate neurodegeneration in late life [87]. No consensus is reached on types of chromosome instability affecting the neurodegenerating brain [88]. Consequently, mechanisms for Alzheimer's disease neurodegeneration remain uncertain. Theoretical solution of this problem has been provided by the DNA replication stress hypothesis of Alzheimer's disease, which proposes DNA replication stress/catastrophe to trigger genome/chromosome instability linking abnormal cell cycle events, chromosomal aneuploidy, and Aβ production and deposition. Since DNA replication stress/catastrophe is able to result in diverse types of somatic chromosomal aberrations, different types of chromosome instability can be involved in Alzheimer's disease neurodegeneration pathway [89].

Ataxia-telangiectasia is an autosomal recessive chromosome instability (DNA damage response) syndrome clinically characterized by cerebellar degeneration, cancer susceptibility, radiation sensitivity, immunodeficiency, and telangiectasia. The syndrome is associated with a specific genetic defect (*ATM* mutations) and disease pathway representing a unique model for understanding neurodegeneration, cancerization, and immunodeficiency [90]. Paradoxically, ataxia-telangiectasia neurodegeneration occurs exclusively in the cerebellum, while other brain areas are insignificantly affected [91]. Molecular neurocytogenetic studies of ataxia-telangiectasia cerebellum and cerebrum have discovered that, despite aneuploidy affecting all brain areas, chromosome-14-specific

instability is confined to the degenerated cerebellum (detected in about 40% of cells). This study demonstrated neurodegeneration to be mediated by chromosome instability whereas it is generally accepted to hallmark cancer [29•].The data on chromosome instability mediating neurodegeneration in the ataxia-telangiectasia brain have been further used for hypothesizing the way of cell therapy for neurodegenerative diseases [92]. Further studies of pathways to genome/chromosome instability, alterations to DNA replication and reparation leading to unrepaired DNA damages in post-mitotic cells of the brain have been highlighted as underlying mechanisms for neurodegenerative diseases [89, 93].

Alzheimer's disease and ataxia-telangiectasia are not the only neurodegenerative conditions studied in the neurocytogenetic context. Mitotic defects preceding neuronal aneuploidy and apoptosis due to *MAPT* mutations have been revealed in frontotemporal dementia [78]. A series of studies have demonstrated that Lewy body disease is associated with neuronal aneuploidy in multiple brain regions [79•, 80]. Somatic gains of the *SNCA* gene are more common in nigral dopaminergic neurons of the Parkinson's disease brain as compared to controls [40]. Overviewing neurocytogenetics of neurodegenerative diseases [3, 63, 80, 87, 94], several important points have to be considered: (i) chromosome/genome instability and neural aneuploidy is likely to mediate neurodegeneration; (ii) alterations to DNA replication and reparation are involved in molecular/cellular neurodegenerative pathways; (iii) molecular cytogenetic analysis is able to reveal disease-associated phenomena/processes, which are able to become drug targets for neurodegenerative diseases.

Neurocytogenetics of Aging

As noticed before, clear correlations between rates of somatic aneuploidy and age are not as yet established. However, neurocytogenetic analysis demonstrates a probable effect of somatic mosaicism on brain aging. For instance, neural aneuploidy generated during early brain development is able to accelerate or to slow down aging in the healthy and diseased brain [95]. In addition, even in case of Alzheimer's disease (i.e., the late-onset neurodegenerative disease probably associated with pathological brain aging), chromosome instability/aneuploidy is likely to originate from the developing brain [96]. A number of studies report a slight increase of neural aneuploidy rates in late life [12, 37•]. There is an opinion that neural aneuploidy and chromosome instability are able to contribute to brain aging in cases of severe late-onset diseases associated with abnormal/accelerated aging [62, 80]. Another opinion suggests neural aneuploidy and chromosome instability to be like a time bomb: it is "set" (formed) at early ontogenetic (developmental) stages, but it "explodes" (expresses) in late life [12, 86, 94, 96]. Nonetheless, aging is assumed to decrease the ability to maintain cellular genome stability in the aged brain [97]. Certainly, there is a need for numerous additional studies to uncover the contribution of somatic genome variations to brain aging.

Conclusions

Human molecular neurocytogenetics is a rapidly developing field. In parallel to studying neurocytogenomic variations in the normal and diseased brain, there have been several efforts to create an integrated pathway for the formation and propagation of somatic genomic pathology in the human brain. Actually, related pathways providing for the theoretical link between somatic genome variations and genetic-environmental interactions in brain disorders are proposed. Particularly, ontogenetic 2-/multiple-hit models of brain diseases based on molecular neurocytogenetic findings suggest that inherited or de novo mutations may cause neural cell susceptibility to genomic instability and susceptibility to unexpected cell death, which are triggered by adverse environmental effects throughout ontogeny [98]. This model has been partially supported by studying natural CNVs of genes involved in cell cycle regulation pathways, which render cellular populations susceptible to somatic mosaicism (aneuploidy) [99]. Similarly, inherited/de novo mutations lead to chromosome instability in cancer cells [47–50]. Bioinformatic analyses have shown that the model is applicable to autism spectrum disorders offering a neurogenomic pathway of autism, which depicts how germline mutations may generate brain-specific somatic mosaicism by genetic-environmental interactions [100]. Ontogenetic 2-/multiple-hit models are also applicable to non-neural and cancer cells, as well [99, 101]. New discoveries in human molecular neurocytogenetics are likely to unravel the mechanisms generating brain-specific chromosome instability. The knowledge about the origins of unstable cellular genomes in the diseased brain may be certainly applied for treatment of neuropsychiatric disorders and neurodegenerative diseases.

Interphase cytogenetics is not only limited to analysis of chromosomal abnormalities/variation but may provide valuable data on nuclear chromosome organization [16]. The latter is critical for understanding the functional implications of chromosome positioning for genome stability and behavior [102]. Specific nuclear chromosome organization has been already associated with complex diseases [102, 103]. However, nuclear chromosome positioning and spatial genome organization is rarely studied in the human brain [1•, 103, 104]. Thus, there is a need for initiating molecular neurocytogenetic research of chromosome organization in nuclei of human brain cells.

Another important issue of molecular neurocytogenetic research is molecular diagnosis of brain diseases caused by brain-specific somatic mosaicism [105]. Taking into account the complexity of molecular (cyto)genetic diagnosis of neurological and

psychiatric diseases using biopsies (blood cells) [21, 59, 81], one can imagine how difficult is the development of diagnostic workflows for brain-specific genome pathology [49, 105]. Nonetheless, ontogenetic 2-/multiple-hit model indicates that a number of biomarkers appear to exist for diagnosing brain-specific chromosome instability [98]. The diagnosis might be based on studying the genetic susceptibility of cellular genomes to instability by uncovering mutations in genes (genomic loci) involved in genome stability maintenance pathways [98, 105]. Consequently, testing of ontogenetic 2-/multiple-hit model is relevant to molecular diagnosis of brain diseases caused by brain-specific genome/chromosome stability.

The last decade has formed strong theoretical and empirical basis of human molecular neurocytogenetics. In this light, one can speculate about bright perspectives of this emerging field of biomedicine. Firstly, it seems that the scope of neurocytogenetics studies needs to be widened to cover fully neurodevelopmental, neurodegenerative and neurobehavioral diseases. In this instance, it is apposite to mention a recent hypothesis suggesting that behavioral phenotype variability may change according to variation of proportions of genetically abnormal cells throughout the lifespan [106]. Therefore, indirect molecular neurocytogenetic studies (i.e., molecular cytogenetic analysis of biopsies for unraveling altered pathways to brain diseases) seem to benefit from the application of molecular cytogenetic monitoring of somatic mosaicism. Secondly, it appears that combination of FISH-based techniques and array CGH/next-generation sequencing is only able to solve all problems arising from technological limitations. Finally, to develop efficient therapies of the debilitating brain diseases, further molecular neurocytogenetic studies are required for unrevealing pathways to genome instability and specific nuclear chromosome organization in the diseased brain.

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Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major Importance

1.• Iourov IY, Vorsanova SG, Yurov YB. Chromosomal variation in mammalian neuronal cells: known facts and attractive hypotheses. Int Rev Cytol. 2006;249:143–91. https://doi.org/10.1016/S0074-7696(06)49003-3 **Defined the essence of human molecular neurocytogenetics as an independent field of biomedical research through postulating the theoretical and technological basis.**

2.• Kingsbury MA, Yung YC, Peterson SE, Westra JW, Chun J. Aneuploidy in the normal and diseased brain. Cell Mol Life Sci. 2006;63:2626–41. https://doi.org/10.1007/s00018-006-6169-5 **Defined the essence of human molecular neurocytogenetics as an independent field of biomedical research through postulating the theoretical and technological basis.**

3. Iourov IY, Vorsanova SG, Yurov YB. Single cell genomics of the brain: focus on neuronal diversity and neuropsychiatric diseases. Curr Genomics. 2012;13:477–88. https://doi.org/10.2174/138920212802510439.

4. Insel TR. Brain somatic mutations: the dark matter of psychiatric genetics? Mol Psychiatry. 2014;19(2):156–8. https://doi.org/10.1038/mp.2013.168.

5. McConnell MJ, Moran JV, Abyzov A, Akbarian S, Bae T, Cortes-Ciriano I, et al. Intersection of diverse neuronal genomes and neuropsychiatric disease: the brain somatic mosaicism network. Science. 2017;356:eaal1641. https://doi.org/10.1126/science.aal1641.

6. Rohrback S, Siddoway B, Liu CS, Chun J. Genomic mosaicism in the developing and adult brain. Dev Neurobiol. 2018. https://doi.org/10.1002/dneu.22626.

7. Iourov IY, Vorsanova SG, Yurov YB. Somatic genome variations in health and disease. Curr Genomics. 2010;11:387–96. https://doi.org/10.2174/2F138920210793176065.

8. Campbell IM, Shaw CA, Stankiewicz P, Lupski JR. Somatic mosaicism: implications for disease and transmission genetics. Trends Genet. 2015;31(7):382–92. https://doi.org/10.1016/j.tig.2015.03.013.

9. Bushman DM, Chun J. The genomically mosaic brain: aneuploidy and more in neural diversity and disease. Semin Cell Dev Biol. 2013;24:357–69. https://doi.org/10.1016/j.semcdb.2013.02.003.

10. Iourov IY, Vorsanova SG, Yurov YB. Chromosomal mosaicism goes global. Mol Cytogenet. 2008;1:26. https://doi.org/10.1186/1755-8166-1-26.

11. De S. Somatic mosaicism in healthy human tissues. Trends Genet. 2011;27:217–23. https://doi.org/10.1016/j.tig.2011.03.002.

12. Yurov YB, Vorsanova SG, Iourov IY. Ontogenetic variation of the human genome. Curr Genomics. 2010;11:420–5. https://doi.org/10.2174/138920210793175958.

13. Vijg J. Somatic mutations, genome mosaicism, cancer and aging. Curr Opin Genet Dev. 2014;26:141–9. https://doi.org/10.1016/j.gde.2014.04.002.

14. Iourov IY, Vorsanova SG, Yurov YB. Intercellular genomic (chromosomal) variations resulting in somatic mosaicism: mechanisms and consequences. Curr Genomics. 2006;7:435–46. https://doi.org/10.2174/138920206779116756.

15. Vorsanova SG, Yurov YB, Iourov IY. Human interphase chromosomes: a review of available molecular cytogenetic technologies. Mol Cytogenet. 2010;3(1):1. https://doi.org/10.1186/1755-8166-3-1.

16. Yurov YB, Vorsanova SG, Iourov IY, editors. Human interphase chromosomes: biomedical aspects. New York: Springer; 2013. https://doi.org/10.1007/978-1-4614-6558-4.

17. Bakker B, van den Bos H, Lansdorp PM, Foijer F. How to count chromosomes in a cell: an overview of current and novel technologies. BioEssays. 2015;37(5):570–7. https://doi.org/10.1002/bies.201400218.

18. Abyzov A, Urban AE, Vaccarino FM. Principles and approaches for discovery and validation of somatic mosaicism in the human brain. Neuromethods. 2017;131:3–24. https://doi.org/10.1007/978-1-4939-7280-7_1.

19. Muotri AR, Gage FH. Generation of neuronal variability and complexity. Nature. 2006;441:1087–93. https://doi.org/10.1038/nature04959.
20. Fricker M, Tolkovsky AM, Borutaite V, Coleman M, Brown GC. Neuronal cell death. Physiol Rev. 2018;98:813–80. https://doi.org/10.1152/physrev.00011.2017.
21. Iourov IY, Vorsanova SG, Yurov YB. Molecular cytogenetics and cytogenomics of brain diseases. Curr Genomics. 2008;9:452–65. https://doi.org/10.2174/138920208786241216.
22. Siegel JJ, Amon A. New insights into the troubles of aneuploidy. Annu Rev Cell Dev Biol. 2012;28:189–214. https://doi.org/10.1146/annurev-cellbio-101011-155807.
23. Taylor TH, Gitlin SA, Patrick JL, Crain JL, Wilson JM, Griffin DK. The origin, mechanisms, incidence and clinical consequences of chromosomal mosaicism in humans. Hum Reprod Update. 2014;20:571–81. https://doi.org/10.1093/humupd/dmu016.
24.• Yurov YB, Iourov IY, Vorsanova SG, Liehr T, Kolotii AD, Kutsev SI, et al. Aneuploidy and confined chromosomal mosaicism in the developing human brain. PLoS One. 2007;2:e558. https://doi.org/10.1371/journal.pone.0000558 **Provides the unique data on chromosomal mosaicism and chromosome instability hallmarking the human developing brain.**
25. Yurov YB, Iourov IY, Monakhov VV, Soloviev IV, Vostrikov VM, Vorsanova SG. The variation of aneuploidy frequency in the developing and adult human brain revealed by an interphase FISH study. J Histochem Cytochem. 2005;53:385–90. https://doi.org/10.1369/jhc.4A6430.2005.
26. Iourov IY, Soloviev IV, Vorsanova SG, Monakhov VV, Yurov YB. An approach for quantitative assessment of fluorescence in situ hybridization (FISH) signals for applied human molecular cytogenetics. J Histochem Cytochem. 2016;53:401–8. https://doi.org/10.1369/jhc.4A6419.2005.
27. Iourov IY. Quantitative fluorescence in situ hybridization (QFISH). Methods Mol Biol. 2017;1541:143–9. https://doi.org/10.1007/978-1-4939-6703-2_13.
28. Iourov IY, Liehr T, Vorsanova SG, Yurov YB. Interphase chromosome-specific multicolor banding (ICS-MCB): a new tool for analysis of interphase chromosomes in their integrity. Biomol Eng. 2007;24:415–7. https://doi.org/10.1016/j.bioeng.2007.05.003.
29.• Iourov IY, Vorsanova SG, Liehr T, Kolotii AD, Yurov YB. Increased chromosome instability dramatically disrupts neural genome integrity and mediates cerebellar degeneration in the ataxia-telangiectasia brain. Hum Mol Genet. 2009;18:2656–69. https://doi.org/10.1093/hmg/ddp207 **Provides direct evidences that neurodegeneration can be mediated by chromosome instability and somatic aneuploidy whereas these phenomena are generally accepted to hallmark cancer.**
30.• Iourov IY, Vorsanova SG, Liehr T, Yurov YB. Aneuploidy in the normal, Alzheimer's disease and ataxia-telangiectasia brain: differential expression and pathological meaning. Neurobiol Dis. 2009;34:212–20. https://doi.org/10.1016/j.nbd.2009.01.003 **Provides direct evidences that neurodegeneration can be mediated by chromosome instability and somatic aneuploidy whereas these phenomena are generally accepted to hallmark cancer.**
31. Iourov IY, Liehr T, Vorsanova SG, Kolotii AD, Yurov YB. Visualization of interphase chromosomes in postmitotic cells of the human brain by multicolour banding (MCB). Chromosom Res. 2006;14:223–9. https://doi.org/10.1007/s10577-006-1037-6.
32. Yurov YB, Iourov IY, Vorsanova SG, Demidova IA, Kravetz VS, Beresheva AK, et al. The schizophrenia brain exhibits low-level aneuploidy involving chromosome 1. Schizophr Res. 2008;98:139–47. https://doi.org/10.1016/j.schres.2007.07.035.
33. Yurov YB, Vorsanova SG, Demidova IA, Kravets VS, Vostrikov VM, Soloviev IV, et al. Genomic instability in the brain: chromosomal mosaicism in schizophrenia. Zh Nevrol Psikhiatr Im S S Korsakova. 2016;116(11):86–91. https://doi.org/10.17116/jnevro201611611186-91.
34. Yurov YB, Vorsanova SG, Demidova IA, Kolotii AD, Soloviev IV, Iourov IY. Mosaic brain aneuploidy in mental illnesses: an association of low-level post-zygotic aneuploidy with schizophrenia and comorbid psychiatric disorders. Curr Genomics. 2018;19:163–72. https://doi.org/10.2174/1389202918666170717154340.
35. Yurov YB, Vorsanova SG, Liehr T, Kolotii AD, Iourov IY. X chromosome aneuploidy in the Alzheimer's disease brain. Mol Cytogenet. 2014;7:20. https://doi.org/10.1186/1755-8166-7-20.
36. Mosch B, Morawski M, Mittag A, Lenz D, Tarnok A, Arendt T. Aneuploidy and DNA replication in the normal human brain and Alzheimer's disease. J Neurosci. 2007;27(26):6859–67. https://doi.org/10.1523/JNEUROSCI.0379-07.2007.
37.• Fischer HG, Morawski M, Brückner MK, Mittag A, Tarnok A, Arendt T. Changes in neuronal DNA content variation in the human brain during aging. Aging Cel. 2012;11:628–33. https://doi.org/10.1111/j.1474-9726.2012.00826.x **Demonstrates that aneuploidy rates can vary with age in the human brain.**
38. Arendt T, Mosch B, Morawski M. Neuronal aneuploidy in health and disease: a cytomic approach to understand the molecular individuality of neurons. Int J Mol Sci. 2009;10:1609–27. https://doi.org/10.3390/ijms10041609.
39. Westra JW, Rivera RR, Bushman DM, Yung YC, Peterson SE, Barral S, et al. Neuronal DNA content variation (DCV) with regional and individual differences in the human brain. J Comp Neurol. 2010;518:3981–4000. https://doi.org/10.1002/cne.22436.
40. Mokretar K, Pease D, Taanman JW, Soenmez A, Ejaz A, Lashley T, et al. Somatic copy number gains of α-synuclein (*SNCA*) in Parkinson's disease and multiple system atrophy brains. Brain. 2018;141:2419–31. https://doi.org/10.1093/brain/awy157.
41. Villela D, Suemoto CK, Leite R, Pasqualucci CA, Grinberg LT, Pearson P, et al. Increased DNA copy number variation mosaicism in elderly human brain. Neural Plast. 2018;2018:2406170–9. https://doi.org/10.1155/2018/2406170.
42.• McConnell MJ, Lindberg MR, Brennand KJ, Piper JC, Voet T, Cowing-Zitron C, et al. Mosaic copy number variation in human neurons. Science. 2013;342:632–7. https://doi.org/10.1126/science.1243472 **Is one of the most relevant reports on high-resolution genome analysis of individual human neurons using state-of-the-art sequencing techniques.**
43.• Knouse KA, Wu J, Whittaker CA, Amon A. Single cell sequencing reveals low levels of aneuploidy across mammalian tissues. Proc Natl Acad Sci U S A. 2014;111:13409–14. https://doi.org/10.1073/pnas.1415287111 **Is one of the most relevant reports on high-resolution genome analysis of individual human neurons using state-of-the-art sequencing techniques.**
44.• van den Bos H, Spierings DC, Taudt AS, Bakker B, Porubský D, Falconer E, et al. Single-cell whole genome sequencing reveals no evidence for common aneuploidy in normal and Alzheimer's disease neurons. Genome Biol. 2016;17:116. https://doi.org/10.1186/s13059-016-0976-2 **Is one of the most relevant reports on high-resolution genome analysis of individual human neurons using state-of-the-art sequencing techniques.**
45. Pfisterer U, Khodosevich K. Neuronal survival in the brain: neuron type-specific mechanisms. Cell Death Dis. 2017;8:e2643. https://doi.org/10.1038/cddis.2017.64.
46. Sheltzer JM, Amon A. The aneuploidy paradox: costs and benefits of an incorrect karyotype. Trends Genet. 2011;27:446–53. https://doi.org/10.1016/j.tig.2011.07.003.
47. Oromendia AB, Amon A. Aneuploidy: implications for protein homeostasis and disease. Dis Model Mech. 2014;7:15–20. https://doi.org/10.1242/dmm.013391.

48. Dürrbaum M, Storchová Z. Effects of aneuploidy on gene expression: implications for cancer. FEBS J 201. 2016;283:791–802. https://doi.org/10.1111/febs.13591.
49. Iourov IY, Vorsanova SG, Yurov YB. Interphase chromosomes of the human brain: the biological and clinical meaning of neural aneuploidy. In: Yurov YB, Vorsanova SG, Iourov IY, editors. Human interphase chromosomes: biomedical aspects. New York: Springer; 2013. https://doi.org/10.1007/978-1-4614-6558-4_4.
50. Heng HH, Bremer SW, Stevens JB, Horne SD, Liu G, Abdallah BY, et al. Chromosomal instability (CIN): what it is and why it is crucial to cancer evolution. Cancer Metastasis Rev. 2013;32:325–40. https://doi.org/10.1007/s10555-013-9427-7.
51. Valind A, Jin Y, Gisselsson D. Elevated tolerance to aneuploidy in cancer cells: estimating the fitness effects of chromosome number alterations by *in silico* modeling of somatic genome evolution. PLoS One. 2013;8:e70445. https://doi.org/10.1371/journal.pone.0070445.
52. Tanaka K, Hirota T. Chromosomal instability: a common feature and a therapeutic target of cancer. Biochim Biophys Acta. 2016;1866:64–75. https://doi.org/10.1016/j.bbcan.2016.06.002.
53. Iourov IY, Vorsanova SG, Yurov YB. Developmental neural chromosome instability as a possible cause of childhood brain cancers. Med Hypotheses. 2009;72:615–6. https://doi.org/10.1016/j.mehy.2008.12.003.
54.• Kingsbury MA, Friedman B, McConnell MJ, Rehen SK, Yang AH, Kaushal D, et al. Aneuploid neurons are functionally active and integrated into brain circuitry. Proc Natl Acad Sci U S A. 2005;102:6143–7. https://doi.org/10.1073/pnas.0408171102 **Demonstrates that abnormal (aneuploid) neurons are an integral part of the mammalian nervous system.**
55. Devalle S, Sartore RC, Paulsen BS, Borges HL, Martins RA, Rehen SK. Implications of aneuploidy for stem cell biology and brain therapeutics. Front Cell Neurosci. 2012;6(36). https://doi.org/10.3389/fncel.2012.00036.
56. Dumanski JP, Piotrowski A. Structural genetic variation in the context of somatic mosaicism. Methods Mol Biol. 2012;838:249–72. https://doi.org/10.1007/978-1-61779-507-7_12.
57. Paquola ACM, Erwin JA, Gage FH. Insights into the role of somatic mosaicism in the brain. Curr Opin Syst Biol. 2017;1:90–4. https://doi.org/10.1016/j.coisb.2016.12.004.
58. Rosenkrantz JL, Carbone L. Investigating somatic aneuploidy in the brain: why we need a new model. Chromosoma. 2017;126:337–50. https://doi.org/10.1007/s00412-016-0615-4.
59. Vorsanova SG, Yurov YB, Soloviev IV, Iourov IY. Molecular cytogenetic diagnosis and somatic genome variations. Curr Genomics. 2010;11:440–6. https://doi.org/10.2174/138920210793176010.
60. Yurov YB, Vorsanova SG, Soloviev IV, Ratnikov AM, Iourov IY. FISH-based assays for detecting genomic (chromosomal) mosaicism in human brain cells. Neuromethods. 2017;131:27–41. https://doi.org/10.1007/978-1-4939-7280-7_2.
61. Iourov IY, Vorsanova SG, Pellestor F, Yurov YB. Brain tissue preparations for chromosomal PRINS labeling. Methods Mol Biol. 2006;334:123–32. https://doi.org/10.1385/1-59745-068-5:123.
62. Andriani GA, Vijg J, Montagna C. Mechanisms and consequences of aneuploidy and chromosome instability in the aging brain. Mech Ageing Dev. 2017;161:19–36. https://doi.org/10.1016/j.mad.2016.03.007.
63. Leija-Salazar M, Piette C, Proukakis C. Review: somatic mutations in neurodegeneration. Neuropathol Appl Neurobiol. 2018;44:267–85. https://doi.org/10.1111/nan.12465.
64.• Yurov YB, Vostrikov VM, Vorsanova SG, Monakhov VV, Iourov IY. Multicolor fluorescent in situ hybridization on post-mortem brain in schizophrenia as an approach for identification of low-level chromosomal aneuploidy in neuropsychiatric diseases. Brain and Development. 2001;23(Suppl 1):S186–90. https://doi.org/10.1016/S0387-7604(01)00363-1 **The first study in the field of human molecular neurocytogenetics.**
65. Bajic V, Spremo-Potparevic B, Zivkovic L, Isenovic ER, Arendt T. Cohesion and the aneuploid phenotype in Alzheimer's disease: a tale of genome instability. Neurosci Biobehav Rev. 2015;55:365–74. https://doi.org/10.1016/j.neubiorev.2015.05.010.
66. Yurov YB, Vorsanova SG, Iourov IY, Demidova IA, Beresheva AK, Kravetz VS, et al. Unexplained autism is frequently associated with low-level mosaic aneuploidy. J Med Genet. 2007;44:521–5. https://doi.org/10.1136/jmg.2007.049312.
67. Vorsanova SG, Yurov IY, Demidova IA, Voinova-Ulas VY, Kravets VS, Solov'ev IV, et al. Variability in the heterochromatin regions of the chromosomes and chromosomal anomalies in children with autism: identification of genetic markers of autistic spectrum disorders. Neurosci Behav Physiol. 2007;37(6):553–8. https://doi.org/10.1007/s11055-007-0052-1.
68. Vorsanova SG, Voinova VY, Yurov IY, Kurinnaya OS, Demidova IA, Yurov YB. Cytogenetic, molecular-cytogenetic, and clinical-genealogical studies of the mothers of children with autism: a search for familial genetic markers for autistic disorders. Neurosci Behav Physiol. 2010;40(7):745–56. https://doi.org/10.1007/s11055-010-9321-5.
69. Dou Y, Yang X, Li Z, Wang S, Zhang Z, Ye AY, et al. Postzygotic single-nucleotide mosaicisms contribute to the etiology of autism spectrum disorder and autistic traits and the origin of mutations. Hum Mutat. 2017;38:1002–13. https://doi.org/10.1002/humu.23255.
70. Iourov I, Vorsanova S, Liehr T, Zelenova M, Kurinnaia O, Vasin K, Yurov Y. Chromothripsis as a mechanism driving genomic instability mediating brain diseases. Mol Cytogenet 2017:10(Suppl 1):20(O2). https://doi.org/10.1186/s13039-017-0319-3.
71. Kim J, Shin JY, Kim JI, Seo JS, Webster MJ, Lee D, et al. Somatic deletions implicated in functional diversity of brain cells of individuals with schizophrenia and unaffected controls. Sci Rep. 2014;4(3807). https://doi.org/10.1038/srep03807.
72. Sakai M, Watanabe Y, Someya T, Araki K, Shibuya M, Niizato K, et al. Assessment of copy number variations in the brain genome of schizophrenia patients. Mol Cytogenet. 2015;8(46):46. https://doi.org/10.1186/s13039-015-0144-5.
73. Arendt T, Brückner MK, Lösche A. Regional mosaic genomic heterogeneity in the elderly and in Alzheimer's disease as a correlate of neuronal vulnerability. Acta Neuropathol. 2015;130:501–10. https://doi.org/10.1007/s00401-015-1465-5.
74.• Arendt T, Brückner MK, Mosch B, Lösche A. Selective cell death of hyperploid neurons in Alzheimer's disease. Am J Pathol. 2010;177:15–20. https://doi.org/10.2353/ajpath.2010.090955 **Shows that neuronal aneuploidy is able to cause selective cell death.**
75. Potter H, Granic A, Caneus J. Role of trisomy 21 mosaicism in sporadic and familial Alzheimer's disease. Curr Alzheimer Res. 2016;13:7–17. https://doi.org/10.2174/1567205013011512071006l6.
76. Granic A, Potter H. Mitotic spindle defects and chromosome mis-segregation induced by LDL/cholesterol-implications for Niemann-Pick C1, Alzheimer's disease, and atherosclerosis. PLoS One. 2013;8:e60718. https://doi.org/10.1371/journal.pone.0060718.
77. Bushman DM, Kaeser GE, Siddoway B, Westra JW, Rivera RR, Rehen SK, et al. Genomic mosaicism with increased amyloid precursor protein (*APP*) gene copy number in single neurons from sporadic Alzheimer's disease brains. elife. 2015;4:e05116. https://doi.org/10.7554/eLife.05116.
78. Caneus J, Granic A, Rademakers R, Dickson DW, Coughlan CM, Chial HJ, et al. Mitotic defects lead to neuronal aneuploidy and

apoptosis in frontotemporal lobar degeneration caused by *MAPT* mutations. Mol Biol Cell. 2018;29:575–86. https://doi.org/10.1091/mbc.E17-01-0031.

79.• Yang Y, Shepherd C, Halliday G. Aneuploidy in Lewy body diseases. Neurobiol Aging. 2015;36:1253–60. https://doi.org/10.1016/j.neurobiolaging.2014.12.016 **Reports on associations between aneuploidy and Lewy body diseases.**

80. Shepherd CE, Yang Y, Halliday GM. Region- and cell-specific aneuploidy in brain aging and neurodegeneration. Neuroscience. 2018;374:326–34. https://doi.org/10.1016/j.neuroscience.2018.01.050.

81. Hochstenbach R, Buizer-Voskamp JE, Vorstman JA, Ophoff RA. Genome arrays for the detection of copy number variations in idiopathic mental retardation, idiopathic generalized epilepsy and neuropsychiatric disorders: lessons for diagnostic workflow and research. Cytogenet Genome Res. 2011;135:174–202. https://doi.org/10.1159/000332928.

82. Foley C, Corvin A, Nakagome S. Genetics of schizophrenia: ready to translate? Curr Psychiatry Rep. 2017;19(61):61. https://doi.org/10.1007/s11920-017-0807-5.

83. Loomes R, Hull L, Mandy WPL. What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. J Am Acad Child Adolesc Psychiatry. 2017;56(6):466–74. https://doi.org/10.1016/j.jaac.2017.03.013.

84. Iourov IY, Yurov YB, Vorsanova SG. Mosaic X chromosome aneuploidy can help to explain the male-to-female ratio in autism. Med Hypotheses. 2008;70:456. https://doi.org/10.1016/j.mehy.2007.05.037.

85. Rivet TT, Matson JL. Gender differences in core symptomatology in autism spectrum disorders across the lifespan. J Dev Phys Dis. 2011;23:399–420. https://doi.org/10.1007/s10882-011-9235-3.

86. Faggioli F, Vijg J, Montagna C. Chromosomal aneuploidy in the aging brain. Mech Ageing Dev. 2011;132:429–36. https://doi.org/10.1016/j.mad.2011.04.008.

87. Iourov IY, Vorsanova SG, Yurov YB. Genomic landscape of the Alzheimer's disease brain: chromosome instability — aneuploidy, but not tetraploidy —mediates neurodegeneration. Neurodegener Dis. 2011, 8:35–7. https://doi.org/10.1159/000315398.

88. Westra JW, Barral S, Chun J. A reevaluation of tetraploidy in the Alzheimer's disease brain. Neurodegener Dis. 2009;6:221–9. https://doi.org/10.1159/000236901.

89. Yurov YB, Vorsanova SG, Iourov IY. The DNA replication stress hypothesis of Alzheimer's disease. ScientificWorldJournal. 2011;11:2602–12. https://doi.org/10.1100/2011/625690.

90. Rothblum-Oviatt C, Wright J, Lefton-Greif MA, McGrath-Morrow SA, Crawford TO, Lederman HM. Ataxia telangiectasia: a review. Orphanet J Rare Dis. 2016;11(159):159. https://doi.org/10.1186/s13023-016-0543-7.

91. Iourov IY, Vorsanova SG, Yurov YB. Ataxia telangiectasia paradox can be explained by chromosome instability at the subtissue level. Med Hypotheses. 2007;68:716. https://doi.org/10.1016/j.mehy.2006.09.021.

92. Yurov YB, Iourov IY, Vorsanova SG. Neurodegeneration mediated by chromosome instability suggests changes in strategy for therapy development in ataxia-telangiectasia. Med Hypotheses. 2009;73:1075–6. https://doi.org/10.1016/j.mehy.2009.07.030.

93. Coppedè F, Migliore L. DNA damage in neurodegenerative diseases. Mutat Res. 2015;776:84–97. https://doi.org/10.1016/j.mrfmmm.2014.11.010.

94. Kennedy SR, Loeb LA, Herr AJ. Somatic mutations in aging, cancer and neurodegeneration. Mech Ageing Dev. 2012;133:118–26. https://doi.org/10.1016/j.mad.2011.10.009.

95. Yurov YB, Vorsanova SG, Iourov IY. GIN'n'CIN hypothesis of brain aging: deciphering the role of somatic genetic instabilities and neural aneuploidy during ontogeny. Mol Cytogenet. 2009;2:23. https://doi.org/10.1186/1755-8166-2-23.

96. Arendt T, Stieler J, Ueberham U. Is sporadic Alzheimer's disease a developmental disorder? J Neurochem. 2017;143:396–408. https://doi.org/10.1111/jnc.14036.

97. Chow HM, Herrup K. Genomic integrity and the ageing brain. Nat Rev Neurosci. 2015;16:672–84. https://doi.org/10.1038/nrn4020.

98. Iourov IY, Vorsanova SG, Yurov YB. Somatic cell genomics of brain disorders: a new opportunity to clarify genetic-environmental interactions. Cytogenet Genome Res. 2013;139:181–8. https://doi.org/10.1159/000347053.

99. Iourov IY, Vorsanova SG, Zelenova MA, Korostelev SA, Yurov YB. Genomic copy number variation affecting genes involved in the cell cycle pathway: implications for somatic mosaicism. Int J Genomics. 2015;2015:757680–7. https://doi.org/10.1155/2015/757680.

100. Vorsanova SG, Yurov YB, Iourov IY. Neurogenomic pathway of autism spectrum disorders: linking germline and somatic mutations to genetic-environmental interactions. Curr Bioinforma. 2017;12:19–26. https://doi.org/10.2174/1574893611666160606164849.

101. Bennett RJ, Forche A, Berman J. Rapid mechanisms for generating genome diversity: whole ploidy shifts, aneuploidy, and loss of heterozygosity. Cold Spring Harb Perspect Med. 2014;4:a019604. https://doi.org/10.1101/cshperspect.a019604.

102. Misteli T. Higher-order genome organization in human disease. Cold Spring Harb Perspect Biol. 2010;2:a000794. https://doi.org/10.1101/cshperspect.a000794.

103. Iourov IY. To see an interphase chromosome or: how a disease can be associated with specific nuclear genome organization. BioDiscovery. 2012;4(5). https://doi.org/10.7750/BioDiscovery.2012.4.5.

104. Rajarajan P, Gil SE, Brennand KJ, Akbarian S. Spatial genome organization and cognition. Nat Rev Neurosci. 2016;17:681–91. https://doi.org/10.1038/nrn.2016.124.

105. Iourov IY, Vorsanova SG, Liehr T, Yurov YB. Mosaike im Gehirn des Menschen. Med Genet. 2014;26:342–5. https://doi.org/10.1007/s11825-014-0010-6.

106. Vorsanova SG, Zelenova MA, Yurov YB, Iourov IY. Behavioral variability and somatic mosaicism: a cytogenomic hypothesis. Curr Genomics. 2018;19:158–62. https://doi.org/10.2174/1389202918666170719165339.