

We can Ourselves have an Effect on the Function of our Genes

Portin P*

Department of Biology, Laboratory of Genetics, University of Turku, FI-20014 Turku, Finland

*Corresponding author: Petter Portin, Laboratory of Genetics, Department of Biology, University of Turku, FI-20014 Turku, Finland, Tel: +358 50 466 5474; E-mail: petter.portin@utu.fi

Rec date: Apr 29, 2015, Acc date: Jun 10, 2015, Pub date: Jun 13, 2015

Copyright: © 2015 Portin P. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Short Communication

It is customary to say that humans are the product of the interaction between genetic and environmental factors. This is, of course, true in the sense that the development of all our characteristics is influenced by both the genes and the environment; both are necessary, and neither can alone achieve anything. This is, however, only a part of a more complex web of interactions. It has, namely, in the last years become more and more evident that human beings can with their own activity have an influence on how our genes work and hence how and where to our characteristics will develop. In addition, humans can, of course, at least to some extent choose the disposition of their environment, such as the type of education and schooling, occupation, place of residence and workplace, for instance.

Here I give a few typical and clear-cut examples of recent scientific results of how we humans can affect the function of our genes.

It has been known for a long time that physical exercise increases the mass and brawn of the skeletal muscles. In the last years it has been demonstrated that this increase is, at least partly, based on the fact that physical exercise can influence the methylation of the genes involved in the energy metabolism of the skeletal muscles, i.e. which genes are open for genetic transcription and which are closed. It has been shown that already a training period of twenty minutes alters the state of these genes so that the regulatory parts of certain genes are shifted from a closed methylated state to a de-methylated open state, and thus resulting in persistent changes in the transcription of genes [1].

The second example involves gene function in the brains. Brains are a similar organ with the skeletal muscles in the sense, that training improves their capacity and function. For example, learning [2] and environmental enrichment [3] alter gene transcription in the brains of young animals. Pathways of gene functions influenced by these experiences include cell-survival-associated genes and genes involved in synaptic plasticity. Thus, it seems that there is a positive feedback loop between learning and the genes associated with learning.

The third example comes from the studies concerning the relationship of musicality and genetics led by Docent Irma Järvelä at The University of Helsinki, Finland. She and her group were able to demonstrate that both music performance [4] and listening to music [5] alters the transcriptome of humans, notably professional musicians and musically experienced people. The genome-wide peripheral blood transcriptome of professional musicians was analyzed after a 2-hr concert performance and after a 'music-free' control session. It was found that certain genes were up-regulated at the transcriptional level measured after the music performance, and that certain other genes were down-regulated. The up-regulated genes were found to affect dopaminergic neurotransmission, motor behavior, neuronal plasticity, and neurocognitive functions including learning and memory, for example [4]. Interestingly, but perhaps not very surprisingly, some of

these genes are involved in song perception and production in songbirds, suggesting an evolutionary conservation in biological processes related to sound perception or sound production.

In musically experienced persons, but not in musically inexperienced participants of the study, certain changes in the transcriptome after listening to music were observed [5]. Genes which were found to be up-regulated at the transcriptional level were partly the same which were up-regulated after music performance and are primarily known to be involved in the secretion and transport of dopamine, neuron projection, protein sumoylation, long-term potentiation and de-phosphorylation. Down-regulated genes are known to be involved in ATP synthase-coupled proton transport, cytolysis, and positive regulation of caspase, peptidase and endopeptidase activities [5]. One of the most up-regulated genes, alpha-synuclein (SNCA) is located in the best linkage region of musical aptitude on chromosome 4q22.1 and is regulated by GATA2, which is known to be associated with musical aptitude [6].

The fourth example deals with human population differences in the transcriptome and suggests that, among other things, the life style of people can have an effect on gene function at the transcriptional level [7,8]. Gene expression in peripheral blood leucocyte samples from 46 desert nomadic, mountain agrarian and coastal urban Moroccan Amazigh individuals, i.e. individuals belonging to the same ethnic group but having different environments and culture, were analyzed. As much as one third of the leucocyte transcriptome was found to be associated with differences among the regions mentioned [7]. The results show a strong genome-wide gene expression signature of regional population differences that presumably include life style among other things. The results imply that life style such as nutrition, geography, and abiotic and biotic environmental factors can play at least as great a role as genetic divergence in modulating gene expression variation in humans [7].

In a subsequent study, the Amazigh individuals were compared with people of Arab descent also from Morocco in order to test whether geography and/or ancestry affects observed associations between genotype and transcript abundance [8]. It was observed that as much as half of the transcriptome is influenced by the environment in a highly coordinated manner such that where a person lives explains up to a quarter of the variation of the transcripts. It was concluded that the environmental influences are probably a combination of biotic and abiotic factors, in addition to cultural and behavioral ones, whereas genetic differences between the two North African ancestries studies are relatively minor [8].

The subsequent examples deal with studies that indicate that different kinds of stress, social factors, and early life experiences can cause epigenetic changes in the genomes of experimental animals and man. Moreover they also indicate that maternal behaviour, too, can

have an epigenetic effect on the DNA in various parts of the brains of the pups of the female rats in question. This fact suggests that perhaps we humans also can, with our behavior, have an influence on the function, not only of our own genes, but also on the genes of our children.

Considering the effect of stress on the epigenetic pattern of the genome of mice, it was firstly observed that early-life stress can dynamically control DNA methylation in post mitotic neurons to generate persistent changes in arginine vasopressin expression that trigger neuroendocrine and behavioral alteration that are frequent features in depression [9]. Secondly, it has been demonstrated that chronic social stress in adult mice induced long-term demethylation of the genomic region that includes the corticotropin-releasing hormone receptor gene (Crf gene). Further, it was observed that demethylation occurred only in the subset of mice that displayed social avoidance, and that site-specific knockdown of the Crf gene attenuated stress-induced social avoidance [10].

It is generally thought that disadvantaged socio-economic position in childhood is associated with increased adult mortality and morbidity. Recent studies, [11,12] have been able to show that this phenomenon is most likely associated with changes in the epigenetic pattern of the genomes of the people involved. It was namely observed, firstly, that methylation differences in megabase-sized regions of the genome were related to the socio-economic position differences of the subjects studied. Specifically, differences in the methylation patterns appeared in promoters of genes enriched in key cell signalling pathways [11]. Secondly, global DNA hypomethylation was observed in the most socio-economically deprived subjects of the cohort studied, and, importantly, associations were found between global DNA methylation content and biomarkers of cardiovascular disease and inflammation [12].

Childhood maltreatment is likely to influence fundamental biological processes and engrave long-lasting epigenetic marks, leading to adverse health outcomes in adulthood [13-15]. DNA methylation profiles spanning 6.5 million base pairs centred at the glucocorticoid receptor gene (NR3C1) in the hippocampus were studied in human adults who experienced abuse as children and non-abused controls. The profiles revealed hundreds of DNA methylation differences, associated with early life experience and distributed across the entire region in nonrandom patterns. These differences seem to specifically target regulatory regions, particularly those of the protocadherin α , β , and γ gene families, encoding for a subgroup of the cadherin superfamily of homophilic cell-adhesion proteins [13].

Experience of abuse as a child is also associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder [14]. DNA methylation pattern in peripheral blood cells and gene expression profiles in patients with posttraumatic stress disorder, who had experienced childhood abuse, was compared with the respective patterns and profiles of patients who had similar clinical symptoms but who had not suffered abuse in childhood, yet later during the course of the lifespan. Almost completely non-overlapping differences in gene expression profiles at the transcriptional level were found. These differences were paralleled by the enrichment of several distinct biological networks between the groups. Moreover, the gene-expression changes were accompanied and likely mediated by changes in DNA methylation in the same loci to a much larger proportion in the childhood abuse group than the control group [14].

Finally, concerning childhood stress, in a longitudinal study, prospective associations between adversities in early childhood and the epigenetic conformation of fifteen-year-old adolescents' genomic DNA of the buccal epithelial cells were reported. Maternal stressors in infancy and paternal stressors in the preschool years were most strongly predictive of differential methylation, and the patterning of such epigenetic marks varied by children's gender [15].

In conclusion, it can be said that different kinds of detrimental experiences in the early life can have persistent adverse effects in man on the function of the genes, most likely mediated by alterations in the epigenome. In contrast to this, the examples presented below show that normal maternal care in rodents has beneficial effects on development of the offspring, also mediated by epigenetic changes, i.e. via a kind of epigenetic inheritance.

The nature of maternal care that an infant receives can affect the child's emotional and cognitive development, which is endured into adulthood. Similarly, maternal behaviour in rodents is associated with long-term programming of individual differences in behavioural and hormonal responses to stress in the offspring. The key mechanistic question is, of course, how such influences become long lasting [16]. Experimental studies have indicated that pup licking and grooming and arched-back nursing by rat mothers alters the epigenome at a glucocorticoid receptor gene in the hippocampus of the offspring [17], which concomitantly alters the hypothalamic-pituitary-adrenal responses to stress in these animals [18]. Likewise, it has also been demonstrated in rats, that the amount of maternal care had an effect on the epigenetics, and consequently on the function of the glutamic acid decarboxylase 1 gene (GAD1) in the hippocampus of the offspring. Those animals that received plenty of maternal care (licking and grooming) showed enhanced hippocampal GAD1 mRNA expression, decreased cytosine methylation, and increased histone 3-lysine 9 acetylation of the GAD1 promoter compared with animals that received less maternal care [19]. These studies might have a bearing on our comprehension of the human mental health. Namely, the forebrain expression of glutamic acid decarboxylase (GAD), the rate-limiting enzyme in GABA synthesis, is decreased in schizophrenic patients [20], and the function of the GABAergic system has been linked to the pathophysiology of other mental diseases also, including depression [19].

The examples given here on the effect of our culture and personal activities on the function of our genes strongly suggest that genes are by no means a destiny. On the contrary, genes provide us a possibility within the contingencies of which we can conduct the course of our lives and the development of our characteristics – physical, psychological and mental. On the other hand, however, we can, with unwise behaviour, cause harmful alterations in the function of our own genes and even of the genes of our children. This reminds us that we are in fact also responsible for our genes.

Acknowledgement

Thanks are given to my friend Marja Vieno, M.Sc. for checking the language.

References

1. Barrès R, Yan J, Egan B, Treebak JT, Rasmussen M, et al. (2012) Acute exercise remodels promoter methylation in human skeletal muscle. *Cell Metab* 15: 405-411.

2. Cavallaro S, D'Agata V, Manickam P, Dufour F, Alkon DL (2002) Memory-specific temporal profiles of gene expression in the hippocampus. *Proc Natl Acad Sci U S A* 99: 16279-16284.
3. Rampon C, Jiang CH, Dong H, Tang YP, Lockhart DJ, et al. (2000) Effects of environmental enrichment on gene expression in the brain. *Proc Natl Acad Sci U S A* 97: 12880-12884.
4. Kanduri C, Kuusi T, Ahvenainen M, Philips AK, Lähdesmäki H, et al. (2015) The effect of music performance on the transcriptome of professional musicians. *Sci Rep* 5: 9506.
5. Kanduri C, Raijas P, Ahvenainen M, Philips AK, Ukkola-Vuoti L, et al. (2015) The effect of listening to music on human transcriptome. *PeerJ* 3: e830.
6. Pulli K, Karma K, Norio R, Sistonen P, Göring HHH, et al. (2008) Genome-wide linkage scan for loci of musical aptitude in Finnish families: evidence for a major locus at 4q22. *Journal of Medical Genetics* 45: 451-456.
7. Idaghdour Y, Storey JD, Jadallah SJ, Gibson G (2008) A genome-wide gene expression signature of environmental geography in leukocytes of Moroccan Amazighs. *PLoS Genet* 4: e1000052.
8. Idaghdour Y, Czika W, Shianna KV, Lee SH, Visscher PM, et al. (2010) Geographical genomics of human leukocyte gene expression variation in southern Morocco. *Nat Genet* 42: 62-67.
9. Murgatroyd C, Patchev AV, Wu Y, Micale V, Bockmühl Y, et al. (2009) Dynamic DNA methylation programs persistent adverse effects of early-life stress. *Nat Neurosci* 12: 1559-1566.
10. Elliott E, Ezra-Nevo G, Regev L, Neufeld-Cohen A, Chen A (2010) Resilience to social stress coincides with functional DNA methylation of the *Crf* gene in adult mice. *Nat Neurosci* 13: 1351-1353.
11. Borghol N, Suderman M, McArdle W, Racine A, Hallett M, et al. (2012) Associations with early-life socio-economic position in adult DNA methylation. *Int J Epidemiol* 41: 62-74.
12. McGuinness D, McGlynn LM, Johnson PC, MacIntyre A, Batty GD, et al. (2012) Socio-economic status is associated with epigenetic differences in the pSoBid cohort. *Int J Epidemiol* 41: 151-160.
13. Suderman M, McGowan PO, Sasaki A, Huang TC, Hallett MT, et al. (2012) Conserved epigenetic sensitivity to early life experience in the rat and human hippocampus. *Proc Natl Acad Sci U S A* 109 Suppl 2: 17266-17272.
14. Mehta D, Klengel T, Conneely KN, Smith AK, Altmann A, et al. (2013) Childhood maltreatment is associated with distinct genomic and epigenetic profiles in posttraumatic stress disorder. *Proceeding of the National Academy of Sciences USA* 110: 8302-8307.
15. Essex MJ, Boyce WT, Hertzman C, Lam LL, Armstrong JM, et al. (2013) Epigenetic vestiges of early developmental adversity: Childhood stress exposure and DNA methylation in adolescence. *Child Development* 84: 58-75.
16. Sapolsky RM (2004) Mothering style and methylation. *Nat Neurosci* 7: 791-792.
17. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, et al. (2004) Epigenetic programming by maternal behavior. *Nat Neurosci* 7: 847-854.
18. Weaver IC (2007) Epigenetic programming by maternal behavior and pharmacological intervention. *Nature versus nurture: let's call the whole thing off. Epigenetics* 2: 22-28.
19. Zhang TY, Hellstrom IC, Bagot RC, Wen X, Diorio J, et al. (2010) Maternal care and DNA methylation of a glutamic acid decarboxylase 1 promoter in rat hippocampus. *J Neurosci* 30: 13130-13137.
20. Heckers S, Stone D, Walsh J, Shick J, Koul P, Benes FM (2002) Differential hippocampal expression of glutamic acid decarboxylase 65 and 67 messenger RNA in bipolar disorder and schizophrenia. *Archives of General Psychiatry* 59:521-529.