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1. Introduction

Epigenetics is a mechanism that regulates gene expression not depending on the underlying DNA sequence, but on the chemical modification of DNA and histone proteins. It is known that several neurodevelopmental disorders are caused by congenital abnormalities in epigenetic mechanisms, including Prader-Willi and Angelman syndromes, which are genomic imprinting disorders [1-3]. The advances in understanding of the epigenetic gene regulation mechanisms and identification of proteins that participate in them have led to the identification of other neurodevelopmental disorders, such as ICF and Rett syndromes, caused by mutations in the genes that encode such proteins [4-8]. The discovery of Rett syndrome, a representative autistic disorder caused by mutations in $\text{MECP2}$ that encodes an epigenetic regulatory protein, introduced to us a new paradigm that neurodevelopmental disorders are not only caused by mutations in the neuronal genes [9, 10], but also caused by abnormal epigenetic regulation of the neuronal genes.

Several lines of evidence suggest that various environmental factors, such as nutrition (e.g. folic acid and royal jelly), environmental chemicals, external electric stimuli to neurons, and mental stress, can change epigenomic status, which supports the hypothesis that the epigenome is more susceptible to environmental factors than the genome [11].

DNA methylation was initially believed to change gradually during the lifetime through studies in cancer. However, it has recently been shown that DNA methylation can be altered during the first week of life after birth in mice, and that the altered epigenomic status in the brain is prolonged throughout the lifetime long with abnormal behavior [12]. It is also reported that epigenetic changes can be induced by malnutrition during the fetal period, which introduces the origin of adult diseases in the fetus in rats [13, 14]. Recent comparative studies between monozygotic twins suggest that epigenomic changes also occur in humans [15, 16].
Epigenetic is a reversible mechanism and thus, it has been accepted as a mechanism for genomic imprinting in which the maternal expression pattern can be erased and reset to be the paternal expression pattern when the imprinted gene is transmitted from the mother to the offspring [17-20]. It has recently been shown that some drugs for mental disorders have an effect on restoration of the epigenetic status and the expression pattern of the neuronal genes based on this epigenomic reversibility [21-25]. It has also been reported that administration of folic acid is effective in treating autistic children possibly by restoring DNA methylation status at the disease-related gene regions [26-28]. Therefore, it is intriguing to think that advanced “epigenomic drug” can be designed that only target to disease-specific gene regions using recent technology such as pyrrole-imidazole polyamide [29, 30].

Epigenetics now challenge the biological dogma that “acquired nature cannot be transmitted to the next generation”, because recent studies have shown that mental stress-induced epigenomic changes cannot be completely erased at the stage of spermatogenesis and can be transmitted to the third generation in mice [20, 31]. However, it is possible that appropriate intervention such as drug, nutrition, and environmental condition can be restore the abnormal epigenomic status and halt its inheritance, if such transmission is true in humans.

In this chapter, we present the epigenetic mechanisms that cause congenital disorders, show examples of environmental factors that can alter the epigenetic status, and discuss recent topics in epigenetics, such as strategies for the treatment of neurodevelopmental disorders utilizing epigenetic reversibility and the possibility of its transgenerational inheritance.

### 2. Importance of proper gene regulation in the brain

The brain is a gene-dosage sensitive organ in which either under-expression or over-expression of the same genes encoding proteins related to brain function results in a range of neurological disorders. For example, Pelizaeus-Merzbacher disease, a severe congenital disease is caused by either a deletion, mutation, or duplication of the proteolipid protein 1 (PLP1) gene [32]. Further, lissencephaly, a rare brain formation disorder, is caused by either deletion or duplication of the platelet-activating factor acetylhydrolase 1B subunit alpha (PAFAH1B1) gene that encodes a neuronal migration factor [33, 34]. Charcot-Marie-Tooth disease, an adult-onset neuromuscular disease is caused by a mutation or duplication of the peripheral myelin protein 22 (PMP22) gene [35], and Parkinson’s disease is caused by a mutation or multiplication of the α-synuclein (SNCA) gene [36]. These are all neurological disorders, and such examples have not been observed in other clinical fields. Thus, these findings suggest that the brain is extremely sensitive to perturbations in gene regulation, and further indicate that the brain is an organ that requires a proper control system for gene expression.

Epigenetic mechanisms are one of the ways by which gene expression is controlled in higher vertebrates. These mechanisms are essential for normal development during embryogenesis [37], and for differentiation of neural cells [38] and other cell types [39]. Understanding of epigenetic mechanisms, including DNA methylation, histone modification, and regulation by
microRNAs, is important in elucidating the pathogenic pathways in neurodevelopmental disorders [40-42].

3. Epigenetic mechanisms that cause congenital neurodevelopmental disorders

Genomic imprinting is an epigenetic phenomenon that was initially discovered in humans and mammals, which determines parental-specific monoallelic expression of a relatively small number of genes during development. Imprinting must be logically imparted in the germ line, where inherited maternal and paternal imprints are erased and new imprinting established according to the individual’s sex (Figure 1) [17]. For example, before the maternal allele-specific DNA methylation that contribute to monoallelic expression is established in a differential methylated region 2 (DMR2) of mouse Igf2 gene, DMR2 is demethylated in both male and female primordial gene cells (PGCs) by 13.5 days post coitum (dpc), indicating that the erasure of imprinting in this region occurs earlier in PGC development [18]. Although DNA methylation is the best established epigenetic mark that is critical for the allele-specific expression of imprinted genes, many aspects of the regulation of DNA methylation are unknown, including how methylation complexes are targeted and the molecular mechanisms underlying DNA demethylation [19]. In this context, one mechanism related to genome-wide DNA demethylation to reset the epigenome for totipotency was recently revealed that erasure of CpG methylation (5mC) in PGCs occurs via conversion to 5-hydroxymethylcytosine (5hmC), driven by high levels of TET1 and TET2, and that global conversion to 5hmC is initiated asynchronously in PGCs at embryonic days (E) 9.5 to E10.5 for imprint erasure [20].

![Figure 1. Erasure and establishment of genomic imprinting. Inherited maternal and paternal imprints are erased and new imprinting established according to the individual’s sex during the process of spermatogenesis and oogenesis.](http://dx.doi.org/10.5772/57534)
The X chromosome has a large number of genes, whereas the Y chromosome has relatively few. Thus, females (XX) have more genes than males (XY). To minimize this sex imbalance, one of the two X chromosomes in females is inactivated by an epigenetic mechanism [3]. Improper X chromosome inactivation (XCI) is thought to be an embryonic lethal condition, as suggested by the findings that a majority of aborted embryonic clones produced by somatic nuclear transfer showed failure of XCI [43, 44], although it is difficult to directly demonstrate failure of XCI in human aborted embryos. Even when failure of XCI occurs in women with one normal X chromosome and a small X chromosome due to a large terminal deletion, and thus the overdosage effect of X-linked genes is small, such affected women show severe congenital neurodevelopmental delays [3], indicating that proper epigenetic gene suppression is essential for normal development.

DNA methylation is a fundamental step in epigenetic gene control, and occurs by the DNA methyltransferase (DNMT)-mediated addition of a methyl group (CH$_3$) to CpG dinucleotides. A defect in one of the DNMTs (e.g., DNMT3B) can cause a syndrome characterized by immunodeficiency, centromere instability, facial anomalies (ICF), and mild mental retardation [4-6]. Methyl-CpG-binding domain proteins (MBDs) are also important molecules in the control of gene expression. Mutations in the methyl-CpG-binding protein 2 gene (MECP2), one of the genes that encodes for MBD protein, can cause Rett syndrome, which is characterized by seizures, ataxic gait, language dysfunction, and autistic behavior [7, 8]. Therefore, it is thought that MeCP2 dysfunction leads to aberrant expression of genes in the brain associated with neurological features of the disease. Recent studies have shown that MeCP2 controls a subset of neuronal genes [45-48] or a potentially large number of genes [49], suggesting that epigenetic dysregulation of multiple neuronal genes may cause neurological features of the disease.

4. Environmental factors that alter the epigenetic status associated with neurodevelopmental disorders

We have previously demonstrated that epigenetic instability at imprinting loci during the process of finding proper methylation sites for diagnosis of Prader-Willi / Angelman syndromes, the epigenetic disorders described above [50]. In our study, the imprinted DNA methylation status at the small nuclear ribonucleoprotein associated polypeptide N (SNRPN) promoter region (e.g., maternally methylated and paternally unmethylated) in chromosome 15q12 was stable among various tissues such as lymphocyte, amniotic fluid cells, cultured chorionic villus samples, various fetal tissues and Epstein-Barr virus lymphoblast cell lines established from lymphocytes. However, at the PW71 locus adjacent to the SNRPN locus, the imprinted methylation status was not consistent among these tissues. This indicates that epigenetic status at the loci associated with neurodevelopmental disorders are susceptible to environmental factors in vitro.

In neurodevelopmental disorders such as autism, both environmental factors (e.g., toxins, infections) and genetic factors (e.g., mutations in synaptic molecules) have historically been
discussed [51]. However, a biological mechanism that links these two groups of factors has not been identified. Epigenetics may be the bridge between these factors, thereby contributing to disease development [11]. Besides the intrinsic (congenital) epigenetic defects (associated with disease as described above), several lines of evidence suggest that extrinsic (environmental) factors, such as malnutrition [13, 14], drugs [21-25], mental stress during the neonatal period [12], and neuronal stimulation [52], alter the epigenetic status and thereby affect brain function. Therefore, it is intriguing to speculate that acquired neurodevelopmental disorders, including autistic disorders, may be the result of epigenetic dysregulation caused by environmental factors (Figure 2).

**Figure 2.** Current understanding of extrinsic mechanisms of neurodevelopmental disorders. Acquired neurodevelopmental disorders are caused by extrinsic mechanism via various environmental factors.

Short-term mental stress after birth may alter the epigenetic status in the brain and result in persistent abnormal behavior [12]. In rat pups from mothers exhibiting low levels of maternal care, DNA methylation at the promoter of the glucocorticoid receptor gene (GR), which is also known as the nuclear receptor subfamily 3 group C member 1 (NR3C1) gene, increased in the hippocampus, which suppressed expression of the gene within the first week of life. In contrast, promoter methylation decreased in the brains of the offspring with high maternal care during the same period [12]. This paradigm was suggested to provide a putative animal model for childhood neglect and maltreatment in humans. Postmortem analysis of the hippocampus of suicide victims with a history of childhood abuse revealed the presence of hypermethylation of the neuron-specific promoter of NR3C1 in combination with a decrease in its expression [53].
This finding suggests that the adverse effects of early-life stress on DNA methylation may last throughout life [54], and also indicates that neurodevelopmental problems may arise from epigenetic dysregulation caused by environmental factors in early life.

Epigenetic mechanisms are also likely to be relevant to drug addiction. Gene expression in the dopaminergic and glutamatergic systems is mediated by epigenetic mechanisms, and cocaine and alcohol are known to alter the epigenetic state (e.g., cocaine induces either hyperacetylation or hypoacetylation of histone H3 or H4 in the nucleus accumbens of mice, and alcohol induces hyperacetylation of histones H3 and H4 in the frontal cortex and the nucleus accumbens of adolescent rats), which may be associated with permanent behavioral consequences [55, 56].

The findings above were mainly obtained in animal studies, and there is little evidence in humans. However, the fact that epigenomic differences are larger in older monozygotic twins than those in younger twins suggests that epigenetic status may be altered during aging by environmental factors in humans [15]. Likewise, in monozygotic twins with discordant severity of Rett syndrome, the epigenomic patterns and expression of neuronal genes have been shown to differ [16]. This indicates that environmental factors may affect the human epigenome and that epigenomic differences induced by environmental factors may contribute to mental phenotypes.

Another phenomenon that may be related to epigenomic changes is the decline in birth weights that has occurred during the past 20 years. This trend is thought to be a result of the popularity of dieting among young women and of the recommendation by obstetric physicians to minimize pregnancy weight gain in order to reduce the risk of gestational diabetes mellitus [57]. Based on current epidemiological studies of populations affected by famines in the Netherlands and China, the generation with lower birth weight is expected to have an increased risk of not only metabolic disorders (e.g., obesity, diabetes mellitus) [58], but also mental disorders [59]. This expectation is referred to as the Developmental Origin of Health and Diseases (DOHaD) [60]. Recent studies have demonstrated that malnutrition during the fetal period causes a hypomethylation imprint on the peroxisome proliferator-activated receptor alpha (PPARα) gene in the rat liver [61]. Similar DNA methylation changes have been identified in the peripheral tissues of people who suffered malnutrition during a period of famine in the Netherlands [62]. It has also been reported that assisted reproductive technologies (ART) (e.g., in vitro fertilization and intracytoplasmic sperm injection), which are now widely used due to increases in maternal age, lead to decreased DNA methylation status at multiple maternally methylated imprinted loci [63, 64]. Therefore, it is intriguing to think that current social factors, such as DOHaD and ART, may be involved in the recent increase of children with mild neurodevelopmental disorders in Japan and other countries [65-70] and that epigenetic alteration may underlie this social phenomenon.
5. Treatment of neurodevelopmental disorders by utilizing epigenetic reversibility

It has been reported that administration of folic acid to pregnant rats alters the DNA methylation status in the offspring [71]. Furthermore, folic acid supplementation in pregnant rats under malnutrition conditions prevents hypomethylation of a hepatic gene in the offspring [13]. In addition to folic acid, various environmental factors, such as royal jelly [72], drugs for mental disorders [21, 23, 25], environmental chemicals [73, 74], and external stimuli (electro-convulsive treatment for psychiatric diseases) [49], have also been reported to alter DNA methylation and histone modification status in the brain and other organs in mice or other species.

As mentioned above, mental stress in the first week of life causes epigenetic abnormalities in the brains of mice. Conversely, several mouse studies have demonstrated that appropriate educational conditions can ameliorate behavior abnormalities. Environmental enrichment (EE), consisting of larger-sized home cages with a variety of objects including running wheels, improved motor coordination and decreased anxiety-related behavior in heterozygous MeCP2+/--female mice, a model of Rett syndrome [75, 76]. EE also improved locomotor activity with reduced ventricular volume, and restored the expression of synaptic markers, such as synaptophysin and PSD95 in the hypothalamus and syntaxin 1a and synaptotagmin in the cortex of hemizygous MeCP2-/- male mice [77, 78].

It is generally thought to be difficult to cure patients with congenital mental disorders caused by mutations that encode neuronal molecules, since it is difficult to distribute gene products to the appropriate brain regions and at the appropriate time of brain development. However, it was recently demonstrated that the epigenetic disorder Rett syndrome may be an exception, partly because MeCP2 does not encode a product required for brain structure, but rather encodes a “lubricant” that works at a relatively later period of brain development. As a consequence, reintroduction of MECP2 into MeCP2 null mice not only before birth [79], but also after birth, is sufficient to rescue Rett-like neurological symptoms [80]. Furthermore, restoration of MeCP2 function in astrocytes substantially improves locomotion, anxiety levels, and respiratory abnormalities in hemizygous MeCP2-Y male mice along with restoring dendritic morphology [81]. These results suggest that up-regulation of MECP2, possibly mediated by drug treatment, might help to improve brain function in Rett syndrome patients. Valproic acid, one of the most popular drugs for epileptic seizure and a known HDAC inhibitor, increases MeCP2 expression [82, 83], as well as fluoxetine, a drug for mental disorders, and cocaine [84]. Taken together, these results indicate that neurodevelopmental disorders caused by epigenetic abnormalities can be treatable.

6. The possibility of transgenerational epigenetic inheritance

According to current understanding in the field of biology, one’s acquired character is not inherited by the next generation of offspring. Based on this notion of Darwinian inheritance,
bad habits acquired during one’s lifetime would not be transmitted to one’s children. However, recent advances in epigenomics and epigenetics have revealed that such undesirable acquired traits might be transmitted into the next generation.

Epigenetic marks, either DNA methylation or histone modifications, allow the mitotic transmission of gene activity states from one cell to its daughter cells. A fundamental question in epigenetics is whether these marks can also be transmitted meiotically through the germ line. In mammals, epigenetic marks should be cleared by demethylating factors such as the cytidine deaminases (e.g., AID, APOBEC1) and re-established in each generation, but this clearing is incomplete at some loci in the genome of several model organisms possibly due to deficiency of demethylating factors (e.g. AID) [85]. A recent study has demonstrated rare regulatory elements that escape systematic DNA demethylation in PGCs, providing a potential mechanistic basis for transgenerational epigenetic inheritance [20]. Therefore, based on this phenomenon, “transgenerational epigenetic inheritance”, which refers to the germ line transmission of an epigenetic mark [86, 87], may provide a direct biological proof for Lamarckism, hypothesis suggesting the heritability of acquired characteristics.

It is important to draw a distinction between transgenerational epigenetic inheritance and heritable germline epimutation. Transgenerational epigenetic inheritance is independent of the DNA sequence, whereas heritable germline epimutation is a direct consequence of a cis-acting epigenetic alteration, such as hypermethylation induced by an expansion of an unstable CGG repeat within exon 1 of the Fragile X Mental Retardation Syndrome 1 gene (FMR1), hypermethylation induced by a deletion in an adjacent gene within the promoter of the globin gene, and hypermethylation induced by repetitive retrotransposons [87, 88]. Such specific-sequence driven-epimutation is observed in an affected mother and son in a family with fragile X syndrome, and it can be classified as a case of heritable germline epimutation [88]. This inheritance pattern is also observed in other species, such as Caenorhabditis elegans. Therefore, the heritability does not necessarily involve transgenerational epigenetic inheritance, as the methylated state could be cleared on passage through the germline and could be re-established according to a certain sequence during zygotic genome activation [88].

Transgenerational inheritance of epigenetic marks was first demonstrated in a specific mouse strain. The methylation status at the Axin (Fu) locus in mature sperm, which reflects the methylation state of the allele in the somatic tissue of the animal is linked to the shape of the animal’s tail and does not undergo epigenetic reprogramming during gametogenesis [89]. Environmental factors, notably the fungicide vinclozolin, stress responses and nutritional challenges, have been associated with transgenerational epigenetic inheritance in animal models. However, it is often difficult to obtain direct evidence of transmission of epigenetic marks per se from transmission of the exposure itself [90, 91]. Therefore, transgenerational effects should be distinguished from parental and grandparental effects. In addition to contributing to their DNA, parents can influence their offspring in many ways: for example, by contributing bioactive molecules in the egg and sperm cytoplasm, and by providing nutrients and hormonal information during embryogenesis. For example, malnutrition during pregnancy does not only affect the pregnant mother and fetus but also the fetus’s primordial germ cells, which can lead to phenotypic changes in the grandchildren (second generation).
In one study, a specific diet (supplementation of folic acid) induced methylation at the Axin (Fu) locus, which altered the hair color of the animals, and this alteration was inherited over 2 generations, but this status was lost by the third generation [92]. These findings indicate that while a specific diet leads to parental and grandparental effects, the acquired epigenetic information is not inherited transgenerationally, and that the Axin (Fu) locus is resistant to environmentally induced acquisition of new germ-line epigenetic information [92].

Transgenerational effects of environmental toxins – namely, the endocrine disruptors vinclozolin (an antiandrogenic compound) and methoxychlor (estrogenic compound)-have been demonstrated in the fourth generation (F4) of rats resulting in decreased spermatogenic capacity and increased male infertility, and the effects on reproduction correlate with altered DNA methylation patterns in the germ line [93]. It has also been demonstrated that plastic-derived endocrine disrupters, including bisphenol A, increase the risk of pubertal abnormalities, testicular diseases and ovarian diseases in the F3 generation of rats, and that differential DNA methylated patterns were identified in the plastic-lineage F3 generation sperm in comparison with control-lineage F3 generation sperm [94]. Therefore, “true” transgenerational epigenetic inheritance up to third generation is suggested to exist in animals. This observation has also been confirmed in Drosophila, in which an aberrant epigenetic mark (defective chromatin state) acquired in one generation induced by environmental stress (e.g. heat shock) was inherited by the next generation [95].

It has also been demonstrated that an aberrant epigenetic mark acquired in one generation by mental stress (maternal separation in early life) can be inherited by the next generation (Figure 3, left) [31]. Chronic maternal separation alters behaviors as well as the profile of DNA methylation in the promoter of several candidate genes in both the germline of the separated mice and brains of the offspring with altered gene expression (e.g. decreases in the expression of corticotropin releasing factor receptor 2 (Crfr2) in the amygdala and the hypothalamus) [31]. In this study, abnormal behavior was observed in the third generation, and altered DNA methylation in the CpG islands of Mecp2, cannabinoid receptor-1 (Cb1), and Crfr2 were observed in F1 sperm and F2 brain. It has also been reported that chronic maternal separation increases cytosine methylation of the estrogen receptor (Er)-alpha1b gene promoter, indicating that individual differences in maternal behavior are epigenetically transmitted from the mother to her female offspring [96]. Further, the third generation of male rats upon exposure to vinclozolin, a commonly-used fungicide, respond differently to chronic restraint (i.e., mental) stress during adolescence; they also show altered gene expression in the cortex and CA1 regions of the brain, although direct epigenetic alteration (e.g., DNA methylation) has not been confirmed [97]. These findings provide biological evidence suggesting that environmental factors, including traumatic experiences in early life, are risk factors for the development of behavioral and emotional disorders.

Environmental stress (e.g., maternal separation) in neonatal period induces epigenomic changes in the brain and sperm in mice. The changes are transmitted to the next generation along with abnormal behavior even when the offspring is reared by a normal mother. However, it is possible to ameliorate these epigenetic changes by providing appropriate environ-
mental factors (e.g., nutrition, neuropsychiatric drugs or brain-stimulating enriched environment).

Recent studies have suggested that epigenetic variations influenced by the environment occur spontaneously and that the specific epigenetic pattern created is inherited over several generations in plant populations. Understanding the emergence and heritability of epigenetic variants is critical for understanding how they might become subject to natural selection and thus affect genetic diversity [98]. In humans, clinical features can vary among family members who share the same disease-causing mutation—a phenomenon referred to as variable expressivity; however, the precise molecular mechanism is not known. Therefore, it is intriguing to speculate that the variable clinical expressivity is caused by the stochastic occurrence of epigenetic variation during development [99] or by the spontaneous epigenetic changes during the transmission to the next generation, as was observed in plants [98, 100].

It has been demonstrated that neuronal plasticity is determined by epigenetic plasticity, such as chromatin remodeling and dynamic DNA methylation changes during brain development [101, 102], and multiple lines of evidence that connect environmental factors to brain functions via epigenetic regulation have been accumulating [21-25]. However, little is known as to whether environment-induced epigenetic changes in the brain are transmitted to the next generation along with abnormal brain functions, including mental disorders [31, 103].

Figure 3. Transgenerational abnormal epigenomic inheritance along with abnormal phenotype.
In this context, whereas it is widely known that maternal nutrition and metabolism are critical determinants of adult offspring health, recent reports describe adverse offspring outcomes associated with the father's diet, indicating nongenetic inheritance of paternal experience [104]. Since the results of this study were interpreted as “you are what your dad ate” [105], we may be able to interpret the results of studies of transgenerational epigenetic inheritance associated with a specific mental state [31, 103] as “you are how your dad behaved”. Determining the underlying mechanisms may require a reevaluation of our understanding of the heritability of epigenetic states.

Based on the evidence described above, the readers of this chapter might draw the conclusion that the field of epigenetics portends adverse news for society. However, if we are able to identify a beneficial environment for human health in terms of epigenetics, it may be possible to sever the environment-induced epigenetic patterns across the generation. Epigenetic markings provide a “memory of past experiences”; these markings persist during the life span of an individual and are transmitted to the offspring. Recent reports indicate that epigenetic marks are a “memory of past experiences” that can be restored by taking advantage of the reversibility of epigenetic modifications [106, 107]. Therefore, drug discovery and identification of beneficial condition to revert abnormal epigenetic modification may make it possible to interrupt the negative chain reaction of transgenerational epigenetic inheritance and promote better health in future generations (Figure 3, right).

7. Conclusion

The failure of epigenetic gene regulation is known to cause various rare congenital disorders. However, this deregulation also cause common diseases that are induced by environmental factors, since the epigenetic status is affected and changed by various environmental factors. Furthermore, the altered epigenetic status in the genome can be transmitted to the succeeding generations. Therefore, precise understanding of gene-environment interactions in light of epigenomics and epigenetics is necessary, which will further our knowledge of neurodevelopmental disorders.

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