Hypothesis: epigenetic effects will require a review of the genetics of child development

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Abstract The worldwide prevalence of developmental disorders in children including birth defects, mental dysfunctions, as well as early-life abnormalities leading to the predisposition for adult diseases is one of the major unsolved problems in medicine and societies. Child development is influenced by both genes and the environment; however, the role of the environment is more emphatic, since the genome is most vulnerable to environmental factors during early development due to the high cellular differentiation rate. This inherent characteristic of child development lays the stress on a probabilistic rather than a deterministic view with regard to the manifestation of developmental disorders. Therefore, the analysis of gene–environment interactions in child development, beyond providing information about the developmental disorders of children, has an additional value that contributes to the knowledge on epigenetics in general and the interface between the genome and the environment playing a significant part in causing a wide range of diseases, in particular. The present study, rather than attempting to give a complete overview on epigenetics, is intended to illustrate that the issue of child development is an attractive target to extend the scope of genetics both in health and disease. Since the results might be extrapolated to the understanding of the pathomechanism of many age-dependent multifactorial diseases, the importance of studying gene–environment interaction in child development also lies in identifying

new and potentially modifiable risk factors for diseases that are, therefore, of public health significance.

Keywords Developmental disorders · Epigenetics · Nature vs nurture · Gene–environment interaction · Genetics in health

Introduction

The first decade after the announcement of the draft sequence of the human genome has given us insight into the pathomechanism of many common complex disorders, but the huge number of genome-wide association studies (GWAS) has not yet resulted in clinically useful knowledge for risk assessment in these traits (Butler 2010; Varmus 2010). Some researchers argue that the present research strategy should be followed involving even more patients, more polymorphisms for simultaneous analyses with more refined bioinformatic techniques (Manolio et al. 2009; Slatkin 2009), while others raise the questions whether or not our understanding of the role of genetics in health and disease should be reconsidered in novel perspective (Clarke and Cooper 2010; Pembrey 2010).

In a recent report, we recommended a novel perspective to understand what is really new in genomic medicine (Kosztolányi and Cassiman 2010). We have suggested to extend the approach to genetic disorders with a developmental aspect of diseases in mind, which, in contrast to the transgenerational aspects, focuses on how the genome, assembled in the zygote, contributes to the development of a new individual and how this becomes gradually manifest during the lifespan of the individual. We also suggested that the result of GWAS should be interpreted in the developmental aspect of diseases.

This study is dedicated in honor of Professor Theodor Hellbrügge.

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One of the most significant characteristics of the developmental aspect is epigenetics, the interface between the genome and the environment in disease causation. The trend to view epigenetics as a revolution in medicine is understandable since it de-emphasizes sequence-based thinking and turns attention instead to gene regulation. In October 2009, the first detailed map of the human epigenome as reference was published, the *Human DNA Methylome*, documenting, within a person, the epigenetic changes in different types of cells and tissues, something that will complement the Human Genome Project (Lister et al. 2009). Soon after, the International Human Epigenome Consortium was launched in Paris with the ambitious plan to map 1,000 reference epigenomes within a decade (www.ihec-epigenomes.org).

In this work, I shall focus on epigenetics from a special viewpoint, namely interactions between inherited genetic makeup and the prevailing environment during childhood. Since the human genome is most vulnerable to environmental factors during early development having high cellular differentiation rate, the epigenetics of child development is worthy of exploring in this context. This work is intended to illustrate that the issue of child development is a promising target whereby the scope of further research can be extended to gain a better understanding of the role of genetics in health and diseases.

Genes and development

Genes that are important for specific events of development have been highly conserved during evolution. Homeobox genes are at the top of genetic hierarchies encoding DNA-binding proteins that regulate gene expression and control various aspects of the complex mechanisms underlying mammalian development, differentiation, and homeostasis (Mark et al. 1997). Since all cells in an organism contain the same DNA nucleotide sequence, only the tissue-specific subpopulation of genes for one type of cell is active or expressed; the others are not needed and are silenced, depending on the requirements of function in a particular tissue. Generally, the activation and silencing of subpopulations of genes determining tissue-specific gene function in different tissues are laid down during development and are stably inherited from cell to cell throughout life. In another point of view, development is *the* program which temporally organizes different combinations of gene activity, allowing cells into various specialized tissues during embryonic and fetal development, a program which governs changes that begin with conception and continues through the life cycle.

Several data indicate that it is the epigenome that contributes significantly to cell differentiation during

development by turning on or switching off genes during shaping of the embryo and fetus.

Development and epigenetics

Epigenetic mechanisms

Epigenetics can be defined as changes in gene expression that occur without an alteration in the DNA nucleotide sequence. The main epigenetic mechanism currently recognized is methylation of cytosine at CpG dinucleotides, but other pathways like histone modification and the action of small non-coding RNAs are supposed to act as epigenetic signal (Bonasio et al. 2010). DNA hypermethylation and histone hypoacetylation have been associated with gene silencing, whereas DNA hypomethylation and histone acetylation generally induce gene transcription. Bjornsson et al. (2008) have found that the epigenetic state of the genome changed over time, and this intra-individual gain and loss of methylation showed familial clustering indicative of a genetic basis. Epigenetic mechanisms contribute to the establishment and maintenance of cell type-specific gene expression pattern, while the process of how epigenetic information propagates through mitotic divisions is not quite clear (Xu et al. 2010). Most recently, Maunakea et al. (2010) have reported a study on DNA methylation pattern across the genome in human brain tissue and found that DNA methylation regulates gene expression through alternative promoters.

Epigenetic processes are known to modify the way genes are expressed during morphogenesis and cell differentiation. In vivo data clearly indicate that developmental changes in methylation and gene expression are temporally correlated (Waterland 2009). The requirement of both parental genomes for normal development is a consequence of differential epigenetic marking in germ cell genesis. On fertilization, both paternal and maternal genomes undergo reprogramming. The paternal genome undergoes active demethylation prior to DNA replication, while the maternal genome undergoes passive demethylation after several cleavages. This wave of epigenetic demethylation is thought to restore the totipotency of the fertilized egg. De novo methylation of both parental genomes occurs around implantation. Although the epigenetic marks are generally stable in somatic cells, recent data (as subsequently will be shown) indicate a role for DNA methylation or demethylation well beyond embryonic development.

Epigenetic phenomena which contribute to the differential regulation of gene expression during development are *X chromosome inactivation* (where sex chromosome dosage compensation occurs via silencing of one X chromosome in each female cell early in embryogenesis), *genomic imprinting* (where differential gene expression is set up in a parent-of-

origin manner), and generation of *metastable epialleles* (identical alleles that are variably expressed established during development in somatic cells). All of these can be associated with developmental disorders, cognitive dysfunctions, a number of congenital disorders, as well as increased susceptibility to common complex diseases (Mill et al. 2008; Kargul and Laurent 2009; Martinez-Frias 2010; Flintoft 2010).

Environmental epigenetics

The epigenome is dynamic, and the epigenetic mechanisms contribute to cell differentiation in response to the prevailing environment. The epigenome is most vulnerable to environmental factors during embryogenesis; however, the epigenome seems to be responsive to environmental signals also during puberty and old age (Jirtle and Skinner 2007).

Experiments on rodent models have shown that various environmental factors like nutrition (diet-derived methyl groups), tobacco smoke, xenobiotic and endocrine active chemicals, metals, and also exposure to biological, emotional, social, behavioral factors, such as maternal care, can potentially alter the epigenome (Dolinay et al. 2007; Breton et al. 2009; Bollati and Baccarelli 2010). Observations on humans are also known which indicate the effect of the environmental exposure on the epigenome determining gene expression pattern throughout the life span (Fraga et al. 2005; Heijmans et al. 2008). There is a substantial inter-individual variation in the epigenetic pattern which is determined, besides the dynamic environmental exposure, also by common genetic variation (Zhang et al. 2010). The epigenome, whether genetically or environmentally determined, contributes to inter-individual variation in gene expression and thus to the variation in common complex disease risk (Relton and Smith 2010).

Child development and epigenetics

Some people believe that children's development is due more to nature (heredity), while others believe it has more to do with nurture (environment). There has also been a debate whether development is more continuous or more discontinuous. Child development is commonly described in terms of critical periods. As can be read in Wikipedia, "a critical period in developmental biology is a time in the early stages of an organism's life during which it displays a heightened sensitivity to certain environmental stimuli, and develops in particular ways due to experiences at this time." Fetal origin of adult diseases, the concept related to the critical period hypothesis could well be explained by epigenetics which is hypothesized to play an important role in developmental plasticity and disease susceptibility (Hall 2007).

Several studies indicate that early-life environmental factors can influence development by epigenetic mechanisms. In a series of examinations, Waterland et al. (2006) found that methyl donor supplementation of female mice before and during pregnancy increased DNA methylation in tail-specific metastable epiallele in the offspring and thereby reduced by half the incidence of tail kinking. Besides nutrition, early-life stress may also make an impact on the epigenome. Weaver et al. (2006) reported that maternal stress and nurturing stably alter the epigenotype in rat offspring and that this epigenetic change can be reversed in adulthood following methionine or histone deacetylase inhibitor infusion. Other experiments in rats (Roth et al. 2009) and mice (Murgatroyd et al. 2009) have also shown that early-life stress caused persistent changes in the methylation of genes in the central nervous system, which caused altered gene expression throughout the life span as well as in the next generation of infants.

A strikingly high number of mental retardation genes encode regulators, several of which regulate chromatin structure in target genes by epigenetic modifications (Grant 2008; Kramer and van Bokhoven 2009). It is noteworthy that epigenetic changes in rat hippocampal tissue may be induced by learning itself (Cavallaro et al. 2002). Peleg et al. (2010) also showed that aged mice displayed specific epigenetic changes during learning and failed to initiate a program associated with memory consolidation, while restoration of histone acetylation reinstated the expression of learning-induced genes and has led to the recovery of cognitive abilities.

Undoubtedly, the results of rodent research should be translated to humans with caution, and the evidence in humans is scant (Miller 2010). In one of the few studies to date, McGowan et al. (2009) showed epigenetic differences between brains obtained from suicide victims with and without a history of childhood abuse as well as controls and concluded that these changes occurred during childhood. A genome-wide decline in DNA methylation occurs in the brain during normal aging, which coincides with a functional decline in learning and memory with age (Liu et al. 2009). Recent data support a role for epigenetics in the multifactorial etiologies of autism spectrum disorders (Grafodatskaya et al. 2010).

Epigenetic mechanisms are being sought to explain also the manifestation of a wide range of age-related complex diseases. Although we should be cautious in public engagement around genetics and epigenetics at the present level of knowledge for disease prediction, there is little doubt that epigenetic analysis will have a crucial impact on our understanding not only of normal development but also of human diseases, and that an early-life epigenetic mechanism can cause long-term changes in chronic disease susceptibility and should be

accorded greater weight in models of disease causation in adulthood (Feinberg 2007; Gluckman et al. 2008; Thomas 2010; Johnstone and Baylin 2010).

Transgenerational effect of the environment

Some studies in the field of epigenetics have highlighted the possible inheritance of behavioral traits acquired by the previous generation. Interest even in Lamarckism has recently increased, although an acceptable molecular explanation for neo-lamarckian inheritance is missing, and new non-lamarckian theories are also proposed for a role of environmentally directed epigenetic changes (Feinberg and Irizarry 2010).

Epigenetic inheritance may be considered as a possible mechanism in explaining the remarkable observations by researchers in Sweden and the UK which showed that the mortality was increased and the longevity was decreased for descendents following overeating among boys during the prepubertal slow growth period in the grandparental generation (Pembrey et al. 2006). The female gamete forms during the mother's own embryonic period, i.e., during the grandmother's pregnancy with the mother. Accordingly, the grandmaternal nutrition environment probably has an effect on the structure of DNA set up in the egg, determining the gene expression profile of the grandchildren.

Recent research discovered that male mice made depressed by early stress and lack of maternal care appeared to pass this behavior and anxiety on to their offspring, suggesting that the impact of stress may be passed on from one generation to the next, presumably through epigenetic marks on sperm cells (Franklin et al. 2010). It was previously assumed that the epigenome is fully erased and re-established between generations; however, the erasure may be incomplete at specific genes, and this may be associated with the epigenetic inheritance of gene profiles.

Whether or not environmental exposure has transgenerational epigenetic effects in child development remains to be elucidated. The analysis of at least three generations is important to demonstrate that the phenotype is not a direct consequence of the environmental exposure on the germ cells that ultimately generate the offspring of the F0 generation (Skinner 2008). Anyway, the role of epigenetic transgenerational phenotypes needs to be seriously considered. It should be kept in mind that the way we live our life may influence the potential of the genes we pass to our offspring.

Public health relevance of the issue

The developmental disturbances of children is one of the major unsolved problems in medicine and societies.

According to the Global Report on Birth Defects of March of Dimes published in 2006 (www.marchofdimes.com/professionals), 6% of all babies, nearly 8 million children, are born each year with serious genetic or partially genetic birth defects, which cause over 3 million deaths annually in young children. An estimated 3.2 million of those who survive may be mentally and physically disabled for life. Over the past decade, tremendous progress has been made in elucidating the molecular events governing normal developmental processes and disease causation, which has led to the identification of numerous genes playing a significant role in different developmental events. However, in spite of encouraging advances, direct contribution to health care has been restricted so far, and major contributions to public health are only just beginning to be made. E.g., in the long-term, large-scale population study ALSPAC (<http://www.bristol.ac.uk/alspac/>) launched in 1991, researchers have been following 14,000 children born in the former county of Avon, England, and their parents to help understand the genetic and environmental factors involved in the development of particular diseases. In the US, a mammoth project designed to follow 100,000 children from birth until age 21 has been initiated to study the impact of both genetic factors and the environment on health (www.nationalchildrensstudy.gov). Recruitment started in early 2009. These studies will certainly render important insights into the role of epigenetics in child development.

The analysis of gene–environment interactions in child development has an additional promise as well, since the results might be extrapolated to understand the pathomechanism of many age-dependent multifactorial diseases. An increasing number of human pathologies have been found to be associated with disturbed epigenetics regulation, including cancer, mental retardation, psychosis, and neurodegenerative disorders. We need to understand how genetic factors and environmental exposures interact in individuals to alter normal biological function and to affect the risk of disease development.

Recent emphasis on translational research is highlighting the role of epidemiology in translating scientific discoveries into population health impact. Personalized medicine or individualized lifestyle recommendations based on the genetic profile are being promoted as the future of public health. The goal of the program of Genes, Environment, and Health Initiative at the National Institutes of Health launched in 2007 (<http://genesandenvironment.nih.gov>) is to develop new non-invasive tools and biomarkers for assessing individual exposures to environmental stressors that interact with genetic variation to result in human disease. Such complex interventions require novel thinking about trial design in a socially and culturally appropriate context. By this way, genetic epidemiology can contribute

to establishing the causal nature of environmentally modifiable risk factors and thus contribute to appropriate preventive strategies. Modern approaches such as bioinformatics, genome expression arrays, and DNA methylation chips will assist us in obtaining these important goals.

Conclusion

The reference epigenome provides the basis for further research evaluating the epigenetic processes in development and diseases. Child development is an attractive field for exploring the interactions between the inherited genetic makeup and the environment. It is not unrealistic to suppose that the role of the mutual relationship of nature and nurture in such a complex issue like development is more intense than we had imagined. An important point in epigenetic modification is the timing of the environmental factor, which is more understandable in relation to development, but should be considered also in disease causation, first of all in common complex disorders where environmental provocations is a well-known triggering factor for manifestation of the inherited polygenic susceptibility. As Marcus Pembrey said (Pembrey 2010): “a gene-centric approach alone will continue to disappoint. Developmental experience, that other great determinant of our constitution, has to be incorporated more fully into our scientific studies.” Gene–environment interactions and the developmental view of genetics should receive more attention in further GWAS and epidemiological studies to get fresh light on the underlying causes of common complex diseases. There is little doubt that epigenetics will have a crucial impact on the delivery of future health care, but this impact must be in the right context.

Conflict of interest The author declares that he has no conflict of interest.

References

- Bjornsson HT, Sigurdsson ML, Fallin MD et al (2008) Intra-individual change over time in DNA methylation with familial clustering. *JAMA* 299:2877–2883
- Bollati V, Baccarelli A (2010) Environmental epigenetics. *Heredity* 105:105–112
- Bonasio R, Tu S, Reinberg D (2010) Molecular signals of epigenetic states. *Science* 330:612–616
- Breton CV, Byun HM, Wenten M et al (2009) Prenatal tobacco smoke exposure affects global and gene-specific DNA methylation. *Am J Respir Crit Care Med* 180:462–467
- Butler D (2010) Human genome at ten: science after the sequence. *Nature* 465:1000–1001
- Cavallaro S, D’Agata V, Manickam P et al (2002) Memory specific temporal profiles of gene expression in the hippocampus. *Proc Natl Acad Sci* 99:16279–16284
- Clarke A, Cooper DN (2010) GWAS: heritability missing in action? *Eur J Hum Genet* 18:859–861
- Dolinay DC, Weidman JR, Jirtle RL (2007) Epigenetic gene regulation: linking early developmental environment to adult disease. *Reprod Toxicol* 23:297–307
- Feinberg AP (2007) Phenotypic plasticity and the epigenetics of human disease. *Nature* 447:433–440
- Feinberg AP, Irizarry RA (2010) Stochastic epigenetic variation as a driving force of development, evolutionary adaptation, and disease. *Proc Natl Acad Sci* 107:1757–1764
- Flintoft L (2010) Complex disease: adding epigenetics to the mix. *Nat Rev Genet* 11:94–95
- Fraga MF, Ballestar E, Paz MF et al (2005) Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci* 102:10604–10609
- Franklin TB, Russig H, Weiss IC et al (2010) Epigenetic transmission of the impact of early stress across generations. *Biol Psychiatry* 68:408–415
- Gluckman PD, Hanson MA, Cooper C, Thornburg KL (2008) Effect of in utero and early-life condition on adult health and disease. *New Engl J Med* 359:61–73
- Grafodatskaya D, Chung B, Szatmari P, Weksberg R (2010) Autism spectrum disorders and epigenetics. *J Am Acad Child Adolesc Psychiatry* 49:794–809
- Grant ME (2008) The epigenetic origins of mental retardation. *Clin Genet* 73:528–530
- Hall J (2007) The importance of the fetal origins of adult disease for geneticists. *Clin Genet* 72:67–73
- Heijmans BT, Tobi EW, Stein AD et al (2008) Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci* 105:17046–17049
- Jirtle RL, Skinner MK (2007) Environmental epigenomics and disease susceptibility. *Nat Rev Genet* 8:253–262
- Johnstone SE, Baylin SB (2010) Stress and the epigenetic landscape: a link to the pathobiology of human diseases? *Nat Rev Genet* 11:806–812
- Kargul J, Laurent GJ (2009) Epigenetics and human disease. *Int J Biochem Cell Biol* 41:1–1
- Kosztolányi Gy, Cassiman J-J (2010) The medical geneticist as expert in the transgenerational and developmental aspects of diseases. *Eur J Hum Genet* 18:1075–1076
- Kramer JM, van Bokhoven H (2009) Genetic and epigenetic defects in mental retardation. *Int J Biochem Cell Biol* 41:96–107
- Lister R, Pelizzola M, Dowen RH et al (2009) Human DNA methylomes at base resolution show widespread epigenomic differences. *Nature* 462:315–322
- Liu L, van Groen T, Kadish I, Tollefsbol TO (2009) DNA methylation impacts on learning and memory in aging. *Neurobiol Aging* 30:549–560
- Manolio TA, Collins FS, Cox NJ et al (2009) Finding the missing heritability of complex diseases. *Nature* 461:747–753
- Mark M, Rijli FM, Chambon P (1997) Homeobox genes in embryogenesis and pathogenesis. *Pediatr Res* 42:421–429
- Martinez-Frias ML (2010) Can our understanding of epigenetics assist with primary prevention of congenital defects? *J Med Genet* 47:73–80
- Maunakea AK, Nagarajan RP, Bilenky M et al (2010) Conserved role of intragenic DNA methylation in regulating alternative promoters. *Nature* 466:253–257
- McGowan PO, Sasaki A, D’Alessio AC et al (2009) Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 12:342–348
- Mill J, Tang T, Kaminsky Z et al (2008) Epigenomic profiling reveals DNA-methylation changes associated with major psychosis. *Am J Hum Genet* 82:696–711

- Miller G (2010) The seductive allure of behavioral epigenetics. *Science* 329:24–27
- Murgatroyd C, Patchev AV, Wu YH et al (2009) Dynamic DNA methylation programs persistent adverse effects of early-life stress. *Nat Neurosci* 12:1559–U108
- Peleg S, Sananbenesi F, Zovoilis A et al (2010) Altered histone acetylation is associated with age-dependent memory impairment in mice. *Science* 328:753–756
- Pembrey M (2010) A decade of progress and misunderstandings. *BioNews* 564, 28 June 2010
- Pembrey ME, Bygren LO, Kaati G et al (2006) Sex-specific, male-line transgenerational responses in humans. *Eur J Hum Genet* 14:159–166
- Relton CL, Smith GD (2010) Epigenetic epidemiology of common complex disease: prospects for prediction, prevention, and treatment. *PLoS Med* 7(10):e1000356. doi:[10.1371/journal.pmed.1000356](https://doi.org/10.1371/journal.pmed.1000356)
- Roth TL, Lubin FD, Funk AJ, Sweatt JD (2009) Lasting epigenetic influence of early-life adversity on the *BDNF* gene. *Biol Psychiatry* 65:760–769
- Skinner MK (2008) What is an epigenetic transgenerational phenotype: F3 or F2? *Reprod Toxicol* 25:2–6
- Slatkin M (2009) Epigenetic inheritance and the missing heritability problem. *Genetics* 182:845–850
- Thomas D (2010) Gene–environment-wide association studies: emerging approaches. *Nat Rev Genet* 11:259–272
- Varmus H (2010) Ten years on—the human genome and medicine. *New Engl J Med* 362:2028–2029
- Waterland RA (2009) Is epigenetics an important link between early life events and adult disease? *Horm Res* 71:13–16
- Waterland RA, Dolinoy DC, Lin JR et al (2006) Maternal methyl supplements increase offspring DNA methylation at axin fused. *Genesis* 44:401–406
- Weaver ICG, Meaney MJ, Szyf M (2006) Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviours in the offspring that are reversible in adulthood. *Proc Nat Acad Sci USA* 103:3480–3485
- Xu M, Long C, Chen X et al (2010) Partitioning of histone H3-H4 tetramers during DNA replication-dependent chromatin assembly. *Science* 328:94–98
- Zhang D, Cheng L, Badner JA et al (2010) Genetic control of individual differences in gene-specific methylation in human brain. *Am J Hum Genet* 86:411–419