Behavioral Variability and Somatic Mosaicism: A Cytogenomic Hypothesis

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Abstract: Behavioral sciences are inseparably related to genetics. A variety of neurobehavioral phenotypes are suggested to result from genomic variations. However, the contribution of genetic factors to common behavioral disorders (i.e. autism, schizophrenia, intellectual disability) remains to be understood when an attempt to link behavioral variability to a specific genomic change is made. Probably, the least appreciated genetic mechanism of debilitating neurobehavioral disorders is somatic mosaicism or the occurrence of genetically diverse (neuronal) cells in an individual’s brain. Somatic mosaicism is assumed to affect directly the brain being associated with specific behavioral patterns. As shown in studies of chromosome abnormalities (syndromes), genetic mosaicism is able to change dynamically the phenotype due to inconsistency of abnormal cell proportions. Here, we hypothesize that brain-specific postzygotic changes of mosaicism levels are able to modulate variability of behavioral phenotypes. More precisely, behavioral phenotype variability in individuals exhibiting somatic mosaicism might correlate with changes in the amount of genetically abnormal cells throughout the lifespan. If proven, the hypothesis can be used as a basis for therapeutic interventions through regulating levels of somatic mosaicism to increase functioning and to improve overall condition of individuals with behavioral problems.

Keywords: Behavior, Brain, Chromosome, Somatic mosaicism, Postzygotic changes, Neurobehavioral disorders.

1. INTRODUCTION

Behavior is determined by interactions between genetic and environmental factors. Specific behavioral patterns are often associated with neurobehavioral disorders with a strong genetic background (i.e. autism and schizophrenia). Actually, there are a growing number of studies associating genomic abnormalities with specific behavioral phenotypes [1, 2]. The term “behavioral phenotype” has been recently introduced to describe a behavior featuring a biological condition associated with a certain genetic abnormality or syndrome [3]. Although many genetic conditions are not associated with highly specific behavioral phenotypes, there is a large number of syndromes originating from a genomic change and demonstrating characteristic behavioral features [4-8]. Nevertheless, underlying biological causes of specific behavioral manifestations resulting from genetic changes are extremely complicated and remain to be understood [9]. Still, genomic variations are consistently associated with specific behavioral phenotypes [10-14].

De novo and inherited genetic mutations leading to genomic variations are currently considered as a major biological cause of interindividual behavioral variability, especially in brain disorders (i.e. autism, schizophrenia, intellectual disability) [5, 8, 9, 11, 15]. Although it is commonly accepted that genomic variations generally affect all the cells of an organism due to meiotic errors [16-18], there are numerous studies evidencing that somatic or postzygotic genomic variations do accumulate during the early brain development and probably brain aging, originating from the failures of DNA replication/repair and cell cycle errors [19-21]. These types of genomic changes are defined as somatic genome variations or somatic mosaicism. Somatic mosaicism has been shown to be one of the promising yet underestimated mechanisms of phenotypic variability [22-26]. For instance, somatic mosaicism in the human brain has been proposed as a common mechanism for neurodevelopmental, neurobehavioral and neurodegenerative disorders [7, 27, 28]. Despite somatic mosaicism being detectable in almost all individuals [27-31], intracellular genomic diversification (genomic and chromosomal instability) has been found to be a highly probable mechanism for brain disorders including neurodegenerative and neurobehavioral diseases (i.e. Alzheimer’s disease, autism and schizophrenia) and may produce dramatic changes in brain cellular physiology and be-
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Mosaic genome variations accumulating or decreasing during lifetime may influence epigenetic and transcriptome patterns, ending up in functional and cellular diversity in the brain. The latter could negatively affect cell signaling pathways and neural circuit function leading to behavioral abnormalities and disease [7, 27, 28, 36, 40-43]. As a result, somatic mosaicism is now being addressed with respect to behavioral disorders [7, 19, 24, 27, 34, 42, 43]. The human brain responsible for speech, movement, cognition and other mental abilities is considered a primary target for studying the effect of somatic mosaicism on behavior and neuropsychiatric diseases. Single-cell analyses of brain cells in the healthy and diseased human brain have demonstrated that somatic mosaicism affects neuronal cell populations and is likely to mediate pathogenic processes associated with brain malfunctioning. Genomic changes are likely to be derived from disturbances in genome maintenance and cell cycle regulation pathways along with environmental influences (genetic-environmental interactions) [7, 27, 28, 32-47]. Accordingly, one can speculate that somatic genomic variations could also affect behavioral phenotypes.

Somatic mosaicism has been found in many genetic syndromes associated with behavioral abnormalities [1, 7, 48-51]. For instance, phenotypic features in patients with mosaic trisomy of chromosome 21 (Down syndrome) are determined by the percentage of trisomic cells present in different tissues [48, 49] (Fig. 1). Furthermore, somatic genome variations are generally dynamic. In other words, the amount of cells exhibiting altered genomes varies throughout lifespan [38, 51-55]. Therefore, one can speculate that variation of mosaicism levels is able to result in appreciable phenotypic changes including behavioral phenotypes. Interestingly, this assumption resembles to some extent the concept of the “dynamic genome”, which is used for explaining genetic-environmental interactions modulating human behavior as well as consequences of stress and genomic adaptation to environmental effects [56-60]. However, similar theories leave aside somatic mosaicism without considering it as a mechanism for behavior variability.

Summarizing data on somatic mosaicism and its possible relevance for neurobiology and behavioral sciences, we have proposed a hypothesis suggesting that the levels of somatic mosaicism are constantly changing throughout ontogeny due to environmental effects affecting behavioral patterns. In its simplest form, the hypothesis can be postulated as follows: the amount of abnormal cells in an organism correlates with the behavioral patterns, i.e. the increase in the abnormal cell proportion is likely to have a negative behavioral effect, whereas a decrease is likely to have a positive one.

Since genomic variations affecting behavior are likely to be those confined to brain tissue [7], one should address somatic mosaicism/mutations in the brain per se. Regardless of overwhelming majority of human brain cells to be postmitotic, non-malignant brain cells are still prone to mutational events and DNA damage, which seem to accumulate during ontogeny in the aging human [61-63]. Notwithstanding, somatic genomic variations essentially are accumulated during the prenatal and early postnatal brain development [37, 55, 64-67]. Therefore, there is a need to modify the hypothesis.

Human brain is a highly plastic structure being especially predetermined to change in early childhood and is composed of a myriad of different neuronal cell types [64]. High levels of mosaic aneuploidy (loss/gain of chromosomes in a cell) hallmark the human developing brain being probably eliminated at later stages of life [51, 53, 55, 65-67]. However, genetically abnormal cells do remain in the postnatal brain.

Fig. (1). Regular versus mosaic Down syndrome: cognitive differences.
CONCLUSION

Consequently, an increase in the levels of abnormal cells might influence brain function, plasticity and performance [7, 27, 32-47]. In the behavioral context, neurodevelopmental diseases may be associated with a tissue-specific somatic mosaicism causing specific alterations to neural plasticity and interaction. We suggest that the higher is the percentage of mosaic cells among brain cells, the more severe are behavioral abnormalities. Additionally, somatic mosaicism in non-neuronal tissues has the potential to influence indirectly behavioral phenotype, as well. Since environmental factors are affecting levels of somatic mutations in mitotic tissues [23-26], these assumptions have relevance to therapeutic interventions [28]. Once the hypothesis is supported, new therapeutic opportunities for devastating neurobehavioral diseases would be available. Firstly, to do so, one needs to observe the effects described above in larger cohorts as well as studying somatic mosaicism in brain tissues. To correlate higher levels of somatic mosaicism with more severe behavioral manifestations, it is mandatory to perform a longitudinal study via genetic methodology and behavioral (psychologic) reports on an individual condition for a rather long period of time. One should keep in mind that it is impossible to obtain brain samples from a living individual to monitor somatic genome variations for a long period. However, it is possible to correlate the results of behavioral studies with somatic mosaicism evaluations in mitotic tissues and assessment of brain tissue susceptibility to genome instability uncovered by whole-genome scanning technologies (as suggested in [28, 68]). In addition, basic research of correlation between somatic mosaicism levels in mitotic and postmitotic neuronal and non-neuronal (brain) tissues should be pursued. Ideally, data on patients with identical underlying causes of neurobehavioral abnormalities should be used to compare behavioral phenotype severity and variability with large genetic datasets in a personalized manner. Longitudinal research by monitoring tissue-specific mosaicism during the ontogeny along with evaluating general health and behavioral condition is likely to provide speculations on the associations between somatic mosaicism and behavioral variability. Finally, if this hypothesis is supported, somatic mosaicism will be referred to as a new connecting (or missing) link between genome, environment and behavior.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Charnley, E. Behavior genetics and postgenomics. Behav. Brain Sci., 2012, 35(5), 331-358.
[2] Plomin, R.; DeFries, J.C.; Knopik, V.S.; Neiderheiser, J. Behavior Genetics, Palgrave Macmillan: Basingstoke, United Kingdom, 2013.
[3] Harris, J.C. Behavioral phenotypes of neurodevelopmental disorders: Portals into the developing brain. In: Neuropsychopharmacology: The Fifth Generation of Progress, Lippincott Williams & Wilkins: Baltimore, MD, USA, 2002, 625-638.
[4] McGuffin, P.; Riley, B.; Plomin, R. Genomics and behavior. Toward behavioral genomics. Science, 2001, 291(5507), 1232-1249. Available from: science.sciencemag.org/content/291/5507/1232.full
[5] Inoue, K.; Lupski, J.R. Genomics and genomics of behavioral and psychiatric disorders. Curr. Opin. Genit. Dev., 2003, 13(3), 303-309.
[6] Plomin, R.; McGuffin, P. Psychopathology in the postgenomic era. Annu. Rev. Psychol., 2003, 54, 205-228. Available from: http://www.anuareviews.org/doi/10.1146/annurev.psych.54.101601.145108
[7] Iourov, I.Y.; Vorsanova, S.G.; Yurov, Y.B. Chromosomal variation in mammalian neuronal cells: Known facts and attractive hypotheses. Int. Rev. Cytol., 2006, 249, 143-191. Available from: europa.mcp.org/abstract/med/16697283
[8] Hochstenbach, R.; Buizer-Voskamp, J.E.; Vorstman, J.A.; Ophoff, R.A. Genome arrays for the detection of copy number variations in idiopathic mental retardation, idiopathic generalized epilepsy and neuropsychiatric disorders: Lessons for diagnostic workflow and research. Cytogenet. Genome Res., 2011, 135(3-4), 174-202.
[9] Geschwind, D.H.; Flint, J. Genetics and genomics of psychiatric disease. Science, 2015, 349(6255), 1489-1494. Available from: http://science.sciencemag.org/content/349/6255/14897cd=cf180550-4d83-402-906-816eefc95666
[10] Steele, P.M.; Medina, J.F.; Nores, W.L.; Mauk, M.D. Using genetic mutations to study the neural basis of behavior. Cell, 1998, 95, 879-882.
[11] Poot, M.; van der Smagt, J.J.; Briëtstra, E.H.; Bourgeron, T. Disentangling the myriad genomics of complex disorders, specifically focusing on autism, epilepsy, and schizophrenia. Cytogenet. Genome Res., 2011, 135(3-4), 228-240.
[12] Vorsanova, S.G.; Yurov, Y.B.; Soloviev, I.V.; Iourov, I.Y. Molecular cytogenetic diagnosis and somatic genome variations. Curr. Genomics, 2010, 11(6), 440-446.
[13] Flint, J.; Munafò, M.R. Candidate and non-candidate genes in behavior genetics. Curr. Opin. Neurobiol., 2013, 23(1), 57-61.
[14] Machiela, M.J.; Zhou, W.; Sampson, J.N.; Dean, M.C.; Jacobs, K.B.; Black, A.; Brinton, L.A.; Chang, I.S.; Chen, C.; Chen, C.; Chen, C.; Chen, I.S.; Bou, M.C.; De Vos, I.; Doherty, J.; Friedenreich, C.M.; Gaudet, M.M.; Haiman, C.A.; Hankinson, S.E.; Hartge, P.; Henderson, B.E.; Hong, Y.-C; Hosgood, H.D.; Hsiung, C.A.; Hu, W.; Hunter, D.J.; Jessop, L.; Kim, H.N.; Kim, Y.H.; Kim, Y.T.; Klein, R.; Kraft, P.; Lan, Q.; Lin, D.; Liu, J.; Le Marchand, L.; Liang, X.; Lissowska, J.; Lu, L.; Magliocco, A.M.; Matsuo, K.; Oson, S.H. Orlov, I.; Park, J.Y.; Pooler, L.; Prescott, J.; Rastogi, R.; Risky, H.A.; Schumacher, F.; Seow, A.; Setiawan, W.V.; Shen, H.; Sheng, X.; Shin, M.H.; Shu, X.O.; Van Den Berg, D.; Wang, J.C.; Wentzensen, N.; Wong, M.P.; Wu, C.; Wu, T.; Wu, Y.L.; Xia, L.; Yang, H.P.; Yang, P.C.; Zheng, W.; Zhou, B.; Abnet, C.C.; Albanes, D.; Aldrich, M.C.; Amos, C.; Amundaddottir, L.L.; Berndt, S.I.; Blot, W.J.; Bock, C.H.; Bracci, P.M.; Burdett, L.; Buring, J.E.; Butter, M.A.; Carreon, T.; Chatterjee, N.; Chung, C.C.; Cook, M.B.; Cullen, M.; Davis, F.G.; Ding, T.; Duell, E.J.; Epstein, C.G.; Fan, J.H.; Figueroa, J.D.; Fraumeni, J.F.; Jr; Freedman, N.D.; Fuchs, C.S.; Gao, Y.T.; Gapturst, S.M.; Patiño-Garcia, A.; García-Closas, M.; Gaziano, J.M.; Giles, G.G.; Gillanders, E.M.; Giovannucci, E.L.; Goldin, L.; Goldstein, A.M.; Greene, N.H.; Hallmans, G.; Harris, C.C.; Henriksson, B.; Holly, E.A.; Hoover, R.N.; Hu, N.; Hutchinson, A.; Jenab, M.; Johannson, C.; Khaw, K.T.; Koh, W.P.; Kolonel, L.N.; Kooperberg, C.; Krogh, V.; Kurtz, R.C.; LaCroix, A.; Landgren, A.; Landti, M.T.; Li, D.; Liao, L.M.; Malats, N.; McGlynn, K.A.; McNeill, L.H.; McWilliams, R.R.; Melin, B.S.; Mirabella, L.; Peplonska, B.; Peters, U.; Petersen, G.M.; Prokunina-Olsson, L.; Purdue, M.; Qiao, Y.L.; Rabe, K.G.; Rajaraman, P.; Real, F.X.; Riboli, E.; Rodriguez-Santiago, Vorsanova et al.
[48] Papavassiliou, P.; York, T.P.; Gursoy, N.; Hill, G.; Nicely, L.V.; Sundaram, U.; McClain, A.; Aggen, S.H.; Eaves, L.; Riley, B.; Jackson-Cook C. The phenotype of persons having mosaicism for trisomy 21/Down syndrome reflects the percentage of trisomic cells present in different tissues. Am. J. Med. Genet. A, 2009, 149A(4), 573-583.

[49] Hultén, M.A.; Jonasson, J.; Nordgren, A.; Iwarsson, E. Germinal and somatic trisomy 21 mosaicism: How common is it, what are the implications for individual carriers and how does it come about? Curr. Genomics, 2010, 11(6), 409-419.

[50] Taylor, T.H.; Griffin, S.A.; Spata, P.J.; Crain, J.L.; Wilson, J.M.; Griffin, D.K. The origin, mechanisms, incidence and clinical consequences of chromosomal mosaicism in humans. Hum. Reprod. Update, 2014, 20(4), 571-581.

[51] Yurov, Y.B.; Vorsanova, S.G.; Iourov, I.Y. Ontogenetic variation of the human genome. Curr. Genomics, 2010, 11(6), 420-425.

[52] Munné, S.; Weier, H.U.; Grifo, J.; Cohen, J. Chromosome mosaicism in human embryos. Biol. Reprod., 1994, 51(3), 373-379.

[53] Yurov, Y.B.; Iourov, I.Y.; Vorsanova, S.G.; Liehr, T.; Kolotii, A.D.; Kutsev, V.S.; Pellestor, F.; Beresheva, A.K.; Demidova, I.A.; Kravets, V.S.; Monakhov, V.V.; Soloviev, I.V. Aneuploidy and confined chromosomal mosaicism in the developing human brain. PLoS One, 2007, 2(6), e558. Available from: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0000558

[54] Peterson, S.E.; Westra, J.W.; Rehen, S.K.; Young, H.; Bushman, D.M.; Paczkowski, C.M.; Yung, Y.C.; Lynch, C.L.; Tran, H.T.; Nickey, K.S.; Wang, Y.C.; Laurent, L.C.; Loring, J.F.; Carpenter, M.K.; Chun, J. Normal human pluripotent stem cell lines exhibit pervasive mosaic aneuploidy. PLoS One, 2011, 6(8), e23018. Available from: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0023018

[55] Yurov, Y.B.; Iourov, I.Y.; Monakhov, V.V.; Soloviev, I.V.; Vostrikov, V.M.; Vorsanova, S.G. The variation of aneuploidy frequency in the developing and adult human brain revealed by an interphase FISH study. J. Histochem. Cytochem., 2005, 53(3), 385-390.

[56] Bell, A.M.; Robinson, G.E. Genomics. Behavior and the dynamic genome. Science, 2011, 332(6034), 1161-1162. Available from: http://science.sciencemag.org/content/332/6034/1161

[57] Heng, H.H.; Liu, G.; Stevens, J.B.; Bremer, S.W.; Ye, C.J.; Abdallah, B.Y.; Horne, S.D.; Ye, C.J. Decoding the genome beyond sequencing: The new phase of genomic research. Genomics, 2011, 96(4), 242-252.

[58] Horne, S.D.; Chowdhury, S.K.; Heng, H.H. Stress, genomic adaptation, and the evolutionary trade-off. Front. Genet., 2014, 5, 92.

Available from: https://www.frontiersin.org/articles/10.3389/fgene.2014.00092/full

[59] Lacourse, E.; Boivin, M.; Brendgen, M.; Petitclerc, A.; Girard, A.; Vitaro, F.; Paquin, S.; Ouellet-Morin, I.; Dionne, G.; Tremblay, R.E. A longitudinal twin study of physical aggression during early childhood: Evidence for a developmentally dynamic genome. Psychol. Med., 2014, 44, 2617-2627. Available from: https://www.cambridge.org/core/core/journals/psychological-medicine/article/a-longitudinal-twin-study-of-physical-aggression-during-early-childhood-evidence-for-a-developmentally-dynamic-genome/99A7F08F3A5D6E4F4EAE91CBF23D4E68

[60] Pingault, J.B.; Rijsdijk, F.; Zheng, Y.; Plomin, R.; Viding, E. Developmentally dynamic genome: Evidence of genetic influences on increases and decreases in conduct problems from early childhood to adolescence. Sci. Rep., 2015, 5, 10053. Available from: https://www.nature.com/articles/srep10053

[61] Lu, T.; Pan, Y.; Kao, S.Y.; Li, C.; Kohane, I.; Chan, J.; Yankner, B.A. Gene regulation and DNA damage in the ageing human brain. Nature, 2004, 429(6994), 883-891. Available from: https://www.nature.com/articles/nature02661

[62] Mattson, M.P.; Magnus, T. Ageing and neuronal vulnerability. Nat. Rev. Neurosci., 2006, 7(4), 278-294.

[63] Bishop, N.A.; Lu, T.; Yankner, B.A. Neural mechanisms of ageing and cognitive decline. Nature, 2010, 464(7288), 529-535. Available from: https://www.nature.com/articles/nature08983

[64] Muotri, A.R.; Gage, F.H. Generation of neuronal variability and complexity. Nature, 2006, 441(7097), 1087-1093. Available from: https://www.nature.com/articles/nature04959

[65] Kingsbury, M.A.; Friedman, B.; McConnell, M.J.; Rehen, S.K.; Yang, A.H.; Kaushal, D.; Chun, J. Aneuploid neurons are functionally active and integrated into brain circuitry. Proc. Natl. Acad. Sci. U.S.A., 2005, 102(17), 6143-6147.

[66] Iourov, I.Y.; Liehr, T.; Vorsanova, S.G.; Kolotii, A.D.; Yurov, Y.B. Visualization of interphase chromosomes in postmitotic cells of the human brain by multicolour banding (MCB). Chromosome Res., 2006, 14(3), 223-229.

[67] Westra, J.W.; Peterson, S.E.; Yung, Y.C.; Mutoh, T.; Barral, S.; Chun, J. Aneuploid mosaicism in the developing and adult cerebellar cortex. J. Comp. Neurol., 2008, 507(6), 1944-1951.

[68] Iourov, I.Y.; Vorsanova, S.G.; Zelenova, M.A.; Korostelev, S.A.; Yurov, Y.B. Genomic copy number variation affecting genes involved in the cell cycle pathway: Implications for somatic mosaicism. Int. J. Genomics, 2015, 2015, 757680. Available from: https://www.hindawi.com/journals/ijg/2015/757680/