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REVIEW ARTICLE

Mosaic Brain Aneuploidy in Mental Illnesses: An Association of Low-level Post-zygotic Aneuploidy with Schizophrenia and Comorbid Psychiatric Disorders

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Abstract: ***Background*:** Postzygotic chromosomal variation in neuronal cells is hypothesized to make a substantial contribution to the etiology and pathogenesis of neuropsychiatric disorders. However, the role of somatic genome instability and mosaic genome variations in common mental illnesses is a matter of conjecture.

***Materials and Methods*:** To estimate the pathogenic burden of somatic chromosomal mutations, we determined the frequency of mosaic aneuploidy in autopsy brain tissues of subjects with schizophrenia and other psychiatric disorders (intellectual disability comorbid with autism spectrum disorders). Recently, post-mortem brain tissues of subjects with schizophrenia, intellectual disability and unaffected controls were analyzed by Interphase Multicolor FISH (MFISH), Quantitative Fluorescent in situ Hybridization (QFISH) specially designed to register rare mosaic chromosomal mutations such as low-level aneuploidy (whole chromosome mosaic deletion/duplication). The low-level mosaic aneuploidy in the diseased brain demonstrated significant 2-3-fold frequency increase in schizophrenia ($p=0.0028$) and 4-fold increase in intellectual disability comorbid with autism ($p=0.0037$) compared to unaffected controls. Strong associations of low-level autosomal/sex chromosome aneuploidy ($p=0.001$, OR=19.0) and sex chromosome-specific mosaic aneuploidy ($p=0.006$, OR=9.6) with schizophrenia were revealed.

***Conclusion*:** Reviewing these data and literature supports the hypothesis suggesting that an association of low-level mosaic aneuploidy with common and, probably, overlapping psychiatric disorders does exist. Accordingly, we propose a pathway for common neuropsychiatric disorders involving increased burden of rare *de novo* somatic chromosomal mutations manifesting as low-level mosaic aneuploidy mediating local and general brain dysfunction.

Keywords: Somatic genome variations, Human brain, Aneuploidy, Chromosomal instability, Genome instability, Ontogeny, Aging, Psychiatric disorders.

1. INTRODUCTION

Multiple genetic and environmental factors contribute to the etiology and pathogenesis of common genetically overlapping mental disorders including schizophrenia (SCZ) and intellectual disability (ID) comorbid with Autism Spectrum Disorders (ASD) [1-10]. Since SCZ was long considered a prototypical mental illness, we have decided to focus our present attention mainly on this disorder. SCZ is a common mental illness occurring in about 1% of the population with estimated heritability of 70-80%. It is repeatedly noticed that such genetic factors as rare inherited and *de novo* chromosomal mutations, DNA Copy Number Variations (CNVs), Single Nucleotide Variants (SNVs), little ins/indel and Single Nucleotide Polymorphisms (SNPs) significantly contribute to the etiology of SCZ. Rare disruptive chromosomal deletions and duplications were found to affect 15% cases of SCZ *versus* 5% controls as documented by large scale population-based studies of non-neural cell genomes [11-16]. In ASD/ID, rare *de novo* germline mutations were identified in 10-13% of patients *versus* 1% in controls [17-19]. The commonest concept underlying genetic research of psychiatric disorders postulates that all the somatic cells of a human share their genomes. Thus, the role of post-zygotic (non-inheritable) *de novo* somatic mutations is generally ignored. However, it has been shown that common biological pathways controlling genome stability during brain development through the ontogeny are functionally variable being able to produce somatic genome variations unequally

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distributed across different human tissues [20-29]. It is important to note that genetic instabilities in the form of spontaneous *de novo* brain-specific mutations, d*e novo* chromosomal microdeletions/duplications, chromosomal mosaic aneuploidy and retrotranspositions of L1 elements have already been demonstrated to be a source for neural genome variability [30-35]. Chromosomal instability *per se* leads to large-scale chromosome alterations (*i.e.* aneuploidy) in germline and somatic cells. As to brain-specific aneuploidy in humans, it has been monitored by several independent laboratories all over the world by such powerful technologies as fluorescence *in situ* hybridization (FISH) and single-cell sequencing that the mean frequency of chromosome-specific aneuploidy is likely to approach 0.3-4% per individual chromosome pair [32, 33, 36-43]. Although FISH is designed to determine chromosome-specific aneuploidy rate, it is possible to conclude that aneuploidy should theoretically affect no fewer than10-30% cells in developing and adult human brain. However, it is difficult to imagine that 10-30 billion nerve cells out of 90 billion neurons populating the normal brain are genetically abnormal [20, 25, 44]. Consequently, further large scale molecular cytogenetic and statistical methods should be used to solve this paradox.

Single-cell sequencing estimates a bit more optimistically the overall aneuploidy level in the normal human brain as about 5% [45-47]. Although the real percentage of neuronal aneuploidy in brain is not yet determined, it is commonly accepted that the brain is genomically a mosaic [40-50]. Similarly, low-level mosaic aneuploidy is considered as an integral component of developing and postnatal human germ-line and somatic cells.

Low-level spontaneous and chromosome-specific aneuploidy involves hundreds or thousands of genes negatively affecting, thereby, brain development and function. One can speculate that chromosomal mosaicism in the brain may contribute not only to functional diversity of neuronal cells or to brain tumors, but also would negatively affect brain functioning and produce a susceptibility to neuropsychiatric and neurodegenerative disorders [3, 7, 20, 33, 36, 38, 41, 42, 48-60]. Nevertheless, the pathogenic role of low-level mosaic aneuploidy affecting brain tissues in health and neuropsychiatric diseases remains to be determined.

In 2001, a pioneer work concerning molecular cytogenetic analyses of low-level aneuploidy in brain tissues of normal control and SCZ, considered by us as “prototypical” mental illness was published [51]. Using FISH with chromosome-enumeration and site-specific DNA probes for chromosomes 1, 7, 8, 13/21, 16, 18, 22, X and Y, we were unable to detect aneuploid neural cells in control. However, increased level of clonal chromosome-specific mosaic aneuploidy (up to 4%) involving chromosomes 1, 18, and X in SCZ brain was uncovered [51, 53]. Still, the involvement of low-level somatic aneuploidy in the pathogenesis of common neuropsychiatric disorders remains a matter of further careful experimental verifications.

Here, we overview recent results of a new set of experiments for determining the cut-offs of low-level aneuploidy in the brain and estimating the pathogenic burden of mosaic aneuploidy in brain disorders (SCZ and ID/ASD) [51, 53, 61, 62]. Our focus was somatic mosaicism affecting sex chromosomes X and Y in the SCZ brain. Additionally, the level of mosaic aneuploidy involving arbitrarily selected autosomes 1, 9, 15, 16, 18 was analyzed to compare the rate of autosome/sex chromosome aneuploidy in neuropsychiatric disorders and controls (SCZ, and ID/ASD).

2. POSTMORTEM BRAIN SAMPLES

The post-mortem brain tissues (the prefrontal cortex - PFC) were obtained from the collection of the Brain Bank of the Mental Health Research Center, Russian Academy of Sciences (MHRC). MHRC ethics committee approval and informed consent for collecting the tissues and genetic analyses were previously obtained. The diagnosis of SCZ had been made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. In total, 22 SCZ and 25 unaffected human brain samples were analyzed (Table **1**). The details of brain samples were published previously [51, 53, 62]. Additionally, the NIH NeuroBioBank (the former "NICHD Brain and Tissue Bank for Developmental Disorders" or the UMB Brain and Tissue Bank, University of Maryland School of Medicine, Department of Pediatrics in Baltimore, Maryland) provided brain tissues of controls and 6 patients with intellectual disability comorbid with autism.

Table 1. Postmortem brain samples selected for the study.

--	**Subject Group**	
--	Control	SCZ
Number (Male/Female)	N=25 (7/18)	N=22 (10/120)
Age (Median)	56.0	62.0
Age (95% CI)	49.3-59.9	51.8-65.6
Age (Mean)	54.6	58.7

The frozen tissue samples from PFC were processed according to our protocol of brain tissue preparation for molecular cytogenetic analysis described in detail elsewhere [63]. The brain samples (3x3x3 mm) were processed through mechanical dissociation using a teflon pestle and glass tube tissue homogenizer. Suspensions of nuclei were fixed with acetic acid solution (45-60% w/v), and post-fixed with methanol/acetic acid mixture (3:1). The suspensions of nuclei obtained were dropped onto wet slides and were then dried overnight at room temperature, dehydrated through ethanol series and processed for FISH.

3. MULTIPROBE FISH (MFISH) AND QUANTITATIVE FISH (QFISH) STUDIES

For multiprobe FISH, chromosomes 1, 9, 15, 16, 18, X and Y-specific DNA probes labeled by FluorX (green), Cy3 (red), or diethylaminocoumarine (blue) were used (Fig. **S1**). High-resolution chromosome-specific MCB patterns were generated with probes for chromosomes 1, 9, 15, 16, 18 and X. For each tissue sample and each chromosome-enumeration probe, 1000 interphase nuclei were scored. The protocol of the technique was described previously in detail [21, 32, 33, 48, 51-54, 62, 64].

To differ between chromosome loss and FISH signal associations (a hallmark of the human brain FISH analysis), nuclei demonstrating one hybridization signal was analyzed additionally by QFISH. Each interphase nucleus showing one hybridization signal was captured for quantification of relative signal intensity. The numerical values of the signal relative intensity in nuclei with one signal (monosomy or associated signals) and two separate signals (disomy) were compared. Single signals exhibiting doubled intensity as to each one in disomic nuclei with non-associated signals were considered as those containing two chromosomes. Step-by-step description of QFISH procedure was provided previously [65, 66]. The evaluation of low-level mosaic aneuploidy was performed through scoring 100-1000 interphase nuclei for each brain sample in MFISH/QFISH studies. The median, mean frequency and 95% Confidence Interval (CI) for chromosome gain/loss frequency were determined. Comparison of stochastic (or background) aneuploidy frequency between two independent groups (control and SCZ, control and AD/autism) was performed using nonparametric statistics (Mann-Whitney U test for independent groups). The Odds Ratio (OR) was used to measure the associations between control and disease in the analysis of data from a case control study.

4. MFISH DATA ON LOW-LEVEL SOMATIC MOSAICISM

The burden of mosaic aneuploidy as the frequency of chromosome-specific aneuploidy (%) per individual chromosome pair using MFISH with chromosome enumeration probes was assessed (Figs. **1**-**3**). Furthermore, the potential burden of low-level aneuploidy involving sex chromosomes in cohort of normal controls and SCZ patients (25 control cases: 7 males and 18 females; 22 cases of SCZ: 10 males and 12 females) was determined. In controls, the mean frequency of aneuploidy involving sex chromosomes was 0.84%, median 0.7 % and 95% CI 0.57-1.13% (Table **2**, Fig. **1A**). Low-level sex chromosome mosaics (aneuploidy frequency more than 2.0%) were found in 2 cases out of 25 controls. Using these experimental data, we have determined the cut-off level of increased aneuploidy as 2.0%. In SCZ patients the mean frequency of aneuploidy involving sex chromosomes X/Y was 2.08%, median 1.75% and 95% CI 1.29-2.86% (Table **2**, Fig. **1B**). In order to determine the rate of mosaic aneuploidy affecting sex chromosomes in male and female brain, we compared relative aneuploidy frequencies (the median value) in 10 males and 12 females with SCZ and in controls (18 males and 7 females). Gender differences were not revealed in these groups (p=0.360 and p=0.222, respectively, Mann-Whitney U test for independent groups).

Cases with low-level sex chromosome mosaicism with frequency more than 2.0% (the cut-off level for normal brain tissues) were found in10 SCZ patients out of 22. It is to note repeatedly that 2 outlier cases were found among 25 control samples. The rate of sex chromosome mosaic aneuploidy was found as 1.75% (the median value) in SCZ and 0.7% in control (the median value) demonstrating 2.5-fold increase in the diseased brain. Thus, an association of low-level mosaic aneuploidy affecting sex chromosomes with SCZ was confirmed (p=0.0028, OR=9.583).

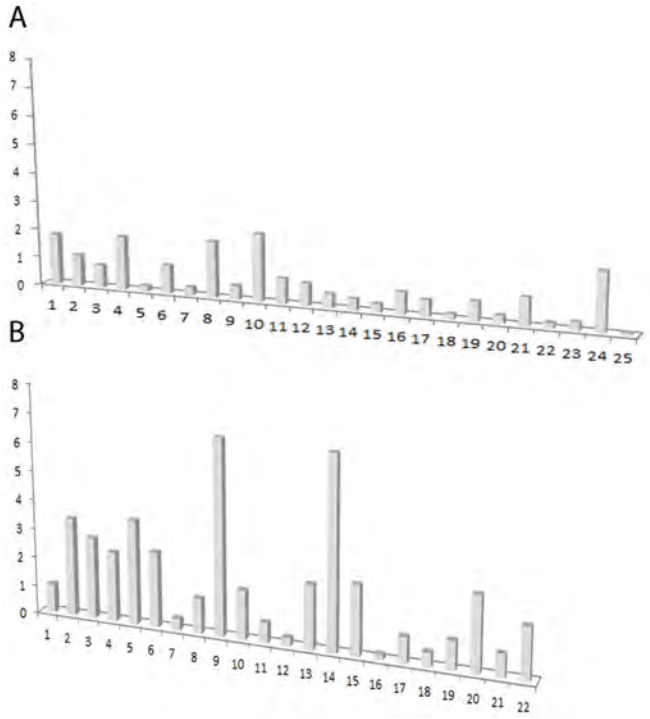

Fig. (1). Aneuploidy frequency (%) involving sex chromosomes in PFC brain cells in controls (**A**) and in SCZ (**B**) according to MFISH (1000 cells per a sex chromosome pair analyzed in 25 control samples and 22 SCZ samples). A — control samples; B — SCZ samples.

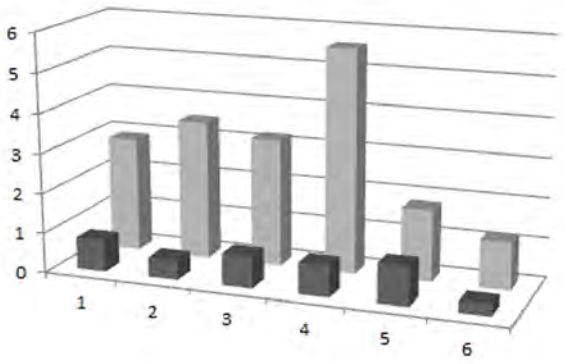

Fig. (2). Aneuploidy frequency (%) involving sex chromosomes in PFC of 6 controls (black) and 6 samples of patients with autism comorbid with intellectual disability (grey) according to MFISH. (1000 cells per a sex chromosome pair analyzed in 6 controls and 6 male patients with autism comorbid with intellectual disability). Abscissa axis: 1-5 = autosomes 1, 9, 15, 16, 18, respectively; 6 = sex chromosomes. Ordinate axis: percentage of abnormal cells.

Since our additional aim was to extend the study to somatic mosaicism in the diseased brain, we have analyzed the burden of low-level aneuploidy involving sex chromosomes in 6 male subjects with idiopathic autism associated comorbid with mental retardation. These postmortem autistic brain tissues as well tissues of age and sex matched controls were kindly provided by the NIH NeuroBioBank. The cases with low-level sex chromosome mosaicism with a frequency more than 2.0% (the cut-off level of background aneuploidy in control) were found in 4 subjects. In control samples, the

mean frequency of aneuploidy involving chromosomes X and Y was 0.70% with median 0.80% and 95% confidential interval 0.43-0.96%. Low-level sex chromosome mosaics (frequency more than 2.0%) were not found in controls. In autism, the mean frequency of aneuploidy involving chromosomes X and Y was 3.03% with median 3.05% and 95% CI 1.43-4.64% (Table **3**). The rate of sex chromosome mosaic aneuploidy demonstrated 3.8-fold increase in diseased brain of males with ID comorbid with ASD (p=0.0037, Mann-Whitney U test). These data confirm possible association of sex chromosome mosaic aneuploidy with ID comorbid with ASD. However, a more representative cohort of affected subjects with autism is strongly required.

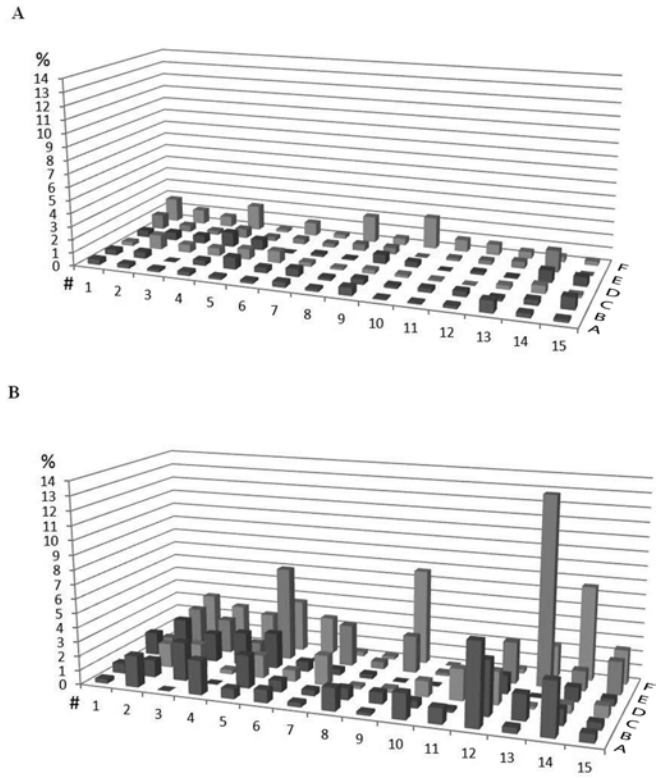

Fig. (3). Aneuploidy frequency (%) in brain cells (prefrontal cortex) in control (**A**) (n=15) and in patients with SCZ (**B**) (n=15) according to MFISH (1000 cells per each chromosome pair analyzed). Rows A, B, C, D, E, F = chromosomes 1, 9, 15, 16, 18, sex chromosomes, respectively.

Additionally, using MFISH and QFISH with chromosome-enumeration probes, we estimated aneuploidy frequency involving different autosomes and sex chromosomes in postmortem brain cells of 15 controls and 15 patients with SCZ. MFISH with DNA probes for autosomes 1, 9, 15, 16, 18 and sex chromosomes allowed us to compare the relative frequency of aneuploidy for five arbitrarily chosen autosomes and sex chromosomes. In total, 90000 cells were scored in 15 controls and 90000 cells were scored in 15 patients with SCZ. Analysis of controls revealed that the mean frequency of aneuploidy was in the range of 0.31 to 0.46% for autosomes 1, 9, 15, 16, 18 and 0.99% for sex chromosomes (Table **4A**). The median of aneuploidy frequency was 0.2-0.5% for autosomes and 0.8% for sex chromosomes with 95% confidential in interval in a range of 0.19-0.44% for chromosome 1; 0.29-0.55% for chromosome 9; 0.26-0.61% for chromosome 15; 0.27-0.65% in chromosome 16; 0.25-0.71% in chromosome 18 and 0.60-1.38% in sex chromosomes (Table **4A**). Individual cases of low-level mosaicism with more than 2% frequency per one homologous chromosome pair were found in two control cases out of 15 samples by a panel of chromosome-enumeration DNA probes for chromosomes 1, 9, 15, 16, 18, X and Y. These data allow us to establish the cut-off level for detecting low-level chromosome-specific aneuploidy involving autosomes and sex chromosomes X/Y in the normal human brain as 2%.

Table 2. The burden of mosaic aneuploidy involving sex chromosomes in normal and SCZ brains (mean aneuploidy rate (%) per individual chromosome; 25000 cells in 25 controls and 22000 cells in 22 SCZ samples scored).

--	Mean Value (M)	Median	95% Confidence Interval
Control (n=25000)	0.84	0.7	0.57-1.13
SCZ (n=22000)	2.08	1.75	1.29-2.86

Mann-Whitney U test for independent groups (control and SCZ): p=0.0028.

Table 3. The burden of mosaic aneuploidy involving sex chromosomes in brain tissues of 6 normal controls and 6 autistic patients (comorbid with mental retardation) (mean aneuploidy rate (%) per individual chromosome; 6000 cells in 6 controls and 6000 cells in 6 autistic samples scored).

--	Mean Value (M)	Median	95% Confidence Interval
Control (n=6000)	0.7	0.8	0.43-0.96
autism (comorbid with mental retardation) (n=6000)	3.03	3.05	1.43-4,64

Mann-Whitney U test for independent groups (control and autism with mental retardation): p=0.0037.

In SCZ patients, the mean frequency of aneuploidy involving autosomes 1, 9, 15, 16, 18 was in the range 1.09-2.73% and 2.42 for sex chromosomes. The median of aneuploidy frequency was 0.5-2.3% for autosomes and 2.4% for sex chromosomes with 95% confidential interval in a range of 0.62-2.33% for chromosome 1; 0.53-1.75% for chromosome 9; 0.64-1.53% for chromosome 15; 0.48-1.68% for chromosome 16; 0.88-4.75% for chromosome 18 and 1.28-3.75% for sex chromosomes (Table **4B**). Low-level mosaicism with frequency more than 2% was found in 18 cases studied by MFISH with DNA probes for chromosomes 1, 9, 15, 16, 18, X and Y: autosomes 1 (2 cases), 9 (2 cases), 16 (2 cases), 18 (6 cases), sex chromosomes (6 cases).

Our study of 15 control and 15 SCZ samples shows that the level of mosaic aneuploidy involving autosomes and sex

Table 4. Aneuploidy frequency (%) in brain cells (prefrontal cortex) in controls (4A) and SCZ (4B)*.

Table 4A: Controls						
Chromosomes (% aneuploidy) (monosomy and trisomy)						
Chromosomes Samples	1	9	15	16	18	X+Y
1	0.4	0.4	0.3	0.5	1.1	1.8
2	0.3	0.5	1.1	0.6	0.5	1.1
3	0.2	0	0.6	0.6	0.3	0.8
4	0.3	0.4	0.6	1.1	0.7	1.9
5	0.2	0.9	0.8	0.8	0.3	0.2
6	0.2	0.4	0.9	0	0.4	1.0
7	0.4	0.6	0.3	0.2	0.3	0.3
8	0.2	0.2	0.1	0.1	0.5	2,0
9	0.6	0.4	0.3	0.7	0.5	0.5
10	0.1	0.2	0.2	0.4	0	2.4
11	0.1	0.3	0.1	0	0.2	0.9
12	0.2	0.4	0	0.2	0.3	0.8
13	0.9	0.2	0.3	0.1	0.5	0.5
14	0.3	0.4	0.6	0.9	1.6	0.4
15	0.2	0.9	0.2	0.7	0	0.3
Statistics						
Chromosome	1	9	15	16	18	X+Y
Number of cells analyzed (N)	N=15000	N=15000	N=15000	N=15000	N=15000	N=15000
Median	0.2	0.4	0.3	0.5	0.4	0.8
95% Confidence interval	0.19-0.44	0.29-0.55	0.26-0.61	0.27-0.65	0.25-0.71	0.60-1.38
Mean value (M)	0.31	0.42	0.43	0.46	0.48	0.99
Table 4B: SCZ						
Chromosomes (% aneuploidy) (monosomy and trisomy)						
Chromosomes Samples	1	9	15	16	18	X+Y
1	0.3	0.7	0.2	1.6	0.6	1.0
2	2.2	1.2	1.7	2.8	3.0	3.4
3	0	2.7	1.9	2.0	2.4	2.8
4	2.4	0	0.3	2.3	0.9	2.4
5	0.7	2.3	1.6	2.5	6.6	3.6
6	0.9	0.8	0.8	0.7	0	2.6
7	0.3	0.4	2.1	0.4	2.9	0.4
8	1.6	0.8	0.2	0.3	0.5	1.2
9	0.2	0.8	0.3	0	2.6	6.7

(Table 4) contd….

Table 4B: SCZ						
Chromosomes (% aneuploidy) (monosomy and trisomy)						
10	1.8	0.5	1.1	0	0.2	1.7
11	1.1	0.2	2.2	0	1.4	0.7
12	5.7	3.8	2.3	1.3	2.9	0.3
13	0.4	1.8	0.2	0	13.2	2.2
14	3.7	1.1	0.6	1.0	1.4	6.6
15	0.6	0.5	0.8	0.5	2.3	2.4
Statistics						
Chromosomes	1	9	15	16	18	X+Y
Number of cells analysed (N)	N=15000	N=15000	N=15000	N=15000	N=15000	N=15000
Median	0.9	0.8	0.8	0.7	2.3	2.4
95% Confidence interval	0.62-2.33	0.59-1.75	0.64-1.53	0.48-1.58	0.88-4.75	1.28-3.58
Mean value (M)	1.47	1.17	1.09	1.03	2.73	2.42
Sampling interpreting 15,000 cells in control and 15,000 cells in SCZ (Mann-Whitney, U test for independent groups).	$p<0.0015$	$p<0.008$	$p<0.029$	$p>0.269$	$p<0.002$	$p<0.008$

* no fewer than 1000 cells per each chromosome pair studied (1, 9, 15, 16, 18), sex chromosome and brain sample in unaffected controls (n=15) and patients with SCZ (n=15) had been analyzed. In total, no fewer than 15000 cells were analyzed for each sample correspondingly. Altogether, 90000 cells were scored for controls and 90000 cells of patients with SCZ. The mean frequency less than 95% was supposed to be significant (Mann-Whitney, U test for independent groups).

chromosomes is dramatically increased in the diseased brain (Table **5**). Analysis of 15000 neural cells per each homologous chromosome pair 1, 9, 15, 16, 18, X and Y in 15 controls and 15 patients with SCZ revealed highly variable patterns of interindividual and interchromosomal distribution of mosaic aneuploidy (Fig. **3A** and **3B**). The considerable increase of aneuploidy frequency is determined for autosomes 1 ($p<0.0016$), 9 ($p<0.0084$), 15 ($p<0.029$), 18 ($p<0.002$) and sex chromosomes ($p<0.0084$). No differences between controls and patients with SCZ only for chromosome 16 ($p>0.269$) is detected. Analysis of aneuploidy frequency using DNA probes for five autosomes and sex chromosomes shows dramatic 2.9-fold increase of aneuploidy rate in SCZ (median value: 0.53% in control, 1.55% in SCZ). Thus, a strong association between SCZ and low-level mosaic aneuploidy involving chromosomes 1, 9, 15, 16, 18, X and Y in the diseased brain ($p=0.000013$, OR=22.25) appears to exist.

5. THE BURDEN OF BRAIN SPECIFIC LOW-LEVEL MOSAIC ANEUPLOIDY IN THE NORMAL AND DISEASED HUMAN BRAIN

Genetic and genomic analysis of somatic mosaicism (the presence of genetically distinct somatic cell populations in an organism) has increasingly become a popular area of biomedical research (*i.e.* medical and psychiatric genetics). As early as 2002, Youssoufian and Pyeritz mentioned that genetic mosaicism could be found, but could not be excluded in any cell population [67]. For instance, the human brain contains nearly 170±13 billion individual neural cells [68, 69]. As adult brain cells are assumed to derive from neural progenitors and glial cells that are generated during prenatal development and few first postnatal years, one can hypothesize that chromosomal aneuploidy is likely to be generated during the early central nervous system development. However, there is no consensus concerning the burden of brain specific mosaic aneuploidy and copy number variation in the normal and diseased human brain [33, 36-62, 70, 71]. In order estimate the chromosome-specific and the average mosaic aneuploidy, various cytogenetic and molecular genetic methods have been developed. Evidently, each of them possesses specific advantages and limitations [72-74].

Table 5. The burden of mosaic aneuploidy in normal and SCZ brains (aneuploidy rate (%) per "mean" chromosome in group of arbitrary selected chromosomes 1, 9, 15, 16, 18, X and Y; 90000 cells were scored in controls and 90000 cells were scored in 15 SCZ).

--	Mean Value (M)	Median	95% Confidence Interval
Control (n=90000)	0.54	0.53	0.41-1.31
SCZ (n=90000)	1.64	1.55	1.32-2.12

Mann-Whitney U test for independent groups (control and SCZ): $p=0.000013$.

Here, we overview the most recent results of an assessment of mosaic chromosome copy number alterations by FISH [62] allowing to estimate chromosome-specific ane-

uploidy rate in brain tissues at molecular level with single cell resolution in control and mental illnesses (SCZ and ID/ASD). We determined the cut-offs for low-level autosomal and sex chromosome-specific aneuploidy in unaffected control brain tissues at frequency less than 2% (Fig. **1**). As more 98% of individual cells from 25000 scored using sex chromosome-specific probes (Table **2**) and 90000 scored by chromosomes 1, 9, 15, 16 and 18 were presumably diploid, we concluded that FISH is a highly informative technique for detecting mosaic cell populations with aneuploidy rate ≥2%. Additionally, analyzing distributions of aneuploidy frequencies (Fig. **2**) in controls, we have noticed highly variable patterns of interindividual and interchromosomal aneuploidy rates in the normal human brain. These variations probably reflect both true low-level aneuploidy and FISH artifacts (somatic chromosome pairing, over-position, signal intensity variation *etc*.), which could lead to an overestimation of chromosome-specific aneuploidy. The results of FISH study of aneuploidy in the adult and developing brain revealed that ≤10-30% of all neural cells could be aneuploid [20, 32-45]. FISH data correlate with results of single cell sequencing demonstrating the occurrence of aneuploidy in normal human brain is ≤5% [45, 47]. However, these single-cell sequencing studies are based on analysis of limited cell number in an individual brain (usually ≤ 100 cells). Thus, these results are based on low power statistics due to small number of cells scored by single cell sequencing approach. One can propose that studies of aneuploidy rates in such a complex organ as the human brain composed by several hundreds of billion neural cells needs more robust statistical analysis. Therefore, these preliminary data should be replicated using more representative number of cells and brain tissue samples.

Interindividual and regional mosaic genome variability and heterogeneity allow speculating that low-level mosaic aneuploidy may play a role in neural diversity not only in healthy brain tissues [75], but also in genetic brain diseases [36-62]. Therefore, the study of mosaic aneuploidy is significant for understanding the role of somatic genome variation in mental disorders. Aneuploidy of somatic cells can be caused by non-heritable genetic and environmental factors (mutagens, viruses, infections *etc*.) and natural aging processes [25, 50, 75]. In conclusion, it is to note that the determination of the intrinsic effect of genetic (inherited and non-heritable) factors and clarification of genetic-environmental interactions in mental illness require large-scale investigations of mosaic aneuploidy in diseased and normal.

According to the study of an extended clinical cohort of patients with SCZ and idiopathic ID comorbid with autism, we were able to show that the frequency of low-level mosaic aneuploidy in brain tissues demonstrates significant 2-3-fold increase in SCZ and ID/ASD (Figs. **1**-**3**, Tables **2**-**5**). We also revealed strong association of low-level autosomal/sex chromosomal aneuploidy with SCZ. Our data confirm the hypothesis for association of low-level mosaic aneuploidy with common and, probably, overlapping psychiatric disorders, such as SCZ and ID/ASD. This association provides the support for a model proposing that the increased burden of rare *de novo* somatic chromosomal mutations or low-level mosaic aneuploidy could play a pathogenic role in SCZ and ID/ASD. We have analyzed mosaic aneuploidy rate in a relatively small clinical cohort of subjects with SCZ and ID/ASD using postmortem brain tissues by FISH technologies (efficient for monitoring chromosome-specific aneuploidy in persons with and without SCZ and ID/ASD). We applied a strategy for personalized genomic analysis to characterize individual pattern of brain-specific chromosome variation in clinical cohort of subjects with mental disorders (25 controls and 22 SCZ patients). This personalized molecular cytogenetic approach with application of DNA probes specific for sex chromosomes has shown that 10 subjects with SCZ (45.5%) were affected by low-level aneuploidy, while only 2 subjects (8%) demonstrated increase of mosaic aneuploidy over the cut-off level (≥2%) in control. We speculate that mosaic low-level aneuploidy is therefore a new example of association of somatic genome instability with common mental brain disorders.

CONCLUDING REMARKS

To summarize our overview of mosaic aneuploidy in the diseased brain, we would like to mention that genetic causes of common mental illnesses are known in approximately 30% of cases: metabolic disorders (≈5%), single-gene disorders (≈5%), and CNVs (≈7-20%) [1-19]. Genetic causes in ≥70% cases of mental disorders (*i.e.* SCZ and ID/ASD) are currently obscure. Accordingly, we speculate that about 45% of SCZ cases and probably some cases of idiopathic ID/ASD could be explained by the phenomenon of somatic genome instability, including a number of cases of mosaic low-level aneuploidy affecting almost exclusively the brain. We propose that low-level aneuploidy affecting neural cells in the developing, adult and aging brain may lead to high "genetic" load of postzygotic large-scale genomic CNV (*i.e.* aneuploidy) and may negatively affect the brain functions. Low-level mosaic aneuploidy may be a kind of a presently unknown and undetectable by current techniques pathogenic factor mediating common neuropsychiatric disorders and could be considered a potential biomarker of mental illnesses. However, the overall burden of rare chromosomal somatic mutations is to be underestimated. The study of low-level mosaicism in health and disease has appreciable significance for understanding the role of somatic genomic instability in the etiology and pathogenesis of mental illnesses.

We propose that increased level of chromosome-specific mosaic aneuploidy affecting sex chromosomes and autosomes leads, probably, to mosaic genetic imbalances in neural cells and abnormal functional activity of the neural network in SCZ and ID/ASD brain. To our knowledge, this overview gives actually the first direct confirmations of the theory that a pathological increase of mosaic aneuploid cell population in the critical brain regions, for example, PFC, may play a role in initiating and propagating comorbid psychiatric brain disorders.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

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