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Transgenerational Inheritance of Longevity: An Epigenetic Phenomenon?

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Over the past decade, there is substantive evidence that adverse consequences of early-life environmental stresses, such as chemicals or diet, can be passed from the first generation to the next [1]. The environmentally induced transgenerational inheritance has been shown for obesity in mice [2], reproductive disease in rat [3,4], and human colorectal cancer [5]. There is some evidence that maternal in utero exposure to the Dutch famine of 1944-45 is associated with increased neonatal adiposity and poor health in later life in F2 generation offspring [6]. Transgenerational effects of the early-life nutritional conditions on the human longevity were also revealed. By the analysis of the data collected by following-up a cohort born in 1905 in Sweden, it has been found that ancestors' early-life nutrition can determine longevity of their offspring [7]. The probands' longevity was influenced by their paternal grandfathers' access to food, but only during the grandfather's slow growth period before the prepubertal peak in growth velocity and a period of relatively low need for food. It has been also reported that the father's poor food supply and the mother's good food supply were associated with a lower risk of cardiovascular death [8]. More recently, transgenerational correlations between food supply in early life of the paternal grandparents and the grandchild's longevity including associations with cardiovascular and diabetic deaths were documented [9-11]. Results obtained by the Modin et al. [12] showed that the social disadvantage imposed on those born outside wedlock in early twentieth century Sweden appears to be reproduced as a health disadvantage in their children and grandchildren, with likely consequences for offspring mortality. Specifically, men and women born outside wedlock were at an increased risk of adult mortality and men were also significantly less likely to reach their 80th birthday compared to those who were born in wedlock. These effects were transmitted to their children and grandchildren potentially influencing longevity and mortality risk in these generations. These data led to the suggestion that epigenetic modifications (heritable changes in gene expression not encoded by the DNA sequence) can be passed through generations, and transgenerationally transmitted abnormal epigenetic states (epimutations) are associated with disease in both humans and animals.

Recently, convincing evidence of the probability of epigenetic inheritance of longevity was obtained in nematode Caenorhabditis elegans. Greer et al. [13] have shown that some changes in chromatin states in a parental generation can affect the lifespan of their descendants. Specifically, they looked at the histone H3 lysine 4 trimethylation (H3K4me3) complex, composed of ASH-2, WDR-5 and the histone methyltransferase SET-2. It has been shown that this complex regulates C. elegans lifespan. The authors mated long-lived mutants of the H3K4me3 modifying complex with genetically wild-type males to generate heterozygous F1 generation progeny. These F1 animals were allowed to self-fertilize to generate both homozygous mutant and wild-type F2 generation offspring. Similarly, F3 to F5 generation progeny were generated. Surprisingly, the genetically wild-type F2, F3, and F4 generation progeny displayed a similar long-lived phenotype as their homozygous mutant controls. This effect was reverted at F5 generation, when the worms' normal life span was restored. One explanation of the transgenerational effects obtained in this study is that the expression pattern of longevity-associated genes can persist through several generations through mechanisms similar to those that underlie well-known epigenetic phenomena such as paramutation or genomic imprinting. Based on genome-wide transcriptional profiling, the authors show that the long-lived wild-type F2-F4 offspring (but not the F5 animals with normal life span) shared a significant subset of differentially regulated genes with long-lived mutant animals. Thus it can be suggested that the loss of H3K4me3 may be inherited at some central loci, such as *miRNA*, transcription factors, or signaling regulators, which are capable of affecting the expression of longevity-associated genes [14].

The possibility of the persistence of epigenetic marks through generations via the gametes is not yet fully proven and is still a controversial topic. It is generally assumed that the global resetting of epigenetic marks takes place in gametogenesis and embryogenesis. It appears, however, that the genome-wide reprogramming in germline cells is in fact not as 'global' as the word might imply. In several cases, epigenetic information is not completely erased in germ cells, and transgenerational inheritance of epigenetic information can occur [15]. A question central to the study of transgenerational inheritance of longevity is about the underlying mechanisms. These mechanisms may include many different factors attributed to epigenetics, such as DNA methylation, histone modifications, and altered expression of protein-encoding messenger RNAs and/or small, non-coding RNAs that regulate gene expression patterns associated with longevity [16]. Identification of epigenetic mechanisms which underlie transgenerational inheritance of human disease and longevity may have wide-ranging implications for human health. It will provide further insights into the risk factors and etiological mechanisms involved in the development of pathological processes, and will provide potential novel therapeutic targets for disease. Moreover, it can revolutionize health care by opening new avenues for personalized, predictive and preventive medicine.

References

- Guerrero–Bosagna C, Skinner MK (2012) Environmentally induced epigenetic transgenerational inheritance of phenotype and disease. Mol Cell Endocrinol 354: 3–8.
- Manikkam M, Guerrero–Bosagna C, Tracey R, Haque MM, Skinner MK (2012) Transgenerational actions of environmental compounds on reproductive disease and identification of epigenetic biomarkers of ancestral exposures. PLoS One 7: e31901.
- Nilsson E, Larsen G, Manikkam M, Guerrero–Bosagna C, Savenkova MI, et al. (2012) Environmentally induced epigenetic transgenerational inheritance of ovarian disease. PLoS One 7: e36129.
- Waterland RA, Travisano M, Tahiliani KG, Rached MT, Mirza S (2008) Methyl donor supplementation prevents transgenerational amplification of obesity. Int J Obes (Lond) 32: 1373–1379.

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- Whitelaw NC, Whitelaw E (2008) Transgenerational epigenetic inheritance in health and disease. Curr Opin Genet Dev 18: 273–279.
- Painter RC, Osmond C, Gluckman P, Hanson M, Phillips DIW, et al. (2008) Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. BJOG 115: 1243–1249.
- Bygren LO, Kaati G, Edvinsson S (2001) Longevity determined by paternal ancestors' nutrition during their slow growth period. Acta Biotheor 49: 53–59.
- Kaati G, Bygren LO, Edvinsson S (2002) Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period. Eur J Hum Genet 10: 682–688.
- Kaati G, Bygren LO, Pembrey M, Sjöström M (2007) Transgenerational response to nutrition, early life circumstances and longevity. Eur J Hum Genet 15: 784–790.
- 10. Pembrey ME (2010) Male–line transgenerational responses in humans. Hum Fertil (Camb) 13: 268–271.

- Pembrey ME, Bygren LO, Kaati G, Edvinsson S, Northstone K, et al. (2006) Sex–specific, male–line transgenerational responses in humans. Eur J Hum Genet 14: 159–166.
- Modin B, Koupil I, Vågerö D (2009) The impact of early twentieth century illegitimacy across three generations. Longevity and intergenerational health correlates. Soc Sci Med 68: 1633–1640.
- 13. Greer EL, Maures TJ, Ucar D, Hauswirth AG, Mancini E, et al. (2011) Transgenerational epigenetic inheritance of longevity in Caenorhabditis elegans. Nature 479: 365–371.
- Pang S, Curran SP (2012) Longevity and the long arm of epigenetics: Acquired parental marks influence lifespan across several generations. Bioessays 34: 652–654
- 15. Lange UC, Schneider R (2010) What an epigenome remembers. Bioessays. 32: 659–668.
- 16. Mango SE (2011) Ageing: generations of longevity. Nature 479: 302-303.