

REVIEW

Open Access



# Somatic mosaicism in the diseased brain

Ivan Y. Iourov<sup>1,2,3\*</sup>, Svetlana G. Vorsanova<sup>1,2</sup>, Oxana S. Kurinnaia<sup>1,2</sup>, Sergei I. Kutsev<sup>4</sup> and Yuri B. Yurov<sup>1,2</sup>

## Abstract

It is hard to believe that all the cells of a human brain share identical genomes. Indeed, single cell genetic studies have demonstrated intercellular genomic variability in the normal and diseased brain. Moreover, there is a growing amount of evidence on the contribution of somatic mosaicism (the presence of genetically different cell populations in the same individual/tissue) to the etiology of brain diseases. However, brain-specific genomic variations are generally overlooked during the research of genetic defects associated with a brain disease. Accordingly, a review of brain-specific somatic mosaicism in disease context seems to be required. Here, we overview gene mutations, copy number variations and chromosome abnormalities (aneuploidy, deletions, duplications and supernumerary rearranged chromosomes) detected in the neural/neuronal cells of the diseased brain. Additionally, chromosome instability in non-cancerous brain diseases is addressed. Finally, theoretical analysis of possible mechanisms for neurodevelopmental and neurodegenerative disorders indicates that a genetic background for formation of somatic (chromosomal) mosaicism in the brain is likely to exist. In total, somatic mosaicism affecting the central nervous system seems to be a mechanism of brain diseases.

**Keywords** Brain, Somatic mosaicism, Aneuploidy, Copy number variations, Gene mutations, Genome instability, Chromosome instability

## Introduction

The human brain is a highly complex system encompassing ~100 billion neurons, up to  $10^{12}$  glial cells and 5,000–200,000 synapses per neuron. Taking into account these astronomical amounts, neuronal and glial cells are unlikely to possess identical genomes [1, 2]. Accordingly, it has been proposed that somatic mosaicism (the presence of genetically (genomically) different cell

populations in the same individual or tissue) in the brain may be a mechanism for neuronal variability in health and disease [3–7]. Somatic mosaicism encompasses all types of intercellular genetic variations. Somatic chromosomal mosaicism (the presence of cell population differing with respect to their chromosome complements) is one of the commonest types of somatic mosaicism. Single gene sequence variations (mutations), copy number variations (CNVs) and retrotransposition of transposable elements also represent common types of genetic variation involved in somatic mosaicism [8–10]. Finally, chromosomal instability (increased rates of non-specific chromosome abnormalities in a cell population) may be an underlying mechanism for the development of the genomically mosaic brain [6, 9, 11–13]. Generally, it is proposed that chromosomal instability and increased rates of somatic mosaicism (i.e. higher than in control brain samples or >1–12% of genomically abnormal brain cells) are likely to cause brain disorders [14–18].

\*Correspondence:

Ivan Y. Iourov  
ivan.iourov@gmail.com

<sup>1</sup>Yurov's Laboratory of Molecular Genetics and Cytogenomics of the Brain, Mental Health Research Center, Moscow, Russia

<sup>2</sup>Vorsanova's Laboratory of Molecular Cytogenetics of Neuropsychiatric Diseases, Veltischev Research and Clinical Institute for Pediatrics and Pediatric Surgery of the Pirogov Russian National Research Medical University of the Russian Ministry of Health, Moscow, Russia

<sup>3</sup>Department of Medical Biological Disciplines, Belgorod State University, Belgorod, Russia

<sup>4</sup>Research Centre for Medical Genetics, Moscow, Russia



© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

During the last two decades, a large amount of data generated by genetic studies of brain cells has been reported. Consequently, somatic mosaicism has been associated with neurodegenerative diseases (e.g. Alzheimer's disease), autism, epilepsy, schizophrenia, and monogenic intellectual disability [3, 5, 9, 11, 12, 15–17, 19–29]. Here, we overview data on somatic mosaicism (from single nucleotide variants to aneuploidy, or losses/gains of whole chromosomes) in the diseased brain.

### Somatic mosaicism in brain diseases

The development of molecular cytogenetic techniques for studying human interphase chromosomes at any stage of the cell cycle and at molecular resolutions has provided an opportunity for uncovering somatic chromosomal mosaicism in the normal and diseased brain [30–33]. In parallel, single cell analysis using whole-genome sequencing has allowed the assessment of genomic variability in the normal and diseased brain [34–39]. Using similar advanced technologies for whole-genome analysis, CNVs confined to the diseased brain have been found [36–38]. **Schizophrenia:** individual cases of schizophrenia have been shown to be associated with aneuploidy and structural chromosomal imbalances in the diseased brain [3, 40–43]. **Neurodegenerative diseases:** Alzheimer's disease cases have been associated with brain-specific aneuploidy [12, 26, 28, 44–47]. Furthermore, chromosome instability manifested as aneuploidy or structural chromosomal abnormalities has been found to mediate neurodegeneration in several devastating brain diseases [12, 28, 45–51]. Somatic mosaicism for single gene mutations (i.e. single nucleotide variants with a proven pathogenic effect) has been associated with Alzheimer's disease [52, 54].

Single gene mutations were also found in individual cases of **autism** [13] and **epilepsy** [24, 27]. Mosaic genetic changes of chromosome X affecting the brain have been hypothesized to produce preponderance of males among individuals with neurodevelopmental diseases (e.g. autism) [54, 55]. Somatic mosaicism generated by LINE-1 retrotransposition [9] has been shown to be involved in the pathogenesis of **schizophrenia** and monogenic **intellectual disability** [56].

Dynamic changes of mosaicism rates (i.e. ontogenetic changes of proportions between normal and abnormal cells) affecting the human brain have been also suggested to modulate human behavior [57–59]. Thus, chromosome instability (chromosome condensation defects or alterations to chromosome structure/morphology without microscopically visible changes of chromosomal DNA) has been shown involved in gulf war illness pathogenesis [60]. Additionally, changing of chromosomal/genomic mosaicism rates has been hypothesized to be involved in behavior variability (e.g. worsening or improvement of

behavioral abnormalities; sporadic occurrence or cease of behavioral abnormalities) in health and neurobehavioral diseases [59]. Table 1 summarizes available data on somatic mosaicism and genome/chromosome instability manifesting as chromosome abnormalities, CNVs, LINE-1 retrotransposition and single gene mutations detected in the diseased brain [3, 15, 26, 35, 40–47, 52, 53, 61–94].

Summarizing data on somatic mosaicism in the diseased brain depicted by Table 1 allows to conclude: (1) somatic mosaicism seems to be an appreciable source for human brain morbidity; (2) spectrum of mosaicism types is truly wide (almost all types of genetic mosaicism are detectable in the diseased brain); (3) pathways affected by the mutated genes are disease-specific and might be intriguing drug targets.

### Consequences and origins of somatic mosaicism in the brain

It is important to note that somatic mosaicism is detectable in biopsies of healthy individuals [57, 95, 96]. Analogously, from 0.5 to 12% of genomically abnormal cells are consistently detected in the unaffected brain [15, 17, 19, 23, 30, 34, 97]. However, clinical cohorts (including cohorts of individuals with neuropsychiatric disorders) generally exhibit high rates of somatic mosaicism, which seems to be involved in the pathogenesis [23, 57, 95, 98–100]. Nonetheless, despite debates regarding mosaicism rates in the normal brain, it is generally accepted that these are likely to be higher in the diseased brain [4, 5, 15, 23, 101, 102]. Furthermore, genomically abnormal (aneuploid) neurons have been demonstrated to be functionally active and integrated into brain circuitry [103]. On the other hand, the Alzheimer's disease brain has not demonstrated increased rates of somatic mosaicism in a case-control study [104]. Still, there are a number of studies demonstrating mosaic mutations (single nucleotide variants and CNVs) of genes mutated in familial Alzheimer's disease in the diseased brain [52, 66]. Taking into account the complexity of the disease, one can suggest that genome/chromosome instability and somatic mosaicism may be a mechanism for a proportion of cases [23, 28, 48]. Additionally, somatic mosaicism and genome instability have been systematically integrated into molecular and cellular pathways of neurodegenerative and neuropsychiatric disorders [12, 26, 28, 29, 38, 105–109]. Bioinformatics analyses and functional genomics studies have indicated that numerous mosaic (brain-specific) gene mutations are pathogenic [24, 39, 63, 92, 107]. Since chromosomal instability, structural variations and aneuploidy significantly affect cellular homeostasis, it has been systematically proposed that somatic mosaicism in the brain is able to cause central nervous system dysfunction or progressive neuronal loss [4, 5, 16, 19, 26, 45, 110].

**Table 1** Spectrum of somatic mosaicism detected in neural cells of the diseased brain

Disease/Disorder	Type of genomic change	Brief description	Chromosome	Locus	Gene	Refs
Alzheimer's disease	Single nucleotide variants	Low-level mosaic single nucleotide variants	1	1q42.13	<i>PS2</i>	[53]
			14	14q24.2	<i>PS1</i>	
			17	17q21.31	<i>MAPT</i>	
			21	21q21.3	<i>APP</i>	
	Single nucleotide variants	Brain-specific single nucleotide variants	2	2q32.2	<i>COL3A1</i>	[61]
			4	4q31.3	<i>LRBA</i>	
	Single gene mutations	Single gene autosomal dominant variants	11	11q24.1	<i>SORL1</i>	[53]
	Single nucleotide variants	Single nucleotide variants in the temporal cortex	1	1q32.2	<i>CD55</i>	[62]
	Single nucleotide variants	Pathogenic somatic mutation leading to a loss-of-function mutation	19	19p13.2	<i>PIN1</i>	[63]
	Single gene mutations	Accumulating of mosaic somatic mutations in autism/intellectual disability genes	20	20q13.13	<i>ADNP</i>	[64]
	Nucleotide repeat expansion	Hexanucleotide repeat expansions	9	9p21.2	<i>C9orf72</i>	[65]
	CNVs	CNVs affecting ~10% of cells	NS*	NS	NS	[52]
	CNV (gain)	Single gene amplification	21	21q21.3	<i>APP</i>	[66]
	CNV (gain)	Single gene gain	12	12q13.12	<i>PRPH</i>	[65]
	DNA content variation	Increased rates of DNA content variation (variations of DNA content in a cell suggested to hallmark aneuploidy/polyploidy)	—	—	—	[47, 67]
	Aneuploidy	Increased rates of aneuploidy	17	—	—	[45, 67]
	Aneuploidy (trisomy/monosomy)	Chromosome-specific (numerical) instability	21	Whole chromosome	—	[15]
Aneuploidy (monosomy)	X chromosome loss (an aging marker)	X	Whole chromosome	—	[46]	
Aneuploidy (chromosome instability)	Chromosome missegregation and aneuploidy probably resulted from mutations in the <i>APP</i> , presenelin 1 and, probably, <i>NPC1</i>	21	—	—	re-viewed by [26]	
Amyotrophic lateral sclerosis (sporadic)	CNVs	Brain-specific CNVs	3	3p26.3p26.2	<i>CNTN4</i>	[68]
			8	8p23.2	<i>CSMD1</i>	
			22	22q11.22	<i>GGTLC2</i>	
Ataxia telangiectasia ( <i>ATM</i> mutations)	LINE-1 retrotransposition	Specific LINE-1 retrotransposition	—	—	—	[69]
	Aneuploidy (chromosome instability) and chromosome 14-specific instability (affecting exclusively this chromosome)	High rates of chromosome instability in degenerating areas of the brain suggested to have <i>ATM</i> mutations (aneuploidy, non-random chromosomal breaks, rearranged chromosomes)	1, 7, 11, 13, 14, 17, 18, 21, X, Y	Whole chromosomes	—	[15, 44]
Autism spectrum disorder	Single gene mutations	Recurrent deleterious mutations	2	2q24.3	<i>SCN1A</i>	[35]
			2	2q24.3	<i>SCN2A</i>	
			3	3p21.31	<i>SETD2</i>	
			6	6q25.3	<i>ARID1B</i>	
	LINE-1 retrotransposition	LINE-1 overexpression in the cerebellum	—	—	—	[70]

**Table 1 (continued)**

Disease/Disorder	Type of genomic change	Brief description	Chromosome	Locus	Gene	Refs
Focal Cortical Dysplasia	Single nucleotide variants	Missense mutations	9	9q34.13	<i>TSC1</i>	[71, 72]
			16	16p13.3	<i>TSC2</i>	
			1	1p36.22	<i>MTOR</i>	[73]
			22	22q12.2q12.3	<i>DEPDC5</i>	[74]
Focal cortical dysplasia, type II	Single nucleotide variants	Somatic doublet mutation	7	7q36.1	<i>RHEB</i>	[75]
Hemimegalen-cephaly	Single nucleotide variants	Missense mutations	1	1q43q44	<i>AKT3</i>	[71, 76]
			3	3q26.32	<i>PIK3CA</i>	
			14	14q32.33	<i>AKT1</i>	
	Single nucleotide variants	Missense mutations	1	1p36.22	<i>MTOR</i>	[73]
	Single nucleotide variants	"Double-hit" single nucleotide variants of two genes	1	1p36.22	<i>MTOR</i>	[77]
			9	9p22.1	<i>RPS6</i>	
Hypothalamic Hamartoma	Single nucleotide variants	Missense mutations	7	7p14.1	<i>GLI3</i>	[78, 79]
			X	Xp22.2	<i>OFD1</i>	
Frontotemporal lobar degeneration	Aneuploidy (trisomy)	Neuronal aneuploidy + apoptosis due to mitotic defects caused by <i>MAPT</i> mutations	12, 21	—	—	[80]
Huntington's disease	Nucleotide repeat expansion	Expansion of an unstable trinucleotide repeat (CAG)	4	4p16.3	<i>HTT</i>	[81]
Lewy body diseases	Aneuploidy (NS)	Increase in neuronal DNA content (probably aneuploidy)	—	—	—	[82]
Niemann-Pick disease, type C1 ( <i>NPC1</i> mutations)	Aneuploidy (trisomy)	Accumulation of (trisomic) cells with additional chromosome 21 in Niemann-Pick disease, type C1	21	—	—	[83]
Nonlesional focal epilepsy	Single gene mutations	Missense mutations, deletions (frameshift), insertions	X	Xp11.23	<i>SLC35A2</i>	[84]
Parkinson's disease	Single nucleotide variants	Questionable <i>SNCA</i> variants	4	4q22.1	<i>SNCA</i>	[85]
	CNV (gains)	Somatic <i>SNCA</i> gains in nigral dopaminergic neurons	4	4q22.1	<i>SNCA</i>	[86]
Rett syndrome ( <i>MECP2</i> mutations)	LINE-1 retrotransposition	Specific LINE-1 retrotransposition	—	—	—	[87]
Schizophrenia	Single nucleotide variants	NS	NS	NS	NS	[88]
	CNV (losses)	Somatic deletions	2	2q31.2	<i>PRKRA</i>	[42]
			5	5q35.2	<i>BOD1</i>	
			7	7p15.2	<i>CBX3</i>	
			4	4q35.2	NS	[43]
			6	6p11.2		
			7	7q11q12		
			11	11p15.4p15.5		
			15	15q11.2		
	LINE-1 retrotransposition	Increased LINE-1 "burden" and LINE-1 insertions in synapse or schizophrenia-related genes	—	—	—	[89, 90]
	Aneuploidy (trisomy)	Low-level mosaic trisomy	18, X	—	—	[3]
	Aneuploidy (trisomy/monosomy)	Low-level mosaic trisomy and monosomy	1	Whole chromosome	—	[40]
	Aneuploidy (trisomy/monosomy)	Increased rates of gonosomal aneuploidy	X, Y	—	—	[41]
Sturge-Weber syndrome (leptomeningeal angiomatosis)	Single nucleotide variants	Missense mutation (R183Q)	9	9q21.2	<i>GNAQ</i>	[91]

**Table 1 (continued)**

Disease/Disorder	Type of genomic change	Brief description	Chromosome	Locus	Gene	Refs
Subcortical band heterotopia ("double cortex" syndrome)	Single gene mutations	Mosaic gene mutations associated with the syndrome	17	17p13.3	<i>PA-FAH1B1 (LIS1)</i>	[92, 93]
Tuberous Sclerosis	Single nucleotide variants	Missense mutations	X	Xq23	<i>DCX</i>	
			16	16p13.3	<i>TSC2</i>	[94]

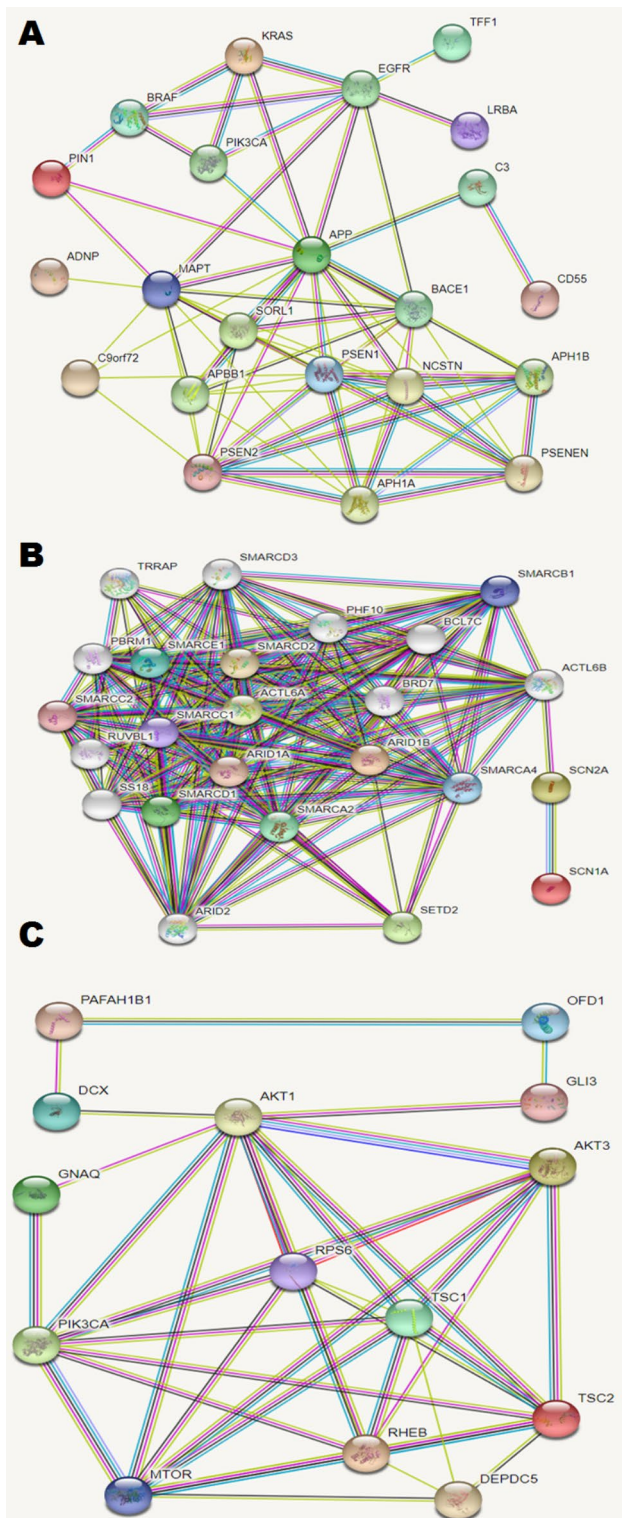
\* NS — non-specific;

However, there is an urgent need for forthcoming studies dedicated to functional consequences of somatic mosaicism in the brain.

A large part of human brain cells are generated during prenatal development without systematic/general renewal of neuronal cell populations after birth. Therefore, it is not surprising that the genetic landscape of the human brain is determined during early ontogeny stages [1, 23]. The developing human brain exhibiting high rates of chromosome instability and mosaicism manifested as aneuploidy [14, 16, 97]. Since these genetic variations are able to underlie neuronal cell death (for details see [110] and [111]) and a progressive decrease of cell numbers is observed in the developing brain during early ontogeny stages [1], it has been suggested that developmental chromosome instability and/or mosaicism underlying programmed cell death might be a regulation mechanism of cell numbers in the mammalian brain [14, 112]. Thus, alterations to pathways regulating programmed neuronal cell death might be responsible for the presence of abnormal cells in the postnatal brain [4, 22]. It is noteworthy that genomically abnormal neuronal cells are prone to cell death [110]. More precisely, aneuploid neurons selectively die in the diseased brain [45] and are susceptible to caspase-mediated death (e.g. apoptotic cell death) [110]. DNA damage in neurons may initiate apoptosis or produce a senescence-like state mediated by chromosome instability [113, 114], which may lead to cell death by another mechanism (e.g. mitotic catastrophe) [115]. Programmed neuronal cell death is a likely mechanism for neurodegeneration in aging-related brain diseases [45, 111, 115]. Furthermore, the genomic variations in the aged brain appear to underlie brain aging and aging-related brain deterioration [12, 25, 115–117]. Additionally, aging-related pathogenic processes in the Alzheimer's disease brain may be associated with X chromosome aneuploidy, a chromosomal hallmark of human aging [46, 117, 118]. A devastating consequence of alterations to programmed neuronal cell death may be the persistence of chromosome instability during early postnatal period, which is able to cause cancer in addition to non-cancerous brain diseases [119, 120]. Alternatively, the persistence of cell populations with altered genome is able to cause non-cancerous brain diseases [4, 5, 16, 37]. Thus, brain-specific somatic mosaicism is likely to result

from developmental genomic instability and its rate fluctuations throughout ontogeny in an appreciable proportion of brain disease cases.

Alzheimer's disease has long been associated with aberrant cell cycle (i.e. cell cycle re-entry, deregulation or endoreduplication) of neuronal cells [45, 47, 48, 121–124]. Mutations in the *APP* found in familial cases of Alzheimer's disease may also cause chromosome mis-segregation leading to aneuploidy [121]. Similarly, *MAPT* mutations associated with frontotemporal lobar degeneration have been shown to produce mitotic defects in neuronal cells resulting in chromosome instability or aneuploidy [80]. Cohesion defects have also been associated with chromosome instability/aneuploidy in the Alzheimer's disease brain [123]. Moreover, DNA replication stress [122] and genomic changes (CNVs) of genes implicated in the cell cycle pathway [125] are likely to be involved in molecular and cellular pathways to brain-specific somatic mosaicism (i.e. pathways of cell cycle regulation and mitotic checkpoint). It appears that these abnormal molecular and cellular processes leading to genome instability are similar to those observed in cancers [126, 127]. Oncogenic parallels are repeatedly noted in neurodegenerative diseases [28, 124]. However, "neurodegenerative" genomic instability originates from interactions between altered genome (mutational burden) and environment rather than from clonal evolution in cancers [28]. A recent study has shed light on a new formation mechanism of mosaicism for structural variations involving the *APP* gene in the Alzheimer's disease brain, i.e. somatic gene recombination in neurons [128]. Finally, a more likely pathway to somatic mosaicism and genome instability in the brain includes specific genomic/genetic burden and the genetic-environmental interactions [129, 130]. In total, it seems that genes mutated in familial cases of complex brain disorders are involved in pathways of cell cycle regulation, mitotic checkpoint, chromatin remodeling, signaling (important for cell metabolism, proliferation and survival). To test briefly possible relevance of these assumptions, one may take a look at interactomes of genes listed in Table 1. Figure 1 demonstrates interactomes of genes involved in brain-specific somatic mosaicism in Alzheimer's disease, autism and epileptic disorders. These diseases have been selected inasmuch as several genes have been repeatedly found mutated



**Fig. 1** Interactomes of genes involved in somatic genome variations affecting the diseased brain (see Table 1) generated by STRING v11 [151]: (A) Alzheimer's disease; (B) autism; (C) epileptic disorders

in the diseased brain. As one can see, these genes share same interactomic networks (apart from *COL3A1* and

*PRPH* in Alzheimer's disease). Moreover, elements of these interactomic networks are involved in a number of pathways, alterations to which might cause cellular genomes to become susceptible to the instability and to be dysregulated at the chromatin level. However, this is not the case for genes mutated in the schizophrenia brain (interactome cannot be generated). Unfortunately, studies aimed at analysis of genetic variation affecting genes of pathways implicated in maintaining genome stability, cell cycle regulation and programmed cell death are rare. Forthcoming studies of somatic genome variation in the brain are likely to be pathway-specific for unraveling the intrinsic causes of brain-specific mosaicism for diagnostic and therapeutic purposes [131].

### What is now and what is next?

Recent studies have additionally supported the idea that somatic mosaicism in the diseased brain may be a mechanism for neurodevelopmental and neurodegeneration disorders [132–134]. Furthermore, clinical (neurodevelopmental) cohorts repeatedly demonstrate high rates of somatic mosaicism [135–137], which may be seen as a mechanism for the disease or a target for therapeutic interventions [23, 138]. In this context, it is to mention an intriguing mechanism for brain-specific chromosome instability and/or aneuploidy termed chromohelkosis (chromosome ulceration or open wound), which results from the co-occurrence of non-mosaic and mosaic chromosome imbalances caused by a susceptibility to genome instability and a genomic rearrangement [139]. Therefore, as noticed previously [129], environmental interactions with changed genomes should not be left aside in studies dedicated to somatic cell genomics of brain disorders. To support this idea, one can refer to the ability of the notorious COVID-19 virus to produce aging-related genome/chromosome instability in the diseased brain [140]. Thus, therapeutic interventions based on analysis of brain-specific somatic mosaicism are to be developed taking into account genetic-environmental interactions.

Successful therapeutic interventions in brain disorders mediated by somatic mosaicism appear to require specific diagnostic approaches. Emerging technologies based on genome scanning techniques, molecular cytogenetic/cytogenomic methods and post-genomic bioinformatic approaches are likely to be the way for the success [131, 141–143]. Cytopostgenomics and systems cytogenomics seem to be the areas of cytogenetic research which would help to develop the approaches to uncover causes and consequences of somatic chromosomal mosaicism in the diseased brain [142, 143]. Analyzing available candidate processes or pathways for therapeutic interventions in brain disorders mediated by somatic mosaicism (e.g. DNA reparation, programmed cell death, neurodegeneration pathway) [144–146] gives an opportunity to suggest

that pathway-centric (cyto)genomic studies are likely to be the most promising. To this end, it is to note that modern molecular cytogenetic and genomic techniques are able to generate new data on the role of somatic mosaicism in the aging and diseased brain [147–150].

### Concluding remarks

Technological advances in sequencing resulted in an overuse of molecular (sequencing) methods comparing to molecular cytogenetic techniques. As a result, little attention is paid to molecular cytogenetic aspects of somatic mosaicism in the human brain. This review represents a unique overview of both molecular genetic and molecular cytogenetic (cytogenomic) data on brain-specific genomic variations at DNA, subchromosomal and chromosomal levels associated with a wide spectrum of non-cancerous brain diseases.

Regardless of a relatively small amount, studies dedicated to somatic mosaicism in the human brain have demonstrated a wide spectrum of genomic variations involved in neurological and psychiatric diseases. Brain-specific genome variations causing neurodegenerative and neuropsychiatric disorders produce several important tasks for current biomedicine. Firstly, the unavailability of tissues for premortem genomic analysis (apart from surgical biopsies) raises important diagnostic issues. Here, we have suggested that a kind of susceptibility of cellular genomes to become unstable (i.e. mutations of genes involved in molecular and cellular pathways to maintain genomic stability throughout cell cycle) appears to exist. Briefly, (i) in the developing human brain, chromosome instability and mosaicism/aneuploidy/CNVs have a high rate, which is, however, significantly diminished in the postnatal brain; (ii) alterations to pathways of genome stability maintenance, cell cycle regulation and programmed cell death should mediate the persistence or increase of genome instability (mosaicisms) rates in the brain; (iii) this persistence/increase affecting a proportion of brain cells may cause central nervous system dysfunction or neuronal loss (brain diseases).

Uncovering the susceptibility to brain-specific chromosome/genome instability might have diagnostic value. Moreover, these pathways to brain-specific genome instability and somatic mosaicism may be a drug target in brain diseases mediated by somatic mosaicism. Actually, pathogenic cascades of brain diseases involving somatic mosaicism and genome instability are suggested to be valuable drug targets. Furthermore, data on somatic mosaicism in surgical biopsies have already been considered useful for the therapeutic interventions. The exciting area of somatic cell genomics brings new insights into genetic (genomic) mechanisms of brain dysfunction, which are required for efficient molecular diagnosis and treatment of neurological and psychiatric illnesses.

### Acknowledgements

Our communication is dedicated to Dr. Ilia Soloviev.

### Author contributions

IYI, SGV and YBY developed the review idea and got funding. IYI wrote the manuscript. IYI, SGV, OSK, SIK and YBY made important contributions. All authors have read and approved the final manuscript.

### Funding

Authors are supported by the Government Assignment of the Russian Ministry of Science and Higher Education, Assignment no. AAAA-A19–119040490101–6 and by the Government Assignment of the Russian Ministry of Health, Assignment no. 121031000238–1.

### Data availability

Not applicable.

### Declarations

#### Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 20 September 2022 / Accepted: 7 October 2022

Published online: 21 October 2022

### References

1. Muotri AR, Gage FH. Generation of neuronal variability and complexity. *Nature*. 2006;441(7097):1087–93. <https://doi.org/10.1038/nature04959>.
2. Herculano-Houzel S. The human brain in numbers: a linearly scaled-up primate brain. *Front Hum Neurosci*. 2009;3:31. <https://doi.org/10.3389/neuro.09.031.2009>.
3. 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 Dev*. 2001;23(Suppl1):186–90. [https://doi.org/10.1016/s0387-7604\(01\)00363-1](https://doi.org/10.1016/s0387-7604(01)00363-1).
4. 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](https://doi.org/10.1016/S0074-7696(06)49003-3).
5. Kingsbury MA, Yung YC, Peterson SE, Westra JW, Chun J. Aneuploidy in the normal and diseased brain. *Cell Mol Life Sci*. 2006;63(22):2626–41. <https://doi.org/10.1007/s00018-006-6169-5>.
6. McConnell MJ, Moran JV, Abyzov A, Akbarian S, Bae T, Cortes-Ciriano I, Erwin JA, Fasching L, Flasch DA, Freed D, Ganz J, Jaffe AE, Kwan KY, Kwon M, Lodato MA, Mills RE, Paquola ACM, Rodin RE, Rosenbluh C, Sestan N, Sherman MA, Shin JH, Song S, Straub RE, Thorpe J, Weinberger DR, Urban AE, Zhou B, Gage FH, Lehner T, Senthil G, Walsh CA, Chess A, Courchesne E, Gleeson JG, Kidd JM, Park PJ, Pevsner J, Vaccarino FM. Brain Somatic Mosaicism Network. Intersection of diverse neuronal genomes and neuropsychiatric disease: The Brain Somatic Mosaicism Network. *Science*. 2017;356(6336):eaal1641. <https://doi.org/10.1126/science.aal1641>.
7. Jourdon A, Fasching L, Scuderi S, Abyzov A, Vaccarino FM. The role of somatic mosaicism in brain disease. *Curr Opin Genet Dev*. 2020;65:84–90. doi:<https://doi.org/10.1016/j.gde.2020.05.002>.
8. Iourov IY, Vorsanova SG, Yurov YB. Intercellular genomic (chromosomal) variations resulting in somatic mosaicism: mechanisms and consequences. *Curr Genomics*. 2006;7(7):435–46. <https://doi.org/10.2174/138920206779116756>.
9. Muotri AR, Chu VT, Marchetto MC, Deng W, Moran JV, Gage FH. Somatic mosaicism in neuronal precursor cells mediated by L1 retrotransposition. *Nature*. 2005;435(7044):903–10. <https://doi.org/10.1038/nature03663>.
10. Maury EA, Walsh CA. Somatic copy number variants in neuropsychiatric disorders. *Curr Opin Genet Dev*. 2021;68:9–17. <https://doi.org/10.1016/j.gde.2020.12.013>.
11. Bushman DM, Chun J. The genomically mosaic brain: aneuploidy and more in neural diversity and disease. *Semin Cell Dev Biol*. 2013;24(4):357–69. <https://doi.org/10.1016/j.semcdb.2013.02.003>.

12. Iourov IY, Yurov YB, Vorsanova SG, Kutsev SI. Chromosome instability, aging and brain diseases. *Cells*. 2021;10(5):1256. doi:<https://doi.org/10.3390/cells10051256>.
13. D’Gama AM, Walsh CA. Somatic mosaicism and neurodevelopmental disease. *Nat Neurosci*. 2018;21(11):1504–14. <https://doi.org/10.1038/s41593-018-0257-3>.
14. Yurov YB, Iourov IY, Vorsanova SG, Liehr T, Kolotii AD, Kutsev SI, Pellestor F, Beresheva AK, Demidova IA, Kravets VS, Monakhov VV, Soloviev IV. Aneuploidy and confined chromosomal mosaicism in the developing human brain. *PLoS ONE*. 2007;2(6):e558. <https://doi.org/10.1371/journal.pone.0000558>.
15. 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(2):212–20. <https://doi.org/10.1016/j.nbd.2009.01.003>.
16. Rohrbach S, April C, Kaper F, Rivera RR, Liu CS, Siddoway B, Chun J. Submegabase copy number variations arise during cerebral cortical neurogenesis as revealed by single-cell whole-genome sequencing. *Proc Natl Acad Sci U S A*. 2018;115(42):10804–9. <https://doi.org/10.1073/pnas.1812702115>.
17. Rohrbach S, Siddoway B, Liu CS, Chun J. Genomic mosaicism in the developing and adult brain. *Dev Neurobiol*. 2018;78(11):1026–48. <https://doi.org/10.1002/dneu.22626>.
18. Sekar S, Tomasini L, Proukakis C, Bae T, Manlove L, Jang Y, Scuderi S, Zhou B, Kalyva M, Amiri A, Mariani J, Sedlaczek FJ, Urban AE, Vaccarino FM, Abyzov A. Complex mosaic structural variations in human fetal brains. *Genome Res*. 2020;30(12):1695–704. <https://doi.org/10.1101/gr.262667.120>.
19. 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(4):1609–27. <https://doi.org/10.3390/ijms10041609>.
20. Iourov IY, Vorsanova SG, Yurov YB. Somatic genome variations in health and disease. *Curr Genomics*. 2010;11(6):387–96. <https://doi.org/10.2174/138920210793176065>.
21. Iourov IY, Vorsanova SG, Yurov YB. Single cell genomics of the brain: focus on neuronal diversity and neuropsychiatric diseases. *Curr Genomics*. 2012;13(6):477–88. <https://doi.org/10.2174/138920212802510439>.
22. Yurov YB, Vorsanova SG, Iourov IY. Human molecular neurocytogenetics. *Curr Genet Med Rep*. 2018;6:155–64. <https://doi.org/10.1007/s40142-018-0152-y>.
23. Iourov IY, Vorsanova SG, Yurov YB, Kutsev SI. Ontogenetic and pathogenetic views on somatic chromosomal mosaicism. *Genes (Basel)*. 2019;10(5):379. <https://doi.org/10.3390/genes10050379>.
24. Koh HY, Lee JH. Brain somatic mutations in epileptic disorders. *Mol Cells*. 2018;41(10):881–8. <https://doi.org/10.14348/molcells.2018.0247>.
25. Zhang L, Vijg J. Somatic mutagenesis in mammals and its implications for human disease and aging. *Annu Rev Genet*. 2018;52:397–419. <https://doi.org/10.1146/annurev-genet-120417-031501>.
26. Potter H, Chial HJ, Caneva J, Elos M, Elder N, Borysov S, Granic A. Chromosome instability and mosaic aneuploidy in neurodegenerative and neurodevelopmental disorders. *Front Genet*. 2019;10:1092. <https://doi.org/10.3389/fgene.2019.01092>.
27. Ye Z, McQuillan L, Poduri A, Green TE, Matsumoto N, Mefford HC, Scheffer IE, Berkovic SF, Hildebrand MS. Somatic mutation: the hidden genetics of brain malformations and focal epilepsies. *Epilepsy Res*. 2019;155:106161. <https://doi.org/10.1016/j.epilepsyres.2019.106161>.
28. Yurov YB, Vorsanova SG, Iourov IY. Chromosome instability in the neurodegenerating brain. *Front Genet*. 2019;10:892. <https://doi.org/10.3389/fgene.2019.00892>.
29. Kaeser G, Chun J. Brain cell somatic gene recombination and its phylogenetic foundations. *J Biol Chem*. 2020;295(36):12786–95. <https://doi.org/10.1074/jbc.REV120.009192>.
30. 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). *Chromosome Res*. 2006;14(3):223–9. <https://doi.org/10.1007/s10577-006-1037-6>.
31. Vorsanova SG, Yurov YB, Soloviev IV, Iourov IY. Molecular cytogenetic diagnosis and somatic genome variations. *Curr Genomics*. 2010;11(6):440–6. <https://doi.org/10.2174/138920210793176010>.
32. Yurov YB, Vorsanova SG, Iourov IY. Human Interphase Chromosomes: Biomedical Aspects. New York: Springer; 2013. <https://doi.org/10.1007/978-1-4614-6558-4>.
33. Hu Q, Maurais EG, Ly P. Cellular and genomic approaches for exploring structural chromosomal rearrangements. *Chromosome Res*. 2020;28(1):19–30. <https://doi.org/10.1007/s10577-020-09626-1>.
34. McConnell MJ, Lindberg MR, Brennand KJ, Piper JC, Voet T, Cowing-Zitron C, Shumilina S, Lasken RS, Vermeesch JR, Hall IM, Gage FH. Mosaic copy number variation in human neurons. *Science*. 2013;342(6158):632–7. <https://doi.org/10.1126/science.1243472>.
35. 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(37):13409–14. <https://doi.org/10.1073/pnas.1415287111>.
36. D’Gama AM, Pochareddy S, Li M, Jamuar SS, Reiff RE, Lam AN, Sestan N, Walsh CA. Targeted DNA sequencing from autism spectrum disorder brains implicates multiple genetic mechanisms. *Neuron*. 2015;88(5):910–7. <https://doi.org/10.1016/j.neuron.2015.11.009>.
37. 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>.
38. 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>.
39. Iourov IY, Vorsanova SG, Yurov YB. The variome concept: focus on CNVariome. *Mol Cytogenet*. 2019;12:52. <https://doi.org/10.1186/s13039-019-0467-8>.
40. Yurov YB, Iourov IY, Vorsanova SG, Demidova IA, Kravetz VS, Beresheva AK, Kolotii AD, Monakhov VV, Uranova NA, Vostrikov VM, Soloviev IV, Liehr T. The schizophrenia brain exhibits low-level aneuploidy involving chromosome 1. *Schizophr Res*. 2008;98(1–3):139–47. <https://doi.org/10.1016/j.schres.2007.07.035>.
41. 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>.
42. Kim J, Shin JY, Kim JI, Seo JS, Webster MJ, Lee D, Kim S. 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>.
43. Sakai M, Watanabe Y, Someya T, Araki K, Shibuya M, Niizato K, Oshima K, Kunii Y, Yabe H, Matsumoto J, Wada A, Hino M, Hashimoto T, Hishimoto A, Kitamura N, Iritani S, Shirakawa O, Maeda K, Miyashita A, Niwa S, Takahashi H, Kakita A, Kuwano R, Nawa H. Assessment of copy number variations in the brain genome of schizophrenia patients. *Mol Cytogenet*. 2015;8:46. <https://doi.org/10.1186/s13039-015-0144-5>.
44. 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(14):2656–69. <https://doi.org/10.1093/hmg/ddp207>.
45. Arendt T, Brückner MK, Mosch B, Lösche A. Selective cell death of hyperploid neurons in Alzheimer’s disease. *Am J Pathol*. 2010;177(1):15–20. <https://doi.org/10.2353/ajpath.2010.090955>.
46. Yurov YB, Vorsanova SG, Liehr T, Kolotii AD, Iourov IY. X chromosome aneuploidy in the Alzheimer’s disease brain. *Mol Cytogenet*. 2014;7(1):20. <https://doi.org/10.1186/1755-8166-7-20>.
47. 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(4):501–10. <https://doi.org/10.1007/s00401-015-1465-5>.
48. Arendt T, Stieler J, Ueberham U. Is sporadic Alzheimer’s disease a developmental disorder? *J Neurochem*. 2017;143(4):396–408. <https://doi.org/10.1111/jnc.14036>.
49. Andriani GA, Vijg J, Montagna C. Mechanisms and consequences of aneuploidy and chromosome instability in the aging brain. *Mech Ageing Dev*. 2017;161(PtA):19–36. <https://doi.org/10.1016/j.mad.2016.03.007>.
50. Hou Y, Song H, Croteau DL, Akbari M, Bohr VA. Genome instability in Alzheimer disease. *Mech Ageing Dev*. 2017;161(PtA):83–94. <https://doi.org/10.1016/j.mad.2016.04.005>.
51. Proukakis C. Somatic mutations in neurodegeneration: An update. *Neurobiol Dis*. 2020;144:105021. <https://doi.org/10.1016/j.nbd.2020.105021>.
52. Sala Frigerio C, Lau P, Troakes C, Deramecourt V, Gele P, Van Loo P, Voet T, De Strooper B. On the identification of low allele frequency mosaic mutations in the brains of Alzheimer’s disease patients. *Alzheimer’s Dement*. 2015;11(11):1265–76. <https://doi.org/10.1016/j.jalz.2015.02.007>.
53. Nicolas G, Acuña-Hidalgo R, Keogh MJ, Quenez O, Steehouwer M, Lelieveld S, Rousseau S, Richard AC, Oud MS, Marguet F, Laquerrière A, Morris CM, Attens J, Smith C, Ansoorge O, Al Sarraj S, Frebourg T, Campion D, Hannequin D, Wallon D, Gillissen C, Chinnery PF, Veltman JA, Hoischen A. Somatic variants in autosomal dominant genes are a rare cause of sporadic Alzheimer’s



- disease. *Alzheimers Dement.* 2018;14(12):1632–9. <https://doi.org/10.1016/j.jalz.2018.06.3056>.
54. 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(2):456. <https://doi.org/10.1016/j.mehy.2007.05.037>.
55. Rivet TT, Matson JL. Review of gender differences in core symptomatology in autism spectrum disorders. *Res Autism Spectrum Dis.* 2011;5(3):957–76. <https://doi.org/10.1016/j.rasd.2010.12.003>.
56. Suarez NA, Macia A, Muotri AR. LINE-1 retrotransposons in healthy and diseased human brain. *Dev Neurobiol.* 2018;78(5):434–55. <https://doi.org/10.1002/dneu.22567>.
57. Iourov IY, Vorsanova SG, Yurov YB. Chromosomal mosaicism goes global. *Mol Cytogenet.* 2008;1:26. <https://doi.org/10.1186/1755-8166-1-26>.
58. Charney E. Behavior genetics and postgenomics. *Behav Brain Sci.* 2012;35(5):331–58. <https://doi.org/10.1017/S0140525X11002226>.
59. Vorsanova SG, Zelenova MA, Yurov YB, Iourov IY. Behavioral variability and somatic mosaicism: a cytogenomic hypothesis. *Curr Genomics.* 2018;19(3):158–62. <https://doi.org/10.2174/1389202918666170719165339>.
60. Liu G, Ye CJ, Chowdhury SK, Abdallah BY, Horne SD, Nichols D, Heng HH. Detecting chromosome condensation defects in gulf war illness patients. *Curr Genomics.* 2018;19(3):200–6. <https://doi.org/10.2174/1389202918666170705150819>.
61. Gomez-Ramos A, Picher AJ, García E, Garrido P, Hernandez F, Soriano E, Avila J. Validation of suspected somatic single nucleotide variations in the brain of Alzheimer's disease patients. *J Alzheimers Dis.* 2017;56(3):977–90. <https://doi.org/10.3233/JAD-161053>.
62. Helgadottir HT, Lundin P, Wallén Artz E, Lindström AK, Graff C, Eriksson M. Somatic mutation that affects transcription factor binding upstream of *CD55* in the temporal cortex of a late-onset Alzheimer disease patient. *Hum Mol Genet.* 2019;28(16):2675–85. <https://doi.org/10.1093/hmg/ddz085>.
63. Park JS, Lee J, Jung ES, Kim MH, Kim IB, Son H, Kim S, Kim S, Park YM, Mook-Jung I, Yu SJ, Lee JH. Brain somatic mutations observed in Alzheimer's disease associated with aging and dysregulation of tau phosphorylation. *Nat Commun.* 2019;10(1):3090. <https://doi.org/10.1038/s41467-019-11000-7>.
64. Ivashko-Pachima Y, Hadar A, Grigg I, Korenková V, Kapitansky O, Karmon G, Gershovits M, Sayas CL, Kooy RF, Attems J, Gurwitz D, Gozes I. Discovery of autism/intellectual disability somatic mutations in Alzheimer's brains: mutated *ADNP* cytoskeletal impairments and repair as a case study. *Mol Psychiatry.* 2021;26(5):1619–33. <https://doi.org/10.1038/s41380-019-0563-5>.
65. Keogh MJ, Wei W, Wilson I, Coxhead J, Ryan S, Rollinson S, Griffin H, Kurzawa-Akanbi M, Santibanez-Koref M, Talbot K, Turner MR, McKenzie CA, Troakes C, Attems J, Smith C, Al Sarraj S, Morris CM, Ansorge O, Pickering-Brown S, Ironside JW, Chinnery PF. Genetic compendium of 1511 human brains available through the UK Medical Research Council Brain Banks Network Resource. *Genome Res.* 2017;27(1):165–73. <https://doi.org/10.1101/gr.210609.116>.
66. Bushman DM, Kaeser GE, Siddoway B, Westra JW, Rivera RR, Rehen SK, Yung YC, Chun J. 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>.
67. 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>.
68. Pamphlett R, Morahan JM, Luquin N, Yu B. Looking for differences in copy number between blood and brain in sporadic amyotrophic lateral sclerosis. *Muscle Nerve.* 2011;44(4):492–8. <https://doi.org/10.1002/mus.22095>.
69. Coufal NG, García-Pérez JL, Peng GE, Marchetto MC, Muotri AR, Mu Y, Carson CT, Macia A, Moran JV, Gage FH. Ataxia telangiectasia mutated (*ATM*) modulates long interspersed element-1 (L1) retrotransposition in human neural stem cells. *Proc Natl Acad Sci U S A.* 2011;108(51):20382–7. <https://doi.org/10.1073/pnas.1100273108>.
70. Shpyleva S, Melnyk S, Pavlov O, Pogribny I, Jill James S. Overexpression of LINE-1 retrotransposons in autism brain. *Mol Neurobiol.* 2018;55(2):1740–9. <https://doi.org/10.1007/s12035-017-0421-x>.
71. D'Gama AM, Woodworth MB, Hossain AA, Bizzotto S, Hatem NE, LaCoursiere CM, Najm I, Ying Z, Yang E, Barkovich AJ, Kwiatkowski DJ, Vinters HV, Madsen JR, Mathern GW, Blümmcke I, Poduri A, Walsh CA. Somatic mutations activating the *MTOR* pathway in dorsal telencephalic progenitors cause a continuum of cortical dysplasias. *Cell Rep.* 2017;21(13):3754–66. <https://doi.org/10.1016/j.celrep.2017.11.106>.
72. Lim JS, Gopalappa R, Kim SH, Ramakrishna S, Lee M, Kim WI, Kim J, Park SM, Lee J, Oh JH, Kim HD, Park CH, Lee JS, Kim S, Kim DS, Han JM, Kang HC, Kim HH, Lee JH. Somatic mutations in *TSC1* and *TSC2* cause focal cortical dysplasia. *Am J Hum Genet.* 2017;100(3):454–72. <https://doi.org/10.1016/j.ajhg.2017.01.030>.
73. Park SM, Lim JS, Ramakrishna S, Kim SH, Kim WK, Lee J, Kang HC, Reiter JF, Kim DS, Kim HH, Lee JH. Brain somatic mutations in *MTOR* disrupt neuronal ciliogenesis, leading to focal cortical dyslamination. *Neuron.* 2018;99(1):83–97.e7. <https://doi.org/10.1016/j.neuron.2018.05.039>.
74. Ribierre T, Deleuze C, Bacq A, Baldassari S, Marsan E, Chipaux M, Muraca G, Roussel D, Navarro V, Leguern E, Miles R, Baulac S. Second-hit mosaic mutation in *mTORC1* repressor *DEPDC5* causes focal cortical dysplasia-associated epilepsy. *J Clin Invest.* 2018;128(6):2452–8. <https://doi.org/10.1172/JCI99384>.
75. Zhao S, Li Z, Zhang M, Zhang L, Zheng H, Ning J, Wang Y, Wang F, Zhang X, Gan H, Wang Y, Zhang X, Luo H, Bu G, Xu H, Yao Y, Zhang YW. A brain somatic *RHEB* doublet mutation causes focal cortical dysplasia type II. *Exp Mol Med.* 2019;51(7):1–11. <https://doi.org/10.1038/s12276-019-0277-4>.
76. Lee JH, Huynh M, Silhavy JL, Kim S, Dixon-Salazar T, Heiberg A, Scott E, Bafna V, Hill KJ, Collazo A, Funari V, Russ C, Gabriel SB, Mathern GW, Gleeson JG. De novo somatic mutations in components of the *PI3K-AKT3-mTOR* pathway cause hemimegalencephaly. *Nat Genet.* 2012;44(8):941–5. <https://doi.org/10.1038/ng.2329>.
77. Pelorosso C, Watrin F, Conti V, Buhler E, Gelot A, Yang X, Mei D, McEvoy-Venneri J, Manent JB, Cetica V, Ball LL, Buccoliero AM, Vinck A, Barba C, Gleeson JG, Guerrini R, Represa A. Somatic double-hit in *MTOR* and *RPS6* in hemimegalencephaly with intractable epilepsy. *Hum Mol Genet.* 2019;28(22):3755–65. <https://doi.org/10.1093/hmg/ddz194>.
78. Hildebrand MS, Griffin NG, Damiano JA, Cops EJ, Burgess R, Ozturk E, Jones NC, Leventer RJ, Freeman JL, Harvey AS, Sadleir LG, Scheffer IE, Major H, Darbro BW, Allen AS, Goldstein DB, Kerrigan JF, Berkovic SF, Heinzen EL. Mutations of the sonic hedgehog pathway underlie hypothalamic hamartoma with gelastic epilepsy. *Am J Hum Genet.* 2016;99(2):423–9. <https://doi.org/10.1016/j.ajhg.2016.05.031>.
79. Saitsu H, Sonoda M, Higashijima T, Shirozu H, Masuda H, Tohyama J, Kato M, Nakashima M, Tsurusaki Y, Mizuguchi T, Miyatake S, Miyake N, Kameyama S, Matsumoto N. Somatic mutations in *GLI3* and *OPD1* involved in sonic hedgehog signaling cause hypothalamic hamartoma. *Ann Clin Transl Neurol.* 2016;3(5):356–65. <https://doi.org/10.1002/acn3.300>.
80. Caneu J, Granic A, Rademakers R, Dickson DW, Coughlan CM, Chial HJ, Potter H. Mitotic defects lead to neuronal aneuploidy and apoptosis in frontotemporal lobar degeneration caused by *MAPT* mutations. *Mol Biol Cell.* 2018;29(5):575–86. <https://doi.org/10.1091/mbc.E17-01-0031>.
81. Telenius H, Kremer B, Goldberg YP, Theilmann J, Andrew SE, Zeisler J, Adam S, Greenberg C, Ives EJ, Clarke LA, Hayden MR. Somatic and gonadal mosaicism of the Huntington disease gene *CAG* repeat in brain and sperm. *Nat Genet.* 1994;6(4):409–14. <https://doi.org/10.1038/ng0494-409>.
82. Yang Y, Shepherd C, Halliday G. Aneuploidy in Lewy body diseases. *Neurobiol Aging.* 2015;36(3):1253–60. <https://doi.org/10.1016/j.neurobiolaging.2014.12.016>.
83. 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(4):e60718. <https://doi.org/10.1371/journal.pone.0060718>.
84. Winawer MR, Griffin NG, Samanamud J, Baugh EH, Rathakrishnan D, Ramalingam S, Zagzag D, Schevon CA, Dugan P, Hegde M, Sheth SA, McKhann GM, Doyle WK, Grant GA, Porter BE, Mikati MA, Muh CR, Malone CD, Bergin AMR, Peters JM, McBrien DK, Pack AM, Akkan L, LaCoursiere CM, Keever KM, Madsen JR, Yang E, Lidov HGW, Shain C, Allen AS, Canoll PD, Crino PB, Poduri AH, Heinzen EL. Somatic *SLC35A2* variants in the brain are associated with intractable neocortical epilepsy. *Ann Neurol.* 2018;83(6):1133–46. <https://doi.org/10.1002/ana.25243>.
85. Proukakis C, Shoaee M, Morris J, Brier T, Kara E, Sheerin UM, Charlesworth G, Tolosa E, Houlden H, Wood NW, Schapira AH. Analysis of Parkinson's disease brain-derived DNA for alpha-synuclein coding somatic mutations. *Mov Disord.* 2014;29(8):1060–4. <https://doi.org/10.1002/mds.25883>.
86. Mokretar K, Pease D, Taanman JW, Soenmez A, Ejaz A, Lashley T, Ling H, Gentleman S, Houlden H, Holton JL, Schapira AHV, Nacheva E, Proukakis C. Somatic copy number gains of  $\alpha$ -synuclein (*SNCA*) in Parkinson's disease and multiple system atrophy brains. *Brain.* 2018;141(8):2419–31. <https://doi.org/10.1093/brain/awy157>.
87. Zhao B, Wu Q, Ye AY, Guo J, Zheng X, Yang X, Yan L, Liu QR, Hyde TM, Wei L, Huang AY. Somatic LINE-1 retrotransposition in cortical neurons and non-brain tissues of Rett patients and healthy individuals. *PLoS Genet.* 2019;15:e1008043. <https://doi.org/10.1371/journal.pgen.1008043>.

88. Fullard JF, Charney AW, Voloudakis G, Uzilov AV, Haroutunian V, Roussos P. Assessment of somatic single-nucleotide variation in brain tissue of cases with schizophrenia. *Transl Psychiatry*. 2019;9(1):21. <https://doi.org/10.1038/s41398-018-0342-0>.
89. Bundo M, Toyoshima M, Okada Y, Akamatsu W, Ueda J, Nemoto-Miyauchi T, Sunaga F, Toritsuka M, Ikawa D, Kakita A, Kato M, Kasai K, Kishimoto T, Nawa H, Okano H, Yoshikawa T, Kato T, Iwamoto K. Increased L1 retrotransposition in the neuronal genome in schizophrenia. *Neuron*. 2014;81(2):306–13. <https://doi.org/10.1016/j.neuron.2013.10.053>.
90. Doyle GA, Crist RC, Karatas ET, Hammond MJ, Ewing AD, Ferraro TN, Hahn CG, Berrettini WH. Analysis of LINE-1 elements in DNA from postmortem brains of individuals with schizophrenia. *Neuropsychopharmacology*. 2017;42(13):2602–11. <https://doi.org/10.1038/npp.2017.115>.
91. Hildebrand MS, Harvey AS, Malone S, Damiano JA, Do H, Ye Z, McQuillan L, Maixner W, Kalnins R, Nolan B, Wood M, Ozturk E, Jones NC, Gillies G, Pope K, Lockhart PJ, Dobrovic A, Leventer RJ, Scheffer IE, Berkovic SF. Somatic *GNAQ* mutation in the forme fruste of Sturge-Weber syndrome. *Neurol Genet*. 2018;4(3):e236. <https://doi.org/10.1212/NXG.0000000000000236>.
92. Jamuar SS, Lam AT, Kircher M, D’Gama AM, Wang J, Barry BJ, Zhang X, Hill RS, Partlow JN, Rozzo A, Servattalab S, Mehta BK, Topcu M, Amrom D, Andermann E, Dan B, Parrini E, Guerrini R, Scheffer IE, Berkovic SF, Leventer RJ, Shen Y, Wu BL, Barkovich AJ, Sahin M, Chang BS, Bamshad M, Nickerson DA, Shendure J, Poduri A, Yu TW, Walsh CA. Somatic mutations in cerebral cortical malformations. *N Engl J Med*. 2014;371(8):733–43. <https://doi.org/10.1056/NEJMoa1314432>.
93. Damiano JA, Do H, Ozturk E, Burgess R, Kalnins R, Jones NC, Dobrovic A, Berkovic SF, Hildebrand MS. Sensitive quantitative detection of somatic mosaic mutation in “double cortex” syndrome. *Epileptic Disord*. 2017;19(4):450–5. <https://doi.org/10.1684/epd.2017.0944>.
94. Qin W, Chan JA, Vinters HV, Mathern GW, Franz DN, Taillon BE, Bouffard P, Kwiatkowski DJ. Analysis of TSC cortical tubers by deep sequencing of *TSC1*, *TSC2* and *KRAS* demonstrates that small second-hit mutations in these genes are rare events. *Brain Pathol*. 2010;20(6):1096–105. <https://doi.org/10.1111/j.1750-3639.2010.00416.x>.
95. Hall JG. Review and hypotheses: somatic mosaicism: observations related to clinical genetics. *Am J Hum Genet*. 1988;43(4):355–63.
96. Hultén MA, Jonasson J, Iwarsson E, Uppal P, Vorsanova SG, Yurov YB, Iourov IY. Trisomy 21 mosaicism: we may all have a touch of Down syndrome. *Cytogenet Genome Res*. 2013;139(9):189–92. <https://doi.org/10.1159/000346028>.
97. 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(3):385–90. <https://doi.org/10.1369/jhc.4A6430.2005>.
98. Yurov YB, Vorsanova SG, Iourov IY, Demidova IA, Beresheva AK, Kravetz VS, Monakhov VV, Kolotii AD, Voinova-Ulas VY, Gorbachevskaya NL. Unexplained autism is frequently associated with low-level mosaic aneuploidy. *J Med Genet*. 2007;44(8):521–5. <https://doi.org/10.1136/jmg.2007.049312>.
99. 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>.
100. Biesecker LG, Spinner NB. A genomic view of mosaicism and human disease. *Nat Rev Genet*. 2013;14(5):307–20. <https://doi.org/10.1038/nrg3424>.
101. Lejva-Salazar M, Piette C, Proukakis C. Review. Somatic mutations in neurodegeneration. *Neuropathol Appl Neurobiol*. 2018;44(3):267–85. <https://doi.org/10.1111/nan.12465>.
102. 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>.
103. Kingsbury MA, Friedman B, McConnell MJ, Rehen SK, Yang AH, Kaushal D, Chun J. Aneuploid neurons are functionally active and integrated into brain circuitry. *Proc Natl Acad Sci U S A*. 2005;102(17):6143–7. <https://doi.org/10.1073/pnas.0408171102>.
104. van den Bos H, Spierings DC, Taudt AS, Bakker B, Porubský D, Falconer E, Novoa C, Halsema N, Kazemier HG, Hoekstra-Wakker K, Guryev V, den Dunnen WF, Foijer F, Tatché MC, Boddeke HW, Lansdorp PM. Single-cell whole genome sequencing reveals no evidence for common aneuploidy in normal and Alzheimer’s disease neurons. *Genome Biol*. 2016;17(11):116. <https://doi.org/10.1186/s13059-016-0976-2>.
105. Smith CL, Bolton A, Nguyen G. Genomic and epigenomic instability, fragile sites, schizophrenia and autism. *Curr Genomics*. 2010;11(6):447–69. <https://doi.org/10.2174/138920210793176001>.
106. 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(1–2):35–7; discussion 38–40. <https://doi.org/10.1159/000315398>.
107. Ye CJ, Stilgenbauer L, Moy A, Liu G, Heng HH. What is karyotype coding and why is genomic topology important for cancer and evolution? *Front Genet*. 2019;10:1082. <https://doi.org/10.3389/fgene.2019.01082>.
108. Rao CV, Asch AS, Carr DJJ, Yamada HY. “Amyloid-beta accumulation cycle” as a prevention and/or therapy target for Alzheimer’s disease. *Aging Cell*. 2020;19(3):e13109. <https://doi.org/10.1111/acel.13109>.
109. Ye CJ, Sharpe Z, Heng HH. Origins and consequences of chromosomal instability: from cellular adaptation to genome chaos-mediated system survival. *Genes (Basel)*. 2020;11(10):1162. <https://doi.org/10.3390/genes11101162>.
110. Peterson SE, Yang AH, Bushman DM, Westra JW, Yung YC, Barral S, Mutoh T, Rehen SK, Chun J. Aneuploid cells are differentially susceptible to caspase-mediated death during embryonic cerebral cortical development. *J Neurosci*. 2012;32(46):16213–22. <https://doi.org/10.1523/JNEUROSCI.3706-12.2012>.
111. Fricker M, Tolkovsky AM, Borutaite V, Coleman M, Brown GC. Neuronal cell death. *Physiol Rev*. 2018;98(2):813–80. <https://doi.org/10.1152/physrev.00011.2017>.
112. Yurov YB, Vorsanova SG, Iourov IY. GIN’nCIN 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>.
113. Fielder E, von Zglinicki T, Jurk D. The DNA damage response in neurons: die by apoptosis or survive in a senescence-like state? *J Alzheimers Dis*. 2017;60(s1):107–31. <https://doi.org/10.3233/JAD-161221>.
114. Lin X, Kapoor A, Gu Y, Chow MJ, Peng J, Zhao K, Tang D. Contributions of DNA Damage to Alzheimer’s Disease. *Int J Mol Sci*. 2020;21(5):1666. <https://doi.org/10.3390/ijms21051666>.
115. Yurov YB, Vorsanova SG, Iourov IY. Ontogenetic variation of the human genome. *Curr Genomics*. 2010;11(6):420–5. <https://doi.org/10.2174/138920210793175958>.
116. Kennedy SR, Loeb LA, Herr AJ. Somatic mutations in aging, cancer and neurodegeneration. *Mech Ageing Dev*. 2012;133(4):118–26. <https://doi.org/10.1016/j.mad.2011.10.009>.
117. Baker DJ, Petersen RC. Cellular senescence in brain aging and neurodegenerative diseases: evidence and perspectives. *J Clin Invest*. 2018;128(4):1208–16. <https://doi.org/10.1172/JCI95145>.
118. Bajic V, Essack M, Zivkovic L, Stewart A, Zafirovic S, Bajic VB, Gojbori T, Isenovic ER, Spremo-Potparevic B. The X Files: “The mystery of X chromosome instability in Alzheimer’s disease”. *Front Genet*. 2020;10:1368. <https://doi.org/10.3389/fgene.2019.01368>.
119. Iourov IY, Vorsanova SG, Yurov YB. Developmental neural chromosome instability as a possible cause of childhood brain cancers. *Med Hypotheses*. 2009;72(5):615–6. <https://doi.org/10.1016/j.mehy.2008.12.003>.
120. Heng HH. Debating cancer: the paradox in cancer research. New Jersey: World Scientific Publishing Company; 2015. <https://doi.org/10.1142/8879>.
121. Granic A, Padmanabhan J, Norden M, Potter H. Alzheimer Abeta peptide induces chromosome mis-segregation and aneuploidy, including trisomy 21: requirement for tau and *APP*. *Mol Biol Cell*. 2010;21(4):511–20. <https://doi.org/10.1091/mbc.e09-10-0850>.
122. 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>.
123. 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>.
124. Nudelman KNH, McDonald BC, Lahiri DK, Saykin AJ. Biological hallmarks of cancer in Alzheimer’s disease. *Mol Neurobiol*. 2019;56(10):7173–87. <https://doi.org/10.1007/s12035-019-1591-5>.
125. 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. <https://doi.org/10.1155/2015/757680>.
126. Varetta G, Pellman D, Gordon DJ. Aurea mediocritas: the importance of a balanced genome. *Cold Spring Harb Perspect Biol*. 2014;6(11):a015842. <https://doi.org/10.1101/cshperspect.a015842>.

127. Zhang CZ, Pellman D. From mutational mechanisms in single cells to mutational patterns in cancer genomes. *Cold Spring Harb Symp Quant Biol*. 2015;80:117–37. <https://doi.org/10.1101/sqb.2015.80.027623>.
128. Lee MH, Siddoway B, Kaeser GE, Segota I, Rivera R, Romanow WJ, Liu CS, Park C, Kennedy G, Long T, Chun J. Somatic *APP* gene recombination in Alzheimer's disease and normal neurons. *Nature*. 2018;563(7733):639–45. <https://doi.org/10.1038/s41586-018-0718-6>.
129. 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(3):181–8. <https://doi.org/10.1159/000347053>.
130. Ghulam A, Lei X, Guo M, Bian C. Comprehensive analysis of features and annotations of pathway databases. *Curr Bioinf*. 2020;15(8):803–20. <https://doi.org/10.2174/1574893615999200413123352>.
131. Iourov IY, Vorsanova SG, Yurov YB. Pathway-based classification of genetic diseases. *Mol Cytogenet*. 2019;12:4. doi:<https://doi.org/10.1186/s13039-019-0418-4>.
132. Bae T, Fasching L, Wang Y, Shin JH, Suvakov M, Jang Y, Norton S, Dias C, Mariani J, Jourdon A, Wu F, Panda A, Pattni R, Chahine Y, Yeh R, Roberts RC, Huttner A, Kleinman JE, Hyde TM, Straub RE, Walsh CA, Brain Somatic Mosaicism Network, Urban AE, Leckman JF, Weinberger DR, Vaccarino FM, Abyzov A. Analysis of somatic mutations in 131 human brains reveals aging-associated hypermutability. *Science*. 2022;377(6605):511–7. doi:<https://doi.org/10.1126/science.abm6222>.
133. Bedrosian TA, Miller KE, Grischow OE, Schieffer KM, LaHaye S, Yoon H, Miller AR, Navarro J, Westfall J, Leraas K, Choi S, Williamson R, Fitch J, Kelly BJ, White P, Lee K, McGrath S, Cottrell CE, Magrini V, Leonard J, Pindrik J, Shaikhouni A, Boué DR, Thomas DL, Pierson CR, Wilson RK, Ostendorf AP, Mardis ER, Koboldt DC. Detection of brain somatic variation in epilepsy-associated developmental lesions. *Epilepsia*. 2022 Aug;63(8):1981–97. doi:<https://doi.org/10.1111/epi.17323>.
134. Miller MB, Huang AY, Kim J, Zhou Z, Kirkham SL, Maury EA, Ziegenfuss JS, Reed HC, Neil JE, Rento L, Ryu SC, Ma CC, Luquette LJ, Ames HM, Oakley DH, Frosch MP, Hyman BT, Lodato MA, Lee EA, Walsh CA. Somatic genomic changes in single Alzheimer's disease neurons. *Nature*. 2022;604(7907):714–22. doi:<https://doi.org/10.1038/s41586-022-04640-1>.
135. Vorsanova SG, Kolotii AD, Kurinnaia OS, Kravets VS, Demidova IA, Soloviev IV, Yurov YB, Iourov IY. Turner's syndrome mosaicism in girls with neurodevelopmental disorders: a cohort study and hypothesis. *Mol Cytogenet*. 2021;14(1):9. doi:<https://doi.org/10.1186/s13039-021-00529-2>.
136. D'Gama AM. Somatic mosaicism and autism spectrum disorder. *Genes (Basel)*. 2021;12(11):1699. doi:<https://doi.org/10.3390/genes12111699>.
137. Vorsanova SG, Demidova IA, Kolotii AD, Kurinnaia OS, Kravets VS, Soloviev IV, Yurov YB, Iourov IY. Klinefelter syndrome mosaicism in boys with neurodevelopmental disorders: a cohort study and an extension of the hypothesis. *Mol Cytogenet*. 2022;15(1):8. doi:<https://doi.org/10.1186/s13039-022-00588-z>.
138. Woodbury-Smith M, Lamoureaux S, Begum G, Nassir N, Akter H, O'Rielly DD, Rahman P, Wintle RF, Scherer SW, Uddin M. Mutational landscape of autism spectrum disorder brain tissue. *Genes (Basel)*. 2022;13(2):207. doi:<https://doi.org/10.3390/genes13020207>.
139. Iourov IY, Vorsanova SG, Yurov YB, Zelenova MA, Kurinnaia OS, Vasin KS, Kutsev SI. The cytogenomic "theory of everything": chromohelkosis may underlie chromosomal instability and mosaicism in disease and aging. *Int J Mol Sci*. 2020;21(21):8328. doi:<https://doi.org/10.3390/ijms21218328>.
140. Iourov IY, Vorsanova SG. COVID-19 and aging-related genome (chromosome) instability in the brain: another possible time-bomb of SARS-CoV-2 infection. *Front Aging Neurosci*. 2022;14:786264. doi:<https://doi.org/10.3389/fnagi.2022.786264>.
141. Iourov IY, Vorsanova SG, Liehr T, Yurov YB. Mosaik im Gehirn des Menschen. Diagnostische Relevanz in der Zukunft? *Med Genet*. 2014;26:342–5. <https://doi.org/10.1007/s11825-014-0010-6>.
142. Iourov IY. Cytopostgenomics: what is it and how does it work? *Curr Genomics*. 2019;20(2):77–8.
143. Iourov IY, Vorsanova SG, Yurov YB. Systems cytogenomics: are we ready yet? *Curr Genomics*. 2021 Feb;22(2):75–8. doi:<https://doi.org/10.2174/1389202922666210219112419>.
144. Caldecott KW, Ward ME, Nussenzweig A. The threat of programmed DNA damage to neuronal genome integrity and plasticity. *Nat Genet*. 2022;54(2):115–20. doi:<https://doi.org/10.1038/s41588-021-01001-y>.
145. Lee S, Lee JH. Brain somatic mutations as RNA therapeutic targets in neurological disorders. *Ann NY Acad Sci*. 2022;1514(1):11–20. doi:<https://doi.org/10.1111/nyas.14786>.
146. Nelson RS, Dammer EB, Santiago JV, Seyfried NT, Rangaraju S. Brain cell type-specific nuclear proteomics is imperative to resolve neurodegenerative disease mechanisms. *Front Neurosci*. 2022;16:902146. doi:<https://doi.org/10.3389/fnins.2022.902146>.
147. Iourov IY, Liehr T, Vorsanova SG, Mendez-Rosado LA, Yurov YB. The applicability of interphase chromosome-specific multicolor banding (ICS-MCB) for studying neurodevelopmental and neurodegenerative disorders. *Res Results Biomed*. 2019;5(3):4–9.
148. Costantino I, Nicodemus J, Chun J. Genomic mosaicism formed by somatic variation in the aging and diseased brain. *Genes (Basel)*. 2021;12(7):1071. doi:<https://doi.org/10.3390/genes12071071>.
149. Iourov IY, Vorsanova SG, Kurinnaia OS, Zelenova MA, Vasin KS, Yurov YB. Causes and consequences of genome instability in psychiatric and neurodegenerative diseases. *Mol Biol (Mosk)*. 2021;55(1):42–53. doi:<https://doi.org/10.31857/S0026898421010158>.
150. Bizzotto S, Walsh CA. Genetic mosaicism in the human brain: from lineage tracing to neuropsychiatric disorders. *Nat Rev Neurosci*. 2022;23(5):275–86. doi:<https://doi.org/10.1038/s41583-022-00572-x>.
151. Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, Simonovic M, Doncheva NT, Morris JH, Bork P, Jensen LJ, Mering CV. STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic Acids Res*. 2019;47(D1):D607–13. <https://doi.org/10.1093/nar/gky1131>.

## Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

## Terms and Conditions

Springer Nature journal content, brought to you courtesy of Springer Nature Customer Service Center GmbH (“Springer Nature”).

Springer Nature supports a reasonable amount of sharing of research papers by authors, subscribers and authorised users (“Users”), for small-scale personal, non-commercial use provided that all copyright, trade and service marks and other proprietary notices are maintained. By accessing, sharing, receiving or otherwise using the Springer Nature journal content you agree to these terms of use (“Terms”). For these purposes, Springer Nature considers academic use (by researchers and students) to be non-commercial.

These Terms are supplementary and will apply in addition to any applicable website terms and conditions, a relevant site licence or a personal subscription. These Terms will prevail over any conflict or ambiguity with regards to the relevant terms, a site licence or a personal subscription (to the extent of the conflict or ambiguity only). For Creative Commons-licensed articles, the terms of the Creative Commons license used will apply.

We collect and use personal data to provide access to the Springer Nature journal content. We may also use these personal data internally within ResearchGate and Springer Nature and as agreed share it, in an anonymised way, for purposes of tracking, analysis and reporting. We will not otherwise disclose your personal data outside the ResearchGate or the Springer Nature group of companies unless we have your permission as detailed in the Privacy Policy.

While Users may use the Springer Nature journal content for small scale, personal non-commercial use, it is important to note that Users may not:

1. use such content for the purpose of providing other users with access on a regular or large scale basis or as a means to circumvent access control;
2. use such content where to do so would be considered a criminal or statutory offence in any jurisdiction, or gives rise to civil liability, or is otherwise unlawful;
3. falsely or misleadingly imply or suggest endorsement, approval, sponsorship, or association unless explicitly agreed to by Springer Nature in writing;
4. use bots or other automated methods to access the content or redirect messages
5. override any security feature or exclusionary protocol; or
6. share the content in order to create substitute for Springer Nature products or services or a systematic database of Springer Nature journal content.

In line with the restriction against commercial use, Springer Nature does not permit the creation of a product or service that creates revenue, royalties, rent or income from our content or its inclusion as part of a paid for service or for other commercial gain. Springer Nature journal content cannot be used for inter-library loans and librarians may not upload Springer Nature journal content on a large scale into their, or any other, institutional repository.

These terms of use are reviewed regularly and may be amended at any time. Springer Nature is not obligated to publish any information or content on this website and may remove it or features or functionality at our sole discretion, at any time with or without notice. Springer Nature may revoke this licence to you at any time and remove access to any copies of the Springer Nature journal content which have been saved.

To the fullest extent permitted by law, Springer Nature makes no warranties, representations or guarantees to Users, either express or implied with respect to the Springer nature journal content and all parties disclaim and waive any implied warranties or warranties imposed by law, including merchantability or fitness for any particular purpose.

Please note that these rights do not automatically extend to content, data or other material published by Springer Nature that may be licensed from third parties.

If you would like to use or distribute our Springer Nature journal content to a wider audience or on a regular basis or in any other manner not expressly permitted by these Terms, please contact Springer Nature at

[onlineservice@springernature.com](mailto:onlineservice@springernature.com)