KOPF CARRIER

February 2015

Kopf Carrier #83

PUBLISHED BY DAVID KOPF INSTRUMENTS ■ TUJUNGA, CALIFORNIA

Neuroscience Reviews: The Mosaic Brain

German Torres*, Kyle Hitscherich
Department of Biomedical Sciences
New York Institute of Technology, College of Osteopathic Medicine
Old Westbury, New York 11568, USA
*Corresponding Author: torresg@nyit.edu

Summary

While chromosomal variation in brain tissue has long been associated with disease, it appears that gain or loss of whole chromosomes (aneuploidy) is often a normal, rather than a pathological, feature of the human brain.

Introduction

Human neurons have historically been viewed as having identical genomes. However, recent studies applying state-of-the-art approaches for evaluating chromosome numbers suggest that the brain is in fact a mix of euploid and aneuploid neurons (Fischer et al., 2012; Bushman and Chun, 2013).

Background

Humans are diploid organisms in that they carry two sets of nuclear chromosomes in their somatic cells. Humans are also haploid in that they carry one chromosome set per nucleus in specialized germ cell lines (i.e., ova and sperm). The diploid and the haploid states are both cases of normal euploidy (Griffiths et al., 1999). However, certain human diseases can arise if loss or gain of whole chromosomes occurs during embryonic development. For instance, an aneuploid condition in which there is only one (i.e., monosomic) copy of chromosomes instead of the usual two found in the diploid state, is known as Turner syndrome (XO karyotype). Conversely, if the aneuploid condition is characterized by a trisomic state in which there is an addition of a sex or autosome chromosome to the diploid progenitor, conditions such as Klinefelter syndrome (XXY karyotype), Down syndrome (trisomy 21) or Edwards syndrome (trisomy 18) are generated in utero (Griffiths et al., 1999). The most likely cause of these aneuploid conditions is a nondisjunction state or the failure of homologous chromosomes or chromatids to segregate to opposite poles at meiotic or mitotic divisions (Griffiths et al., 1999). Against this background, constitutive chromosome aberrations as those observed in Down syndrome suggest that brains with a more than diploid DNA content are at risk of accumulating amyloid β plaques and neurofibrillary tangles, a phenomenon that is remarkably similar to that of Alzheimer's disease pathology (Wisniewski, 1990; Patterson and Costa, 2005). However, the surprising findings that aneuploidy, DNA copy number variation (CNV), long interspersed nucleotide element-1 (LINE-1) and retrotransposons routinely occur in healthy neurons, has replaced the aforementioned pathological view with the notion that the

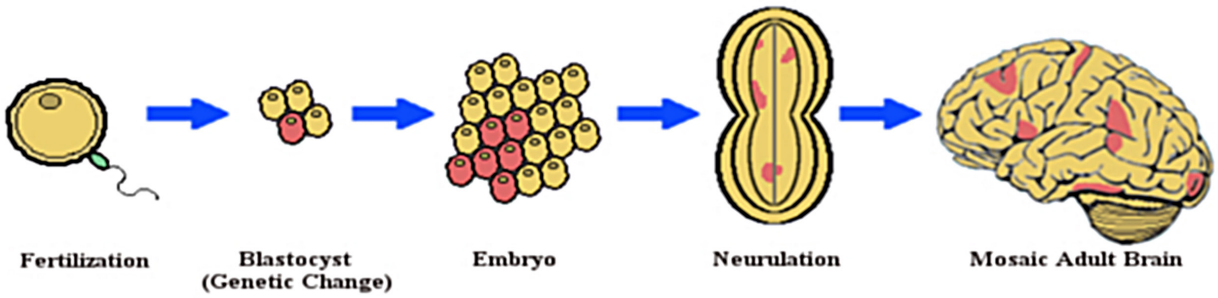

Fig. 1. Genomes in individual neurons are not functionally equivalent. During embryonic development, a mutation (i.e., genetic change) occurs within a subset of neurons (red cells) which will harbor the genetic change. Baseline levels of gene expression will therefore vary from cell to cell; from person to person.

brain is a mosaic entity with varied levels of DNA exceeding those hypothesized by the traditional euploidy state (Fig. 1).

The Mosaic Brain

There is now ample evidence that the human brain (and body) is mosaic owing to the loss or gain of whole chromosomes or the random infiltration of mobile DNA fragments (e.g., LINE-1) into the neuron genome (Muotri et al., 2005). For example, the frequency of mosaicism in fetal neurons is estimated to reach 30-35% of the brain parenchyma with an average aneuploidy frequency of 1.25-1.45% per chromosome, irrespective of cell lineage or cell phenotype (Pack et al., 2005; Yurov et al., 2007). In contrast, the frequency of adult cortical and hippocampal neurons harboring DNA content above the diploid level is about 11.0 % in non-diseased human brains (Rehen et al., 2005; Mosch et al., 2007; Lourov et al., 2009; Fischer et al., 2012). Differences in aneuploidy rates between fetal and adult neurons might be explained by differences in apoptotic cell death, autophagy or other developmental programs of cell pruning or cell elimination (Fischer et al., 2012). Indeed, a caspase-mediated mechanism of selective cell death is seen in fetal mouse brain, more specifically in aneuploidy cells of the cerebral cortex, indicating a preferential removal of neurons with higher than normal DNA content throughout development (Haydar et al., 1999; Kuan et al., 2000). It should be noted that human embryonic stem cells and human induced pluripotent stem cell lines also show small but constant structural alterations in their genomes, suggesting that aneuploidy and CNV are inherent characteristics of stem cell biology as well (Draper et al., 2004; McConnell et al., 2013). Taken together, these findings highlight the pervasiveness of mosaic aneuploidy in the human brain and indicate that some of us have more copies of certain genes than do others.

Functional Significance of Mosaicism

The fact that a single brain has multiple genomes raises several important questions. First, is the small frequency of aneuploidy high enough to affect neurons, tissues, developmental stages, individuals, the sexes or species? Second, is the amount of DNA exceeding the diploid level evolutionarily conserved across generations? At first glance, it would seem that aneuploidy or LINE-1 insertions into the circuitry of the brain would not be evolutionarily conserved as these structural modifications are only confined to human embryonic growth. In other words, mosaic aneuploidy only occurs in somatic cells not in the germ cell lines.

The answer to the first question is, unfortunately, not well known. Our current understanding of aneuploidy in the developing brain and its impact on single neuron function is obscure, although it is thought that low concentrations of aneuploidy are enough to cause debilitating symptoms in neurodegenerative diseases (Arendt et al., 2010; Fischer

et al., 2012). It should be noted that the systematic search for disease-causing mutations is only beginning as advanced molecular-cytogenetic techniques at the single-cell level are now being developed to detect brain conditions, including intellectual disabilities and autism spectrum disorders (Bushman and Chun, 2013). In this context, it is conceivable that the clinical consequences of mosaicism depend on which chromosome is involved, the developmental timing of the underlying mutational event, affected cell subpopulation phenotypes and the sex in which aneuploidy occurs. Recent studies indicate that chromosomes 1, 12, 17, 21 show significant genomic heterogeneity both in vivo and in vitro conditions (Rehen et al., 2005; Devalle et al., 2012), suggesting therefore the potential of aneuploidy neurons to influence cell survival, proliferation rates, protein synthesis and/or signaling cascades between synapses. There is also evidence that clonal mosaicism increases in frequency with age and could preferentially be biased for males (Machiela and Chanock, 2013). Finally, owing to the unique chromosome organization and number between mammalian species, it is thought that aneuploidies are species-specific and therefore the functional consequences of mosaicism would vary according to species and their evolutionary trajectory across geological time (Bushman and Chun, 2013).

In regards to the second question, although mosaicism is exclusively confined to somatic neurons, this particular phenomenon acts as if the aneuploidy mechanism was encoded in the germ cell line. That is, each generation

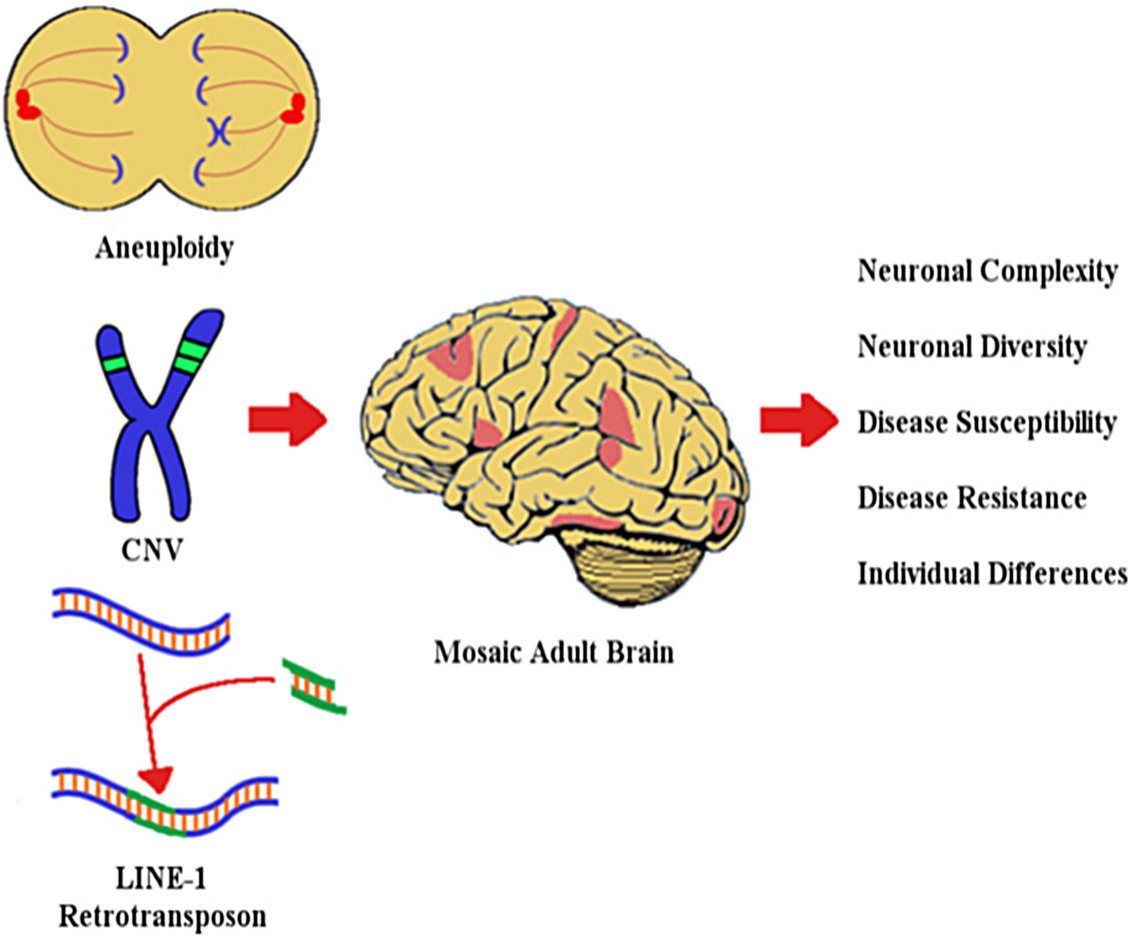

Fig. 2. Aneuploidy, CNV and LINE-1 phenomena are present in all of us. Fragmentation of genomes may generate diversity in the adult brain which could provide a basis for individual differences (i.e., individual genes, individual differences).

undergoes a similar, but not identical, process of chromosomal mosaicism. If this is the case, then, it is conceivable that the mechanism to generate aneuploidies would most likely be encoded in the genes and those of other species. Regardless of the selective evolutionary pressures that allow aneuploidy to be conserved, it is intriguing to hypothesize that loss or gain of chromosomes among populations of brain cells may contribute to individual differences or to human diversity (Muotri et al., 2005). For instance, this would help explain behavioral differences between two closely related individuals (e.g., twins). Also, genetic variation would help explain resistance to disease or tolerance to disease among healthy populations (Fig. 2). Linking an aneuploidy event with a particular behavioral function still is in its infancy. However, the fact that unique genomic events happen in individual neurons makes this line of investigation a potentially fruitful endeavor for understanding brain anatomy and cell function.

Conclusions

Mutations are the raw material of evolution and the cause of genetic diseases. However, the existence of a normally mutable genome in human neurons, suggests that mosaicism is a relatively stable process with important implications for cell behavior, individual differences and population diversity.

References

Arendt T, Brückner MK, Mosch B, Lösche A. Selective cell death of hyperploid neurons in Alzheimer's disease. Am J Pathol. 2010 Jul;177(1):15-20. doi: 10.2353/ajpath.2010.090955. Epub 2010 May 14

Bushman DM, Chun J. The genomically mosaic brain: aneuploidy and more in neural diversity and disease. Semin Cell Dev Biol. 2013 Apr;24(4):357-69. doi: 10.1016/j.semcdb.2013.02.003. Epub 2013 Mar 4. Review.PMID: 23466288

Devalle S, Sartore RC, Paulsen BS, Borges HL, Martins RA, Rehen SK. Implications of aneuploidy for stem cell biology and brain therapeutics. Front Cell Neurosci. 2012 Sep 5;6:36. doi: 10.3389/fncel.2012.00036. eCollection 2012

Draper JS, Smith K, Gokhale P, Moore HD, Maltby E, Johnson J, Meisner L, Zwaka TP, Thomson JA, Andrews PW. Recurrent gain of chromosomes 17q and 12 in cultured human embryonic stem cells. Nat Biotechnol. 2004 Jan;22(1):53-4. Epub 2003 Dec 7

Fischer HG, Morawski M, Brückner MK, Mittag A, Tarnok A, Arendt T. Changes in neuronal DNA content variation in the human brain during aging. Aging Cell. 2012 Aug;11(4):628-33. doi: 10.1111/j.1474-9726.2012.00826.x. Epub 2012 May 24

Griffiths JF, Gelbart WM, Miller JH, Lewontin RC. Modern Genetic Analysis. W.H. Freeman and Company, New York. 1999

Haydar TF, Kuan CY, Flavell RA, Rakic P. The role of cell death in regulating the size and shape of the mammalian forebrain. Cereb Cortex. 1999 Sep;9(6):621-6. Review

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 May;34(2):212-20. doi: 10.1016/j.nbd.2009.01.003. Epub 2009 Jan 21

Kuan CY, Roth KA, Flavell RA, Rakic P. Mechanisms of programmed cell death in the developing brain. Trends Neurosci. 2000 Jul;23(7):291-7. Review

Machiela MJ, Chanock SJ. Detectable clonal mosaicism in the human genome.

Semin Hematol. 2013 Oct;50(4):348-59. doi: 10.1053/j.seminhematol.2013.09.001. Review

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 Nov 1;342(6158):632-7. doi: 10.1126/science.1243472

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 Jun 27;27(26):6859-67

Muotri AR, Chu VT, Marchetto MC, Deng W, Moran JV, Gage FH. Somatic mosaicism in neuronal precursor cells mediated by L1 retrotransposition. Nature. 2005 Jun 16;435(7044):903-10

Patterson D1, Costa AC. Down syndrome and genetics - a case of linked histories. Nat Rev Genet. 2005 Feb;6(2):137-47

Pack SD, Weil RJ, Vortmeyer AO, Zeng W, Li J, Okamoto H, Furuta M, Pak E, Lubensky IA, Oldfield EH, Zhuang Z. Individual adult human neurons display aneuploidy: detection by fluorescence in situ hybridization and single neuron PCR. Cell Cycle. 2005 Dec;4(12):1758-60. Epub 2005 Dec 7

Rehen SK, Yung YC, McCreight MP, Kaushal D, Yang AH, Almeida BS, Kingsbury MA, Cabral KM, McConnell MJ, Anliker B, Fontanoz M, Chun J. Constitutional aneuploidy in the normal human brain. J. Neurosci. 2005 Mar 2;25(9):2176-80

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 Jun 27;2(6):e558

Wisniewski KE. Down syndrome children often have brain with maturation delay, retardation of growth, and cortical dysgenesis. Am J Med Genet Suppl. 1990;7:274-81

Bibliographies

Dr. German Torres (torresg@nyit.edu) received a Ph.D. in Neuroscience from the University of California at Santa Barbara and is currently an Associate Professor in the Department of Biomedical Sciences at the New York Institute of Technology, College of Osteopathic Medicine. His specific research interests are centered on the biological basis of brain disorders.

Kyle Hitscherich (khitsche@NYIT.edu) OMS I, received his B.A. in Cellular Biology and Neuroscience from Rutgers University in 2013. He is currently enrolled at the New York Institute of Technology, College of Osteopathic Medicine (NYIT COM) and will be graduating with a D.O. degree in 2018.

Editor's Column

Welcome to the 83rd issue of the *Kopf Carrier*. David Kopf Instruments has been publishing the *Carrier* since December 1973! This means that this is the 42nd year that this publication has gone out to the Neuroscience Community. David Kopf intended the publication as a means of disseminating new and underreported techniques and ideas to neuroscientists around the world. At first, the publication came out on an irregular and at times infrequent basis. As it became more and more recognized in the scientific community, authors were more easily recruited and the newsletter appeared more frequently. In early 1983, David Kopf asked me to become Science Editor for the company and to take over publication of the *Carrier* with the charge that it appear on a more regular basis, have no advertising, and that I was free to publish articles on any topic relevant to the field, no matter how controversial. I published my first issue of the *Carrier* in June 1983. Thus, I am entering my 32nd year as editor of this valuable publication. Many of you have told me that when it was sent out in paper format, you kept a complete file of all issues, as they were often useful in training students in the various techniques and instruments that had been discussed. Now all back issues are online at the Kopf Instruments website, and the publication is disseminated electronically. How publishing has changed. It has been a pleasure and honor serving as editor, and I hope to continue for a while longer.

This issue of the *Carrier* is another in our Neuroscience Reviews series, whose lead author is German Torres, Ph.D. He and his co-author, Kyle Hitscherich, BA, are at the New York Institute of Technology, College of Osteopathic Medicine (NYIT COM), where Kyle is a first year student. Their article on "The Mosaic Brain" is a very interesting discussion of the emerging evidence that the gain or loss of whole chromosomes in neurons during development may be a normal and beneficial process, although in other cases, the known cause of highly debilitating and life threatening conditions.

As I write this editorial, I am looking out the window at a fresh blanket of snow with a few flakes still falling. No, I am not at home in Florida, but rather visiting our son and his family in Shelby Township, MI, just north of Detroit. We spent December and a lot of January in Ohio and Michigan, visiting here and our other son's family in Ohio. We do have a condo in Dublin, OH, and a grandparent's apartment here in Michigan, so we are comfortable in both places. We also come up here for 2-3 months in the summer to be with the families. It is a great joy for grandma and grandpa to spend time with the growing grandkids. In a few days we go back to Florida for a while. It is good to be reminded of what winter is like (I think).

As I pointed out above, the *Carrier* was conceived by David Kopf as a means of conveying to the Neuroscience Community, various ideas, techniques and commentary that might not otherwise be available. Kopf Instruments also has, on its website, a listing of various stereotaxic atlases that have been published. Through these means, Kopf Instruments augments its value to the community in ways other than providing the world's largest and best-known line of stereotaxic instruments and accessories.

I would welcome commentary from our readers that would appear in the *Carrier*, as well as the submission of articles that any reader might like to author. There is a stipend for any published article. If you have any comments or questions, please address them to me at the phone or email address below.

Michael M. Patterson, Ph.D.
Science Editor
David Kopf Instruments
954-288-5518
954-452-6812 (FAX)
drmikep1@me.com