Epigenetic mechanisms of gene expression regulation in neurological diseases

Monika Gos

Department of Medical Genetics, Institute of Mother and Child, Warsaw, Poland, Email: monika.gos@imid.med.pl

Neurological diseases are a heterogenous group of disorders that are related to alterations in nervous system function. The genetic background of neurological diseases is heterogenous and may include chromosomal aberrations, specific gene mutations and epigenetic defects. This review is aimed at presenting of selected diseases that are associated with different epigenetic alterations. The imprinting defects on chromosome 15 are the cause of Prader-Willi and Angelman syndromes that both are characterized by intellectual disability, developmental delay and specific behavioral phenotype. Besides the imprinting defect, these diseases can also be caused by deletion of chromosome 15 or uniparental disomy. Aberrant epigenetic regulation is also specific for Fragile X syndrome that is caused by expansion of CGG repeats in the *FMR1* gene that leads to global methylation of the promoter region and repression of *FMR1* transcription. A number of neurological diseases, mainly associated with intellectual impairment, may be caused by mutations in genes encoding proteins involved in epigenetic regulation. The number of such diseases is rapidly growing thanks to the implementation of genomic sequencing for the identification of their molecular causes. One of the best known diseases linked to defects in epigenetic modifiers is Rett syndrome caused by a mutation in the *MECP2* gene or its variant – Rett-like syndrome caused by a mutation in *CDKL5* or *FOXG1* genes. As the epigenetic signature is potentially reversible, much attention is focused on possible therapies with drugs that influence DNA or histone modifications. This is especially important in the case of neurological disorders in which epigenetic changes are observed as the effect of the disease.

Key words: epigenetic regulation, epigenetic modifiers, genomic imprinting, Prader-Willi syndrome, Angelman syndrome, Rett syndrome, Fragile X syndrome

INTRODUCTION

Neurological diseases are a heterogenous group of disorders caused by alterations in nervous system function. The causes of these diseases are various and include genetic causes, congenital abnormalities, injuries of brain, spinal cord or specific nerves, infections or other environmental factors. Also the spectrum of clinical phenotypes of patients is wide depending on the observed abnormalities of the central or peripheral nervous system.

There is a growing evidence that genetic factors strongly influence the etiology of neurological diseases. The genetic background of neurological diseases is heterogenous and may include chromosomal aberrations (e.g. aneuploidies, deletion or duplication of specific chromosome regions) and gene mutations. Epigenetic regulation is known to alter gene expression in a heritable manner that is not due to changes in DNA sequence. Specific mechanisms are responsible for the regulation of the level of transcription or translation (Feinberg 2008). The most commonly examined mechanism that regulates gene expression is DNA methylation – a covalent modification of cytosine most commonly located in so-called "CpG islands". These islands are characteristic for promoter regions of genes, where methylation represses gene expression. There are several enzymes that are responsible for DNA methylation establishment, the so-called "DNA methyltransferases", DNMT3 is responsible for *de novo* DNA methylation, while DNMT1 is responsible for the methylation of hemimethylated DNA during the replication process (Razin and Kantor 2005). DNA methylation is not only respon-

Correspondence should be addressed to M. Gos
Email: monika.gos@imid.med.pl

sible for gene expression silencing, but also is important for global chromosome X inactivation and genomic imprinting. Moreover, methylation is specific for repetitive sequences, transposons and endogenous retroviruses that might prevent their mobility in the genome. DNA methylation indirectly regulates the chromatin structure and its accessibility for transcription factors. The DNA methylation mark is a sign for methyl-binding proteins for binding and recruitment of other proteins forming a repression complex. As a consequence the chromatin becomes more densly packed, cannot be accessed by transcription factors and gene expression is silenced (Portela and Esteller 2010).

The second mechanism that is involved in gene expression regulation are covalent modifications of the histone proteins forming the core of nucleosomes. The N-terminal ends of these proteins, especially of histone 3 and 4, undergo modifications such as: methylation, acetylation, phosphorylation, ubiquitination and others. The character of the modification and its localization is responsible for the effect which it exerts on gene expression. Acetylation and deacetylation, catalyzed by histone acetyltrasferases (HAT) and histone deactylases (HDAC) are responsible for expression activation and repression, respectively (Portela and Esteller 2010). Histone methylation can have both an activating and an inhibiting effect that depends on the localization of the lysine that is covalently modified. For example, the methylation of lysine 4 and lysine 36 in histone 3 (H3K4, H3K36) was found to be associated with open chromatin structure and activation of gene expression. In contrast, methylation of lysine 9 and 27 in histone 3 is associated with silencing of mRNA transcription. The methylation of histone proteins is catalyzed by histone methyltransferases and histone demethylases (Lennartsson and Ekwall 2009, Nimura et al. 2010). Modifications of histone proteins directly influence chromatin structure, for example, acetylation and deacetylation are responsible for chromatin decondensation and compaction, respectively. They are also responsible for the interaction between chromatin and transcription factors and forming of transcriptional complexes (Lennartsson and Ekwall 2009).

DNA methylation and histone modifications are not separate mechanisms that have an impact on gene expression, they act together to influence the chromatin structure. The transcriptionally silent chromatin structure is associated with DNA methylation, histone deacetylation and methylation of specific lysines in H3 and H4. In contrast, DNA methylation is not observed when the chromatin structure is open, while the histones are acetylated and methylated on specific positions (Ikegami et al. 2009, Portela and Esteller 2010).

Another mechanism that is involved in epigenetic regulation of gene expression is the mechanism driven by non-coding RNA. This mechanism acts on the RNA level and regulates gene expression posttranscriptionally by specific interaction between target RNA and so-called interference RNA. This interaction leads to the recruitment of specific protein complexes that are responsible for the target RNA degradation and decreasing the level of specific proteins. The detailed description of the mechanisms of action of non-coding RNA can be found elsewhere (Bicker and Schratt 2008, Bian and Sun 2011, Qureshi and Mehler 2012).

The alterations of epigenetic regulation are frequently observed in case of common diseases like cancer, that affect mainly elderly populations (Miremadi et al. 2007). However, the defects of epigenetic regulation can also be found in the case of inherited diseases. Epigenetic alterations might be the direct cause of the disease, may also be observed as the effect associated with a specific disease. For the purpose of this review we have divided neurological diseases into three groups: neurological diseases that are associated with improper epigenetic (methylation) pattern, neurological diseases associated with mutations in specific genes that encode proteins responsible for proper epigenetic regulation and neurological diseases in which the epigenetic changes are an effect of the specific disease (Urdinguio et al. 2009).

As the listing of all the diseases that are caused by improper epigenetic regulation is not the aim of this review, the selected diseases that are investigated at the Department of Medical Genetics of the Institute of Mother and Child are discussed. Other diseases related to gene expression alterations like, e.g., immunodeficiency, centromeric instability and facial anomalies (ICF), Coffin-Lowry, Rubinstein-Taybi and X-linked α-thalassemia/mental retardation syndromes have been widely described in the literature (e.g. Ausio et al. 2003). Also the epigenetic changes found in neurodegenerative diseases have been reviewed in Urdinguio and coauthors (2009).

IMPROPER EPIGENETIC PATTERN

The first group of neurological diseases that are associated with improper gene expression regulation includes genetic disorders that are associated with alterations of the methylation pattern in specific chromosomal regions. The methylation pattern can be changed due to an imprinting defect or the presence of a specific mutation.

Imprinting defects

Normally, autosomal genes are expressed from both alleles and if one of them is silent this might lead to haploinsufficiency, lower expression of the specific gene cause a disease. This is clearly seen in case of chromosome monosomies that are lethal and the fetuses carrying this defect die *in utero* (the rare exception is X chromosome monosomy – 45,X – that is a cause of Turner syndrome) or dominant diseases, in which the presence of a mutation in one allele results in a specific clinical phenotype. However, in the genome, there are specific regions that contain genes whose expression is regulated by their parental inheritance, that are specifically expressed only from the paternal or maternal allele (Isles and Wilkinson 2000). This expression is regulated by epigenetic marks, the so-called genomic imprinting, specifically DNA methylation and histone modifications that are established on the chromosomes depending on their parental origin. The genomic imprinting is established in the germ cell line after the erasure of existing epigenetic marks, is parent-specific and stably passed during divisions of the zygote after fertilization and through the lifespan (Kinoshita et al. 2008).

In humans, about 60 genes that were found to be imprinted, although it was suggested that there can be up to 1 000. The imprinted genes are localized on chromosomes 6, 7, 11, 14 and 15 and are organized into clusters. The regulation of gene expression in these clusters is not restricted to single genes, there is a special regulatory center called the imprinting center (IC). The imprinting center regulates the parent-specific expression of genes localized in the cluster. The presence of genomic imprinting makes the maternal and paternal genomes not equivalent and was suggested to be the mechanism that prevents parthenogenesis (Kinoshita et al. 2008).

The defects of genomic imprinting are very rare, but if they occur in germ line cells that undergo fertilization, it is impossible to repair them. Usually the imprinting defect affects only one cluster of genes, but recently published data suggest that global demethylation and deregulation of gene expression in several clusters can also occur. Improper imprinting can be caused by defects in imprinting erasure or establishment in germ line cells as well as by defects of imprinting maintenance during the cell divisions. The latter, leads to the occurrence of mosaicism – a state where the defect is present only in a fraction of cells, while the others are normal (Horsthemke 2010).

The imprinting defect can be the effect of primary epimutation, when the improper imprinting is observed but no changes in DNA sequence are detected. This is the cause of the majority of imprinting defects and can be associated with the presence of specific haplotypes (e.g., AS-H3 haplotype in Angelman syndrome). The defects can be also caused by secondary epimutation, when the mutation in DNA leads to improper epigenetic signature establishment. The mutation can be a cis-acting mutation, like the defects in the imprinting regulatory center (deletions in PWS-IC in Prader-Willi syndrome), or trans-acting, when the mutation is present in genes coding for imprinting regulatory factors (e.g. mutations in *NLRP2* in familial cases of Beckwith-Wiedeman syndrome) (Horsthemke and Wagstaff 2008, Horsthemke 2010).

The imprinting defect is the cause of improper gene expression. The gene whose expression from a specific allele should be silenced is expressed, while the gene that should be expressed might be repressed by an improper epigenetic mark. These result in improper gene dosage and can be the cause of alterations in organism growth and development (especially the development of the nervous system, Smith et al. 2006, Butler 2009). Similar effects can be observed when deletion of imprinted region, uniparental disomy of a specific chromosome, translocations involving chromosomes with an imprinted region or mutations in imprinted genes are present (Yamazawa et al. 2010).

Prader-Willi and Angelman syndromes (PWS, AS)

Chromosomal aberrations affecting imprinted genes or specific imprinting defects might result in so-called imprinting diseases (Table I), among which Angelman and Prader-Willi syndromes are the ones that have neurological character. Patients affected with these diseases display developmental delay, especially delay of motor skills and speech, and intellectual disability (Dagli and Williams 2011, Driscoll et al. 2012).

Table I

Diseases related to defects of genomic imprinting

Disease	Locus	Important genes in the region	Prevalence	Reference
Prader-Willi syndrome	15q11-q13	*HBII-85*	1/10 000–25 000	Buiting 2010
Angelman syndrome	15q11-q13	*UBE3A*	1/12 000–20 000	
Beckwith-Wiedemann syndrome	11p15.5	*H19, IGF2, KCNQ1OT1, CDKN1C*	1/15 000	Choufani et al. 2010
Silver-Russell syndrome	11p15.5, 7p11.2-p13	*H19, IGF2, GRB10, MEST*	1/3 000–100 000	Eggermann 2010
Transient neonatal diabetes mellitus	6q24	*PLAGL1, HYMAI*	1/400 000	MacKay and Temple 2010
Pseudohypoparathyroidism Ib	20q13.11	*GNAS*	?	Kelsey 2010

Moreover, in Prader-Willi patients, in the perinatal period hypotonia and failure to thrive due to problems with breast feeding are observed. Later in life, due to improper pituitary-hypothalamic axis function, growth hormone deficiency is found in over 85% patients. The hypothalamic dysfunction also results in lack of satiety, hyperfagia and excessive obesity if the food intake is not controlled. In males, hypogonadism is also frequently observed (Jin 2012). Patients with Angelman syndrome, besides severe psychomotor delay and problems with speech, display ataxia of gait and a specific behavioral phenotype (happy phenotype with frequent laughing and excitability). The frequent finding in AS patients is also microcephaly, seizures, an abnormal, specific EEG pattern and hypopigmentation (Tan et al. 2011, Williams C.A. et al. 2010).

Both these diseases are caused by an imprinting defect on chromosome 15 in the q11-q13 region (Chamberlain and Lalande 2010b). This region contains several genes whose expression is controlled by a bipartite (AS/PWS-IC) imprinting center (Kantor et al. 2006). The *NDN1*, *MKRN3*, *C15orf2* (*NPAP1*), *MAGEL2* genes, *SNURF-SNRPN* transcript, that is alternatively spliced and encodes SNURF protein and SmN protein involved in mRNA splicing in the brain, and C/D box small nucleolar RNA genes, are specifically expressed from the paternal chromosome (Neumann et al. 2012). On the maternal one, they are methylated and specific expression of *UBE3A* and *ATP10A* takes place. Other genes that are located in this region are expressed from both maternal and paternal chromosomes (Horsthemke and Buiting 2006).

Angelman syndrome is caused by the lack of maternal contribution in the 15q11-1q13 region. It can be caused by the presence of a large deletion on the maternal chromosome (65–75% of cases), paternal uniparental disomy of chromosome 15 (3–7%) or an imprinting defect that results in the presence of the paternal imprint on both chromosomes (3%). The disease can be also caused by mutations in *UBE3A* gene (5–11% of cases) that seems to be crucial in the AS pathogenesis (Dagli and Williams 2011). The *UBE3A* gene displays tissue specific imprinting – it is specifically expressed in the brain from the maternal allele (Chamberlain and Lalande 2010a). It encodes the E6AP ubiquitin protein ligase that is responsible for ubiquitination of proteins and targeting them for degradation in proteasomes (Dindot et al. 2008). The mouse model, lacking *Ube3a* from the maternal chromosomes, display specific Parkinson-like seizures and abnormal dopamine neurotransmission, whose proper function can be restored with L-DOPA treatment (Riday et al. 2012).
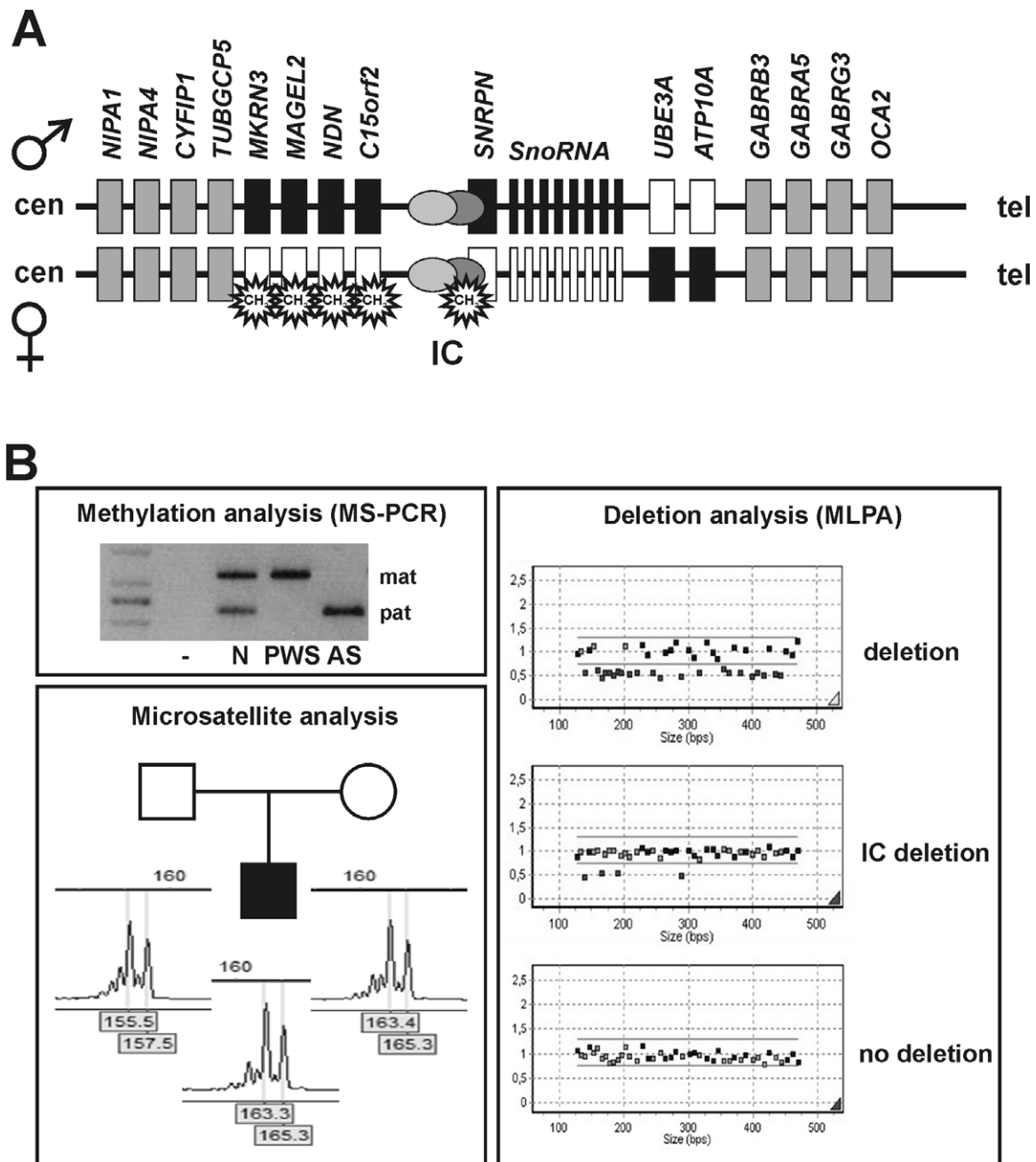
Fig. 1. The chromosomal organization of the 15q11-q13 region (A) involved in Prader-Willi and Angelman syndromes and examples of tests used in the molecular diagnosis of these diseases (B). (A) Each rectangle represents a single gene; grey – non-imprinted genes, black – imprinted genes expressed specifically from paternal (upper panel) or maternal (lower panel) chromosome, white – imprinted genes that are specifically silenced on the paternal or maternal chromosome; the methylated (silenced) genes on the maternal chromosome were marked with the star. The bipartite imprinting center (IC) is shown is grey. (B)The confirmation of clinical diagnosis of PWS and AS syndrome can be done by methylation-specific PCR (MS-PCR) that identifies maternal (methylated) and paternal (non-methylated) chromosomes. For the assessment of relative risk, it is necessary to further characterize the defect that is the cause of improper methylation pattern. This can be performed by Multiplex Ligation Dependent Probe Amplification (MLPA) technique that allows for the identification of deletion or imprinting center deletion. If the deletion is not identified, microsatellite analysis in proband and its parents can be performed to test for possible uniparental disomy (UPD). The biparenrtal inheritance and lack of deletion suggests that other factors are responsible for the presence of improper imprinting.

In contrast to AS, Prader-Willi syndrome is caused by the lack of the paternal contribution in the 15q11-q13 region that can be the result of a paternal chromosome 15 deletion (65–75% of cases), maternal uniparental disomy (20–30%) or an imprinting defect that results in the presence of methylation on the paternal chromosome (2.5%) (Driscoll et al. 2012). Untill recently, the specific gene that was specifically linked to PWS pathogenesis had not been identified although genes in the 15q11-q13 region encode proteins expressed in the nervous system. In 2008, a patient with a PWS-like phenotype was described. The patient displayed hyperfagia and severe obesity, mild learning difficulties and hypogonadism and in cytogenetic studies was found to carry a small microdeletion on chromosome 15 that encompassed only the *HBII-85* gene (Sahoo et al. 2008). This gene encodes small nucleolar RNA (snoRNA) that is specifically expressed during neuronal differentiation and in mature neurons in the cortex and hypothalamus, especially in the regions that control food intake and energy balance (Zhang et al. 2012). In the case of Prader-Willi patients, the early diagnosis is crucial as the treatment with growth hormone is very effective when started in early childhood (Jin 2012).

Fragile X syndrome

The fragile X syndrome (FXS, FraX) is another disease in which an improper epigenetic mark on the DNA is observed. This disorder is one of the most common causes of genetically caused intellectual disability. Patients suffering from this disease, besides intellectual impairment, also were found to have delayed speech and psychomotor development, specific facial dysmorphy (long face, large, protruding ears), psychological disturbances (hyperreactivity, ADHD, autism spectrum behaviors) and macroorchidism. Mainly males are affected with FXS and its frequency is estimated at 1/4 000. In women (frequency of 1/8 000) less severe clinical features are observed and the clinical expression depends on the ratio of inactivation of the X chromosome with the mutation (Garber et al. 2008, Saul and Tarleton 2012).

The fragile X syndrome is caused by a mutation in the *FMR1* gene located on the X chromosome. The *FMR1* gene encodes FMRP – an RNA interacting protein that is responsible for mRNA transport from the nucleus to dendrites and regulation of protein synthesis at synapses via interaction with polyribosomes (Pfeiffer and Huber 2009). One of the processes that is regulated by the FMRP protein, is the regulation of the AMPA receptor internalization after mGluR activation with glutamate that is important for the learning process and memory formation (reviewed in: Rzońca and Gos 2012).

In the 5' untranslated region of the *FMR1* gene, there is a CGG repeat sequence that is highly polymorphic and unstable. On average there are 30 CGG repeats in this region, but in patients with FXS the number of repeats exceeds 200 (Willemsen et al. 2011). The abundance of cytosine and guanine nucleotides results in the global methylation of the repeat region and neighboring regulatory elements. This leads to the repression of *FMR1* gene expression and lack of the protein (Oostra and Willemsen 2009, Godler et al. 2010). The insufficient level of FMRP protein results in excess of AMPA internalization, altered cell morphology and therefore inappropriate neuron functioning. It was shown on the mouse model without the *Fmr1* gene that the administration of antagonists of mGluR5 signaling (e.g. fenobam or MPEP) lowered the level of AMPA internalization and rescued the proper neuron morphology and wild-type phenotype in knock-out mice (Levenga et al. 2010, Willemsen et al. 2011, Vinueza Veloz et al. 2012).

Chromosome X skewing

X-linked intellectual disability (XLID) is a group of disorders affecting mainly males that besides intellectual impairment (IQ<70) below the age of 18 display significant limitations of at least two adaptive skills. These findings might not be associated with other clinical features (non-syndromic form), but can also be accompanied by dysmorphy, malformations or other neurological abnormalities (syndromic form) (Gecz et al. 2009, Rejeb et al. 2009). So far over 215 conditions associated with XLID have been described and some of them are linked to genes that code for proteins involved in neuronal differentiation, synaptic plasticity, synaptic vesicle cycling, regulation of the actin cytoskeleton, chromatin remodeling and regulation of gene expression. In families with XLID a specific pattern of disease occurrence is observed – the disorder affects male family members while the women are only carriers of mutations in different genes localized on the X chromosome and rarely display clinical fea-

tures that depend on the X chromosome inactivation ratio (Chiurazzi et al. 2008).

The X chromosome inactivation is strictly regulated process of repression of gene transcription on the X chromosome because of dosage compensation between the sexes. As the process is random and both X chromosomes should be inactivated in an equal ratio, in the adult organism mosaicism is observed. The X chromosome inactivation starts in the early embryo, when the fetus has about 200 cells and involves many epigenetic mechanisms. The process starts from the expression of the *XIST* transcript from the X chromosome that will be inactivated (Xi) – a non-coding RNA particle that accumulates within the territory of Xi. This is the signal for deacetylation of histone H3 and demethylation of lysine 4 of H3 (H3K4) that are followed by ubiquitination of H2A and methylation of lysine 27 of H3 (H3K27) as well as binding of repressor proteins from the Trithorax and polycomb families and SAF-A scaffold factor. Moreover, the promoter regions on the inactivated X chromosome become methylated by DNMT1 and SmcHD1 proteins. All these modifications act together and repress gene expression from the inactivated X chromosome (Gendrel and Heard 2011, Ohhata and Wutz 2012).

The X chromosome inactivation is random and the ratio between the active and inactive chromosomes is equal (Gendrel and Heard 2011). However, in women from XLID families, non-random X chromosome inactivation is observed that is a signal that a specific mutation may exist on the inactivated chromosome. The higher proportion of one X chromosome inactivation can be due to the fact that a mutation in a specific gene might negatively affect cell viability or proliferation rate. Therefore the silencing of a specific X chromosome will have a positive impact on cell growth and division. In the case of XILD families, mothers carrying the mutation display an altered X-inactivation pattern with a ratio ≥80:≤20. In the case of women with the mutation and random X chromosome inactivation, the clinical features typical for a specific X-linked disease might be observed (Plenge et al. 2002, Knudsen et al. 2006, Yonath et al. 2011).

Assisted reproductive technologies (ART) and epigenetic disturbances

In developing countries, over 1% of pregnancies were suggested to involve one of the techniques used in assisted reproductive technologies (ART) like hormone stimulation of oocyte production, *in vitro* maturation of oocytes, *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), *in vitro* culture of preimplantation embryos and cryopreservation of gametes or embryos. Recently published data have suggested a link between ART and a higher risk of imprinting defects and thus imprinting disorder development.

In fact, the external factors that act on gametes and developing embryos *in vitro* might influence the epigenetic regulation of gene expression including imprinting. In particular, two important phases of imprinting pattern development can be affected by ART methods. Firstly, ART may influence the establishment of maternal imprinting in oocytes that naturally takes place just prior to ovulation. In the case of ovary stimulation, the oocytes are collected directly from the organ and cultured *in vitro* which giving rise to the possibility that the imprinting process might be disturbed. Secondly, the *in vitro* culture of early embryos might also influence the global demethylation of the genome that takes place just after fertilization. Although during this process the parental imprint is maintained it cannot be excluded it might be also affected by environmental factors (Owen and Segars Jr 2009).

Several studies performed on animal models confirmed the relationship between assisted reproductive technologies and higher incidence of imprinting changes in embryos. Experiments on mice have shown that the culture media might affect the process of imprinting and gene expression. In mouse embryos cultured in Whitten's medium, the abnormal higher expression of the *H19* gene (this expression is essential for proper fetal growth) due to the loss of methylation on the paternal allele was observed. This was not found when the embryos were cultured in KSOM media containing amino acids. Further analysis has shown that the culture conditions might also affect the expression of other imprinted, growth-related genes like *IGF2*, *GRB10* or *GRB7*. It was also shown that the mouse two-cells embryos cultured *in vitro* have a higher methylation level and a lower degree of demethylation of male pronuclei. Also observations on cattle embryos confirm the relationship between ART and imprinting defects as their *in vitro* culture leads to the hypomethylation of the *IGF2R* gene resulting in a well-known phenotype – large offspring syndrome characterized by fetal overgrowth and perinatal death (Iliadou et al. 2011, El Hajj and Haff 2013).

Table II

Diseases associated with mutations is specific genes encoding epigenetic modifiers

Disease	Locus	Gene	Function	References
DNMT1-Related Dementia, Deafness, and Sensory Neuropathy	19p13.2	*DNMT1*	DNA methyltransferase	Klein et al. 2011
Immunodeficiency-Centromeric Instability-Facial Anomalies Syndrome	20q11.21	*DNMT3B*	DNA methyltransferase	Ehrlich et al. 2008
Rett syndrome and Rett-like syndrome	Xq28	*MECP2* *CDKL5* *FOXG1*	methyl-DNA binding protein MECP2 and DNMT1 kinase (?) transcriptional repressor	Christodoulou and Ho 2012
Autism	18q21.1 18q21.2 19p13.3 3q21.3	*MBD1* *MBD2* *MBD3* *MBD4*	methyl-DNA binding proteins	Li et al. 2005, Cukier et al. 2010
Genitopatellar syndrome Say-Barber-Biesecker-Young-Simpson syndrome	10q22.2	*MYST4 (KAT6B)*	histone acetyltransferase	Campeau et al. 2012
Rubinstein-Taybi Syndrome	16p13 22q13	*CREBBP, EP300*	histone acetyltransferase	Roelfsema and Peters 2007
Brachydactyly-mental retardation syndrome	2q37.3	*HDAC4*	histone deacetylase	Williams S.R. et al. 2010
Wilson-Turner X-linked mental retardation syndrome Cornelia de Lange syndrome	Xq13.1	*HDAC8*	histone deacetylase	Harakalova et al. 2012 Deardorff et al. 2012
Kleefstra syndrome	9q34	*EHMT1* *MLL3* *MBD5* *SMARCB1* *NR1I3*	histone methyltransferase histone methyltransferase methyl-DNA binding protein subunit of the SWI/SNF complex nuclear receptor	Kleefstra et al. 2012
Weaver syndrome 2	7q36.1	*EZH2*	histone methyltransferase	Gibson et al. 2012
Wiedemann-Steiner syndrome	11q23.3	*MLL*	histone methyltransferase	Jones et al. 2012

Table II (cont)

Sotos syndrome Weaver syndrome	5q35	*NSD1*	histone methyltransferase	Rio et al. 2003
Autism	1q21.3	*SETDB1*	histone methyltransferase	Cukier et al. 2012
CHARGE syndrome	8q12	*CHD7*	DNA helicase	Legendre et al. 2012
Autism, autism spectrum disorders	14q11.2	*CHD8*	DNA helicase	O'Roak et al. 2012
α-thalassaemia ID syndrome	Xq13	*ATRX*	DNA helicase	Van Bokhoven and Kramer 2010
Potocki-Shaffer syndrome	11p11.2	*PHF21A*	part of BHC repression complex	Kim et al. 2012
XLID	Xp11.22	*PHF8*	histone demethylase	Qiu et al. 2010
XLID, speech delay, hyperactivity, violent behavior, seizures	Xp11	*JARID1C*	histone demethylase	Santos-Rebouças et al. 2011
XLID, absent speech, seizures	Xq24	*UBE2A*	ubiquitin transferase	de Leeuw et al. 2010
XLID	Xp11.22	*HUWE1*	ubiquitin transferase	Froyen et al. 2008
Coffin-Lowry syndrome	Xp22	*RPS6KA3*	histone and TFs kinase	Pereira et al. 2010
Nicolaides-Baraitser syndrome (ID, epilepsy)	9p24.3	*SMARCA2*	subunit of DNA Remodeling complex	Van Houdt et al. 2012
Coffin-Siris syndrome (CSS) – MRD16	11p13.2	*SMARCA4*	subunit of DNA Remodeling complex	Tsurusaki et al. 2012
Coffin-Siris syndrome (CSS) – MRD14	1p36.11	*ARID1A*	subunit of DNA Remodeling complex	Tsurusaki et al. 2012

The table was prepared based on the list of genes involved in epigenetic regulation published in a paper by Weng and coworkers (2012)

The studies on epigenetic alterations in human embryos and gametes are limited due to ethical considerations. However, a higher incidence of Beckwith-Wiedemann, Silver-Russell or Angelman syndromes was reported in several clinical studies on French, Australian, American and Japanese population. On the other hand, studies on large cohorts from Denmark, Netherlands or Sweden have failed to find such relationship – the frequency of imprinting defects in ART children was comparable with the general population or no cases were found after ART. Concerning the rarity of disorders caused by epigenetic alterations, the overall risk of imprinting disorders in children born with assisted reproductive technologies is still low (Manipalviratn et al. 2009, Owen and Segars Jr 2009, van Montfoort et al. 2012).

All studies published so far have identified 1021 BWS patients. In this group, forty two patients after ART with Beckwith-Wiedemann syndrome were identified. The intracytoplasmic sperm injection and *in vitro* fertilization were applied in 16 and 20 cases, respectively (for 6 patients the ART type was not known) (van Montfoort et al. 2012). In the case of Angelman syndrome, together seven patients after ART (6 after ICSI, 1 after IVF) have been described in the literature (Manipalviratn et al. 2009).

It was found that the majority of BWS and AS cases born after ART display imprinting defects. The loss of methylation on the maternal allele of *KCNQ1OT1* due to the imprinting defect was found in 26 out of 32 (81.2%) patients with BWS (van Montfoort et al. 2012). In five out of seven AS cases (71.4%) the loss of *SNRPN* gene methylation on maternal chromosome was found, that was due to the imprinting defect and only in 2 cases the deletion of 15q11-q13 region was identified (Manipalviratn et al. 2009). The rate of imprinting defects in naturally conceived children affected with these diseases is much lower and was estimated at 50–60% and 1–3% for BWS and AS, respectively (Manipalviratn et al. 2009, van Montfoort et al. 2012).

Large epidemiological studies have found that assisted reproductive technologies slightly increase the risk of birth defects. However, it is difficult to distinguish whether such risk results from the technologies used or parental factors related to the infertility problems or pregnancy itself. The good example are neural tube defects (NTD), particularly anencephaly that occurred more frequently in twin pregnancies after ART (8 cases, 1.1%) then in naturally conceived twin pregnancies (1 case, 0.1%, OR-24.6, *P*<0.001). Such relationship was not found for singleton pregnancies as no case of anencephaly after ART in these pregnancies was identified (Ben-Ami et al. 2011). In addition, the incidence of neural tube defects can be modified by several external factors particularly by administration of folic acid – a key player in methionine and homocysteine metabolism (Gos and Szpecht-Potocka 2002). It was suggested that inadequate folate intake can lead to alternations in the level of the S-adenosylomethionine (indispensable for DNA methylation) and impaired DNA methylation. The analysis of global DNA methylation level as well as methylation of specific sequences (e.g., LINE-1 sequences and the *MGMT* gene) has shown that the methylation level was lower in NTD patients, which was associated with a higher risk of disease occurrence (Wang et al. 2010, Tran et al. 2012).

The assisted reproductive technologies are also associated with 2–3 times higher risk of low birth weight that was shown to be a susceptibility factor for adult obesity, type 2 diabetes and hypertension. Although there are no longitudinal studies that assess the risk of these common diseases in children born after ART, it has been suggested that subtle epigenetic changes caused by ART might influence the susceptibility to these disorders in adulthood (Chen et al. 2010, Savage et al. 2011, El Hajj and Haff 2013).

DEFECTS OF EPIGENETIC MODIFIERS

A number of neurological diseases, mainly associated with intellectual impairment, may be caused by mutations in genes encoding proteins involved in epigenetic regulation. This group includes proteins that are direct modifiers of the chromatin structure and that directly modify the DNA (DNA methyltransferases), histone proteins (histone acetyltransferases, histone deacetylases, histone methyltransferases and histone demethylases), helicases or other histone modifying enzymes. Also the mutations in genes encoding proteins that indirectly modify chromatin structure like chromatin, DNA, methyl-DNA and histone binding proteins, specific kinases or transcription regulators may be the causes of neurological disorders (Table II). The proteins from the second group bind to chromatin or DNA and indirectly modulate the chromatin structure by the regulation of activity of direct chromatin

modifiers or their recruitment to repression or transcription complexes (Kramer and van Bokhoven 2009, van Bokhoven and Kramer 2010). The interesting fact is that somatic mutations in the genes coding for epigenetic modifiers are frequently found in all types of cancers, confirming the fact that global alterations in gene expression might induce tumor development (Miremadi et al. 2007).

The neurological disorders that are caused by germinal mutations in genes coding for epigenetic modifiers are mainly characterized by intellectual disability that can be accompanied by other neurological features like seizures, hypotonia, autism spectrum behaviors and delayed psychomotor development. Another clinical finding in patients is the presence of specific dysmorphic features, characteristic for the specific disease (von Bokhoven and Kramer 2010). One of the most interesting diseases related to mutations in epigenetic regulators is the group of diseases associated with mutations in the *MECP2* gene, that are also included in the group of X-linked intellectual disabilities.

The *MECP2* gene, localized on the X chromosome, encodes a methyl-CpG binding protein, a highly conserved nuclear protein that binds to methylated DNA sequences and recruits repressors and chromatin remodeling proteins like HDAC1&2, H3K9 methyltransferase and DNMT1 methyltransferase that form the SIN3A corepressor complex. This complex is responsible for chromatin compaction and suppression of gene expression. The MECP2 protein is present in all tissues, binds to methylated DNA independently of the DNA sequence and is responsible specifically for the inhibition of transcription from the methylated promoters (Banerjee et al. 2012).

The expression of MECP2 is especially high in the brain and changes together with the development of the nervous system. Its expression is high during embryonic development, low at birth and then starts to grow. MECP2 expression is not observed in immature neurons, but is rather specific for the neuron maturation process and is further maintained in mature cells. It is especially important for maintenance and modulation of synapses and dendritic complexity. Mouse models lacking *Mecp2* expression did not display significant changes in brain structure, but the processes of neuronal maturation and synaptogenesis were delayed and specific morphological and functional alterations in neurons (e.g., reduced dendritic branching, affected axonal arborization, improper synaptic

scaling) were found (Kishi and Macklis 2005, Stuss et al. 2012).

The control of transcription and translation by MECP2 depends on the recruited molecules and protein-protein interactions. One of the genes, whose expression is controlled by MECP2 binding to methylated sequences, is the *BDNF* gene coding for brain derived neurotrophic factor. This protein is important for neuron development, synaptic maturation and plasticity. It binds to TrkB protein and activates the PI3K/AKT signaling pathway that regulates specific cellular processes like proliferation and differentiation (Cowansage et al. 2010, Díaz de León-Guerrero et al. 2011).

Mutations in *MECP2* are associated with specific clinical phenotypes associated with intellectual disability and delayed psychomotor development. The first phenotype – Rett syndrome (occurrence rate: 1/10 000–150 000) is rather specific for girls, as it was suggested that mutations in the *MECP2* gene are lethal for male fetuses with a normal karyotype. Rare cases when the male survive till birth were reported, but the newborns displayed severe neonatal encephalopathy and intellectual disability or displayed typical Rett syndrome features in the case of a 47,XXY karyotype or mosaicism (Schwartzman et al. 2001, Psoni et al. 2010). The clinical course of the disease is highly specific – the perinatal period and first months of life have a normal course, and after 18 months of life a regression of the acquired skills occurs. The disease has a progressive character – the presence of stereotypies leads to the loss of proper hand use, after an autistic like period, the loss of cognitive, motor and social skills is observed followed by severe intellectual disability, motor impairments and seizures (generalized tonic-clonic seizures or partial complex seizures). Postnatal deceleration of head growth and breathing disturbances are also common in Rett syndrome patients (Christodoulou and Ho 2012).

The phenotypes of patients with a pathogenic mutation in the *MECP2* gene depend on two factors: the pattern of X chromosome inactivation and the character and localization of the mutation. If the X chromosome with the *MECP2* mutation is more favorably inactivated, a milder clinical phenotype is observed. A less severe course of the disease is also found in patients carrying missense mutations or with mutations localized in the C-terminal part of the protein (Knudsen et al. 2006, Lima et al. 2009, Ravn et al. 2011, Temudo et al. 2011).

The second phenotype associated with alterations of the *MECP2* gene is the *MECP2* duplication syndrome that affects mainly males and results in severe to profound intellectual disability, early onset hypotonia, delayed psychomotor development, progressive spasticity of the lower limbs, predisposition to infections (observed in about 75% of the affected males), epileptic seizures (up to 50%) and other clinical features like autistic behavior, gastrointestinal dysfunction and facial dysmorphism (Ramocki et al. 2010, Van Esch 2010). The *MECP2* duplication is usually inherited from healthy mothers as females carrying this mutation display extreme to complete skewing of the X chromosome. It was reported, however, that these women can display neuropsychiatric symptoms like depression or anxiety. In addition, cases of females that had a *MECP2* duplication due to genomic insertion or X-autosome unbalanced translocation have been described that presented with severe ID and other features characteristic for affected males (Bijlsma et al. 2012).

MECP2 mutations are found in about 95–97% of typical Rett syndrome patients. However, the mutation detection rate is much lower in patients displaying the so-called Rett-like phenotypes (50–70%; Christodoulou and Ho 2012). The careful molecular examination of these patients revealed that also mutations in *CDKL5* and *FOXG1* genes are responsible for the specific phenotype. Both these genes encode proteins involved in indirect modification of chromatin structure and therefore gene expression (Guerrini and Parrini 2012). The *CDKL5* encodes a cyclin dependent-like kinase 5 that was shown to interact with MECP2 and was suggested to regulate the phosphorylation of this protein (Mari et al. 2005). Further studies have revealed that only a small fraction of *CDKL5* mutations is responsible for the Rett-like phenotype and that the alterations in *CDKL5* gene rather are responsible for early onset epileptic encephalopathy with intractable seizures and intellectual impairment (Lin et al. 2005, Bahi-Buisson and Bienvenu 2012, Fehr et al. 2013). This was explained by the functional analysis of the protein – it was found to interact with DNMT1 – DNA methyltransferase, to be present in nuclear speckles and to regulate the activity of the splicing machinery in transcriptionally active sites, and to regulate neuronal morphogenesis and dendritic arborization by interaction with RAC1 protein and F-actin. CDKL5 is a ubiquitous protein but is expressed at very high levels in the brain, especially during early postnatal stages in maturing neurons of the hippocampus and the cerebral cortex (Kameshita et al. 2008, Ricciardi et al. 2009, Chen et al. 2010).

The second gene, mutated in Rett-like patients, is *FOXG1* – encoding forkhead box protein G1, a transcriptional repressor that recruits a histone demethylase (KDM5B) and Groucho protein thus inhibiting expression of specific genes. The FOXG1 is involved in the regulation of the development of the brain and the telencephalon from which the cerebral cortex and basal ganglia are formed (Guerrini and Parrini 2012). It is especially important for progenitor to neuron transition and cell proliferation in the telencephalon (inhibits *BMP4* and induces *FGF8* expression). It is also expressed in the mature brain and was suggested to promote the survival of differentiated, postmitotic neurons (Florian et al. 2012). Patients carrying *FOXG1* mutations have a phenotype quite similar to Rett syndrome, that differs from the typical RTT form by the presence of frank dyskinesia, the absence of the period of normal development after birth and severe postnatal microcephaly (Van der Aa et al. 2011, Roche-Martinez et al. 2011, Guerrini and Parrini 2012).

EPIGENETIC ALTERATIONS IN NEUROLOGICAL DISEASES

Epigenetic alterations can also be caused by the existing neurological disease, which has been demonstrated by the molecular comparison of epigenetic marks in tissues from persons with a specific disease and healthy ones as well as by the analyses performed on animal models for a particular disease. Such epigenetic changes are commonly observed in different neurological disorders like Alzheimer's, Parkinson's and Huntington's diseases, spinal muscular atrophy, Freidreich's ataxia, adrenoleukodystrophy, multiple sclerosis, amyotrophic lateral sclerosis and epilepsy (reviewed in Urdinguio et al. 2009).

Epigenetic changes observed in patients with neurological diseases mainly include methylation changes – hypo- or hypermethylation of the genes whose expression might be crucial for proper functioning of the affected tissue. A good example is the elevated methylation level of the *RELN* gene in patients with temporal lobe epilepsy. The gene encodes the neural factor reelin

that regulates cell positioning, neuronal migration, synaptic function and plasticity, while its lower expression levels may affect all these processes (Qureshi and Mehler 2010, Shorvon 2011). Hypomethylation of the *TNF* gene in cortex and higher level of the TNFα cytokine in the cerebrospinal fluid was found in patients with Parkinson's disease. The elevated level of TNFα in these patients was suggested to induce apoptosis in neuronal cells (Mogi et al. 1996). Also, in the case of multiple sclerosis some differences in the methylation pattern were found – the methylation of cytosines in white matter is much lower as compared to healthy controls. More specifically, the *PADI2* gene encoding peptidyl arginine deiminase type II was found to be hypomethylated in multiple sclerosis patients. The higher expression of the PADI2 protein, responsible for the citrullination of myelin basic protein, stimulates myelin autocleavage and formation of specific epitopes that are presented to immunological system and stimulate the immunological response (Calabrese et al. 2012).

Altered modifications of histone proteins, especially hypoacetylation and H3K9 hypertrimethylation that lead to gene silencing due to chromatin compaction, have also been found in patients with neurological disorders, e.g., Huntington's disease, Friedreich's ataxia, multiple sclerosis, spinal muscular atrophy and Parkinson's disease (Urdinguio et al. 2009). In the case of Huntington's disease, the altered histone modifications are due to direct interaction of the mutant (>39polyQ) HTT protein with the CBP, a protein functioning as histone acetyltransferase, which leads to the sequestration of CBP in aggregates formed in cytoplasm and nucleus (Choi et al. 2012).

Moreover, the mouse models for specific neurological disorders have been extensively studied to assess the character and level of epigenetic changes in neural tissues. For example, in animal models of epileptogenesis induced with kainic acid or pilocarpine, changes in chromatin structure due to transient phosphorylation of H3S10 and deacetylation of H3K14 as well as changes in the expression of miRNA have been found. These observations have led to the development of new epigenetic drugs used for the treatment of epilepsy patients. One of those drugs – valproic acid, despite its function as an activator of GABAergic function, can also inhibit histone deacetylases responsible for gene expression silencing (Urdinguio et al. 2009, Kobow and Blümcke 2011, Lubin 2012).

CONCLUSIONS

The epigenetic regulation of gene expression in highly important for organism development. The appropriate genes are activated and subsequently silenced by epigenetic mechanisms during the differentiation of tissues and organs. The strict regulation of gene expression is especially important in the case of nervous system development, where the tight changes might result in improper synaptic signaling or nervous cell differentiation and give a broad spectrum of clinical phenotypes.

It is generally known that gene expression might be modified by environmental factors, probably by affecting epigenetic marks that act on the transcription level. As the epigenetic changes are commonly found in neurodegenerative diseases and other neurological conditions it was suggested that drugs that influence the epigenetic imprint might be useful in therapy (Kelly et al. 2010). For example HDAC inhibitors, like suberoylanilide hydroxamic acid (SAHA), trichostatin A and sodium butyrate were tested as a potential drugs for Alzheimer disease, Huntington disease, multiple sclerosis or Rubinstein-Taybi syndrome (Urdinguio et al. 2009). In the case of Angelman syndrome, it was proposed that silent paternal copy of the *UBE3A* gene can be activated with the usage of topotecan, a topoisomerase inhibitor, a drug that is related to the regulation of DNA topology (Huang et al. 2011). However, all these substances would not only regulate the expression of genes that are related to specific disease, but also other genes, also imprinted ones. Therefore their use in clinical treatment needs further evaluation and rigorous clinical testing.

So far, besides diseases due to improper genetic imprinting, over 25 monogenic disorders have been described that are caused by mutations in genes that encode different factors involved in epigenetic regulation (Table II). However, in the era of genomic analyses, when the exome or whole genome next generation sequencing or whole-genome microarrays are applied for the molecular diagnosis of neurological diseases, it is highly probable that the number of such diseases will grow rapidly.

ACKNOWLEDGMENTS

REFERENCES

Ausió J, Levin DB, De Amorim GV, Bakker S, Macleod PM (2003) Syndromes of disordered chromatin remodeling. Clin Genet 64: 83–95.

Bahi-Buisson N, Bienvenu T (2012) CDKL5-Related Disorders: From Clinical Description to Molecular Genetics. Mol Syndromol 2: 137–152.

Banerjee A, Castro J, Sur M (2012) Rett syndrome: genes, synapses, circuits, and therapeutics. Front Psychiatry 3: 34.

Ben-Ami I, Edel Y, Barel O, Vaknin Z, Herman A, Maymon R (2011) Do assisted conception twins have an increased risk for anencephaly? Hum Reprod 26: 3466–3471.

Bian S, Sun T (2011) Functions of noncoding RNAs in neural development and neurological diseases. Mol Neurobiol 44: 359–373.

Bicker S, Schratt G (2008) microRNAs: tiny regulators of synapse function in development and disease. J Cell Mol Med 12: 1466–1476.

Bijlsma EK, Collins A, Papa FT, Tejada MI, Wheeler P, Peeters EA, Gijsbers AC, van de Kamp JM, Kriek M, Losekoot M, Broekma AJ, Crolla JA, Pollazzon M, Mucciolo M, Katzaki E, Disciglio V, Ferreri MI, Marozza A, Mencarelli MA, Castagnini C, Dosa L, Ariani F, Mari F, Canitano R, Hayek G, Botella MP, Gener B, Mínguez M, Renieri A, Ruivenkamp CA (2012) Xq28 duplications including *MECP2* in five females: Expanding the phenotype to severe mental retardation. Eur J Med Genet 55: 404–413.

Buiting K (2010) Prader-Willi and Angelman syndrome. Am J Med Genet C Semin Med Genet 154C: 365–376.

Butler MG (2009) Genomic imprinting disorders in humans: A mini-review. J Assist Reprod Genet 26: 477–486.

Calabrese R, Zampieri M, Mechelli R, Annibali V, Guastafierro T, Ciccarone F, Coarelli G, Umeton R, Salvetti M, Caiafa P (2012) Methylation-dependent PAD2 upregulation in multiple sclerosis peripheral blood. Mult Scler 18: 299–304.

Campeau PM, Lu JT, Dawson BC, Fokkema IF, Robertson SP, Gibbs RA, Lee BH (2012) The *KAT6B*-related disorders genitopatellar syndrome and Ohdo/SBBYS syndrome have distinct clinical features reflecting distinct molecular mechanisms. Hum Mutat 33: 1520–1525.

Chamberlain SJ, Lalande M (2010a) Angelman syndrome, a genomic imprinting disorder of the brain. J Neurosci 30: 9958–9963.

Chamberlain SJ, Lalande M (2010b) Neurodevelopmental disorders involving genomic imprinting at human chromosome 15q11-q13. Neurobiol Dis 39: 13–20.

Chen Q, Zhu YC, Yu J, Miao S, Zheng J, Xu L, Zhou Y, Li D, Zhang C, Tao J, Xiong ZQ (2010) CDKL5, a protein associated with rett syndrome, regulates neuronal morphogenesis via Rac1 signaling. J Neurosci 30: 12777–12786.

Chen M, Norman RJ, Heilbronn LK (2011) Does in vitro fertilisation increase type 2 diabetes and cardiovascular risk? Curr Diabetes Rev 7: 426–432.

Chiurazzi P, Schwartz CE, Gecz J, Neri G (2008) XLMR genes: update 2007. Eur J Hum Genet 16: 422–434.

Choi YJ, Kim SI, Lee JW, Kwon YS, Lee HJ, Kim SS, Chun W (2012) Suppression of aggregate formation of mutant huntingtin potentiates CREB-binding protein sequestration and apoptotic cell death. Mol Cell Neurosci 49: 127–137.

Choufani S, Shuman C, Weksberg R (2010) Beckwith-Wiedemann syndrome. Am J Med Genet C Semin Med Genet 154C: 343–354.

Christodoulou J, Ho G (2012) MECP2-related disorders. In: GeneReviews™ [Internet] (Pagon RA, Bird TD, Dolan CR, et al., Eds). University of Washington, Seattle, WA. [Available at: http://www.ncbi.nlm.nih.gov/books/NBK1497/]

Cowansage KK, LeDoux JE, Monfils MH (2010) Brain-derived neurotrophic factor: a dynamic gatekeeper of neural plasticity. Curr Mol Pharmacol 3: 12–29.

Cukier HN, Lee JM, Ma D, Young JI, Mayo V, Butler BL, Ramsook SS, Rantus JA, Abrams AJ, Whitehead PL, Wright HH, Abramson RK, Haines JL, Cuccaro ML, Pericak-Vance MA, Gilbert JR (2012) The expanding role of MBD genes in autism: Identification of a MECP2 duplication and novel alterations in MBD5, MBD6, and SETDB1. Autism Res 5: 385–397.

Cukier HN, Rabionet R, Konidari I, Rayner-Evans MY, Baltos ML, Wright HH, Abramson RK, Martin ER, Cuccaro ML, Pericak-Vance MA, Gilbert JR (2010) Novel variants identified in methyl-CpG-binding domain genes in autistic individuals. Neurogenetics 11: 291–303.

Dagli AI, Williams CA (2011) Angelman syndrome. In: GeneReviews™ [Internet] (Pagon RA, Bird TD, Dolan CR, et al., Eds). University of Washington, Seattle, WA [Available at http://www.ncbi.nlm.nih.gov/books/NBK1144/]

de Leeuw N, Bulk S, Green A, Jaeckle-Santos L, Baker LA, Zinn AR, Kleefstra T, van der Smagt JJ, Vianne Morgante AM, de Vries BB, van Bokhoven H, de Brouwer AP (2010) *UBE2A* deficiency syndrome: Mild to severe intellectual disability accompanied by seizures, absent speech, urogenital, and skin anomalies in male patients. Am J Med Genet A 152A: 3084–3090.

Deardorff MA, Bando M, Nakato R, Watrin E, Itoh T, Minamino M, Saitoh K, Komata M, Katou Y, Clark D, Cole KE, De Baere E, Decroos C, Di Donato N, Ernst S, Francey LJ, Gyftodimou Y, Hirashima K, Hullings M, Ishikawa Y, Jaulin C, Kaur M, Kiyono T, Lombardi PM, Magnaghi-Jaulin L, Mortier GR, Nozaki N, Petersen MB, Seimiya H, Siu VM, Suzuki Y, Takagaki K, Wilde JJ, Willems PJ, Prigent C, Gillessen-Kaesbach G, Christianson DW, Kaiser FJ, Jackson LG, Hirota T, Krantz ID, Shirahige K (2012) HDAC8 mutations in Cornelia de Lange syndrome affect the cohesin acetylation cycle. Nature 489: 313–317.

Díaz de León-Guerrero S, Pedraza-Alva G, Pérez-Martínez L (2011) In sickness and in health: the role of methyl-CpG binding protein 2 in the central nervous system. Eur J Neurosci 33: 1563–1574.

Dindot SV, Antalffy BA, Bhattacharjee MB, Beaudet AL (2008) The Angelman syndrome ubiquitin ligase localizes to the synapse and nucleus, and maternal deficiency results in abnormal dendritic spine morphology. Hum Mol Genet 17: 111–118.

Driscoll DJ, Miller JL, Schwartz S (2012) Prader-Willi syndrome. In: GeneReviews™ [Internet] (Pagon RA, Bird TD, Dolan CR, et al., Eds). University of Washington, Seattle, WA. [Available at: http://www.ncbi.nlm.nih.gov/books/NBK1330/]

Eggermann T (2010) Russell-Silver syndrome. Am J Med Genet C Semin Med Genet 154C: 355–364.

Ehrlich M, Sanchez C, Shao C, Nishiyama R, Kehrl J, Kuick R, Kubota T, Hanash SM (2008) ICF, an immunodeficiency syndrome: DNA methyltransferase 3B involvement, chromosome anomalies, and gene dysregulation. Autoimmunity 41: 253–271.

Fehr S, Wilson M, Downs J, Williams S, Murgia A, Sartori S, Vecchi M, Ho G, Polli R, Psoni S, Bao X, de Klerk N, Leonard H, Christodoulou J (2013) The CDKL5 disorder is an independent clinical entity associated with early-onset encephalopathy. Eur J Hum Genet 21: 266–273.

Feinberg AP (2008) Epigenetics at the epicenter of modern medicine. JAMA 299: 1345–1350.

Florian C, Bahi-Buisson N, Bienvenu T (2012) FOXG1-Related Disorders: From Clinical Description to Molecular Genetics. Mol Syndromol 2: 153–163.

Froyen G, Corbett M, Vandewalle J, Jarvela I, Lawrence O, Meldrum C, Bauters M, Govaerts K, Vandeleur L, Van Esch H, Chelly J, Sanlaville D, van Bokhoven H, Ropers HH, Laumonnier F, Ranieri E, Schwartz CE, Abidi F, Tarpey PS, Futreal PA, Whibley A, Raymond FL, Stratton MR, Fryns JP, Scott R, Peippo M, Sipponen M, Partington M, Mowat D, Field M, Hackett A, Marynen P, Turner G, Gécz J (2008) Submicroscopic duplications of the hydroxysteroid dehydrogenase HSD17B10 and the E3 ubiquitin ligase HUWE1 are associated with mental retardation. Am J Hum Genet 82: 432–443.

Garber KB, Visootsak J, Warren ST (2008) Fragile X syndrome. Eur J Hum Genet 16: 666–672.

Gécz J, Shoubridge C, Corbett M (2009) The genetic landscape of intellectual disability arising from chromosome X. Trends Genet 25: 308–316.

Gendrel AV, Heard E (2011) Fifty years of X-inactivation research. Development 138: 5049–5055.

Gibson WT, Hood RL, Zhan SH, Bulman DE, Fejes AP, Moore R, Mungall AJ, Eydoux P, Babul-Hirji R, An J, Marra MA; FORGE Canada Consortium, Chitayat D, Boycott KM, Weaver DD, Jones SJ (2012) Mutations in EZH2 cause Weaver syndrome. Am J Hum Genet 90: 110–118.

Godler DE, Tassone F, Loesch DZ, Taylor AK, Gehling F, Hagerman RJ, Burgess T, Ganesamoorthy D, Hennerich D, Gordon L, Evans A, Choo KH, Slater HR (2010) Methylation of novel markers of fragile X alleles is inversely correlated with FMRP expression and FMR1 activation ratio. Hum Mol Genet 19: 1618–1632.

Gos M, Szpecht-Potocka A (2002) Genetic basis of neural tube defects. II. Genes correlated with folate and methionine metabolism. J Appl Genet 43: 511–524.

Guerrini R, Parrini E (2012) Epilepsy in Rett syndrome, and CDKL5- and FOXG1-gene-related encephalopathies. Epilepsia 53: 2067–2078.

El Hajj N, Haaf T (2013) Epigenetic disturbances in in vitro cultured gametes and embryos: implications for human assisted reproduction. Fertil Steril. 2013 Jan 25. pii: S0015–0282(13)00006-X. [Epub ahead of print]

Harakalova M, van den Boogaard MJ, Sinke R, van Lieshout S, van Tuil MC, Duran K, Renkens I, Terhal PA, de Kovel C, Nijman IJ, van Haelst M, Knoers NVAM, van Haaften G, Kloosterman W, Hennekam RCM, Cuppen E, Ploos van Amstel HK (2012) X-exome sequencing identifies a HDAC8 variant in a large pedigree with X-linked intellectual disability, truncal obesity, gynaecomastia, hypogonadism and unusual face. J Med Genet 49: 539–543.

Horsthemke B, Buiting K (2006) Imprinting defects on human chromosome 15. Cytogenet Genome Res 113: 292–299.

Horsthemke B, Wagstaff J (2008) Mechanisms of imprinting of the Prader-Willi/Angelman region. Am J Med Genet A 146A: 2041–2052.

Horsthemke B (2010) Mechanisms of imprint dysregulation. Am J Med Genet C Semin Med Genet 154C: 321–328.

Huang HS, Allen JA, Mabb AM, King IF, Miriyala J, Taylor-Blake B, Sciaky N, Dutton JW Jr, Lee HM, Chen X, Jin J, Bridges AS, Zylka MJ, Roth BL, Philpot BD (2011) Topoisomerase inhibitors unsilence the dormant allele of *Ube3a* in neurons. Nature 481: 185–9.

Ikegami K, Ohgane J, Tanaka S, Yagi S, Shiota K (2009) Interplay between DNA methylation, histone modification and chromatin remodeling in stem cells and during development. Int J Dev Biol 53: 203–214.

Iliadou AN, Janson PC, Cnattingius S (2011) Epigenetics and assisted reproductive technology. J Intern Med 270: 414–420.

Isles AR, Wilkinson LS (2000) Imprinted genes, cognition and behaviour. Trends Cogn Sci 4: 309–318.

Jin DK (2012) Endocrine problems in children with Prader-Willi syndrome: special review on associated genetic aspects and early growth hormone treatment. Korean J Pediatr 55: 224–231.

Jones WD, Dafou D, McEntagart M, Woollard WJ, Elmslie FV, Holder-Espinasse M, Irving M, Saggar AK, Smithson S, Trembath RC, Deshpande C, Simpson MA (2012) *De novo* mutations in *MLL* cause Wiedemann-Steiner syndrome. Am J Hum Genet 91: 358–364.

Kameshita I, Sekiguchi M, Hamasaki D, Sugiyama Y, Hatano N, Suetake I, Tajima S, Sueyoshi N (2008) Cyclin-dependent kinase-like 5 binds and phosphorylates DNA methyltransferase 1. Biochem Biophys Res Commun 377: 1162–1167.

Kantor B, Shemer R, Razin A (2006) The Prader-Willi/Angelman imprinted domain and its control center. Cytogenet Genome Res 113: 300–305.

Kelly TK, De Carvalho DD, Jones PA (2010) Epigenetic modifications as therapeutic targets. Nat Biotechnol 28: 1069–1078.

Kim HG, Kim HT, Leach NT, Lan F, Ullmann R, Silahtaroglu A, Kurth I, Nowka A, Seong IS, Shen Y, Talkowski ME, Ruderfer D, Lee JH, Glotzbach C, Ha K, Kjaergaard S, Levin AV, Romeike BF, Kleefstra T, Bartsch O, Elsea SH, Jabs EW, MacDonald ME, Harris DJ, Quade BJ, Ropers HH, Shaffer LG, Kutsche K, Layman LC, Tommerup N, Kalscheuer VM, Shi Y, Morton CC, Kim CH, Gusella JF (2012) Translocations disrupting *PHF21A* in the Potocki-Shaffer-syndrome region are associated with intellectual disability and craniofacial anomalies. Am J Hum Genet 91: 56–72.

Kinoshita T, Ikeda Y, Ishikawa R (2008) Genomic imprinting: a balance between antagonistic roles of parental chromosomes. Semin Cell Dev Biol 19: 574–579.

Kishi N, Macklis JD (2005) Dissecting MECP2 function in the central nervous system. J Child Neurol 20: 753–759.

Kleefstra T, Kramer JM, Neveling K, Willemsen MH, Koemans TS, Vissers LE, Wissink-Lindhout W, Fenckova M, van den Akker WM, Kasri NN, Nillesen WM, Prescott T, Clark RD, Devriendt K, van Reeuwijk J, de Brouwer AP, Gilissen C, Zhou H, Brunner HG, Veltman JA, Schenck A, van Bokhoven H (2012) Disruption of an EHMT1-associated chromatin-modification module causes intellectual disability. Am J Hum Genet 91: 73–82.

Klein CJ, Botuyan MV, Wu Y, Ward CJ, Nicholson GA, Hammans S, Hojo K, Yamanishi H, Karpf AR, Wallace DC, Simon M, Lander C, Boardman LA, Cunningham JM, Smith GE, Litchy WJ, Boes B, Atkinson EJ, Middha S, B Dyck PJ, Parisi JE, Mer G, Smith DI, Dyck PJ (2011) Mutations in *DNMT1* cause hereditary sensory neuropathy with dementia and hearing loss. Nat Genet 43: 595–600.

Knudsen GP, Neilson TC, Pedersen J, Kerr A, Schwartz M, Hulten M, Bailey ME, Orstavik KH (2006) Increased skewing of X chromosome inactivation in Rett syndrome patients and their mothers. Eur J Hum Genet 14: 1189–1194.

Kobow K, Blümcke I (2011) The methylation hypothesis: do epigenetic chromatin modifications play a role in epileptogenesis? Epilepsia 52 (Suppl 4): 15–19.

Kramer JM, van Bokhoven H (2009) Genetic and epigenetic defects in mental retardation Int J Biochem Cell Biol 41: 96–107.

Legendre M, Gonzales M, Goudefroye G, Bilan F, Parisot P, Perez MJ, Bonnière M, Bessières B, Martinovic J, Delezoide AL, Jossic F, Fallet-Bianco C, Bucourt M, Tantau J, Loget P, Loeuillet L, Laurent N, Leroy B, Salhi H, Bigi N, Rouleau C, Guimiot F, Quélin C, Bazin A, Alby C, Ichkou A, Gesny R, Kitzis A, Ville Y, Lyonnet S, Razavi F, Gilbert-Dussardier B, Vekemans M, Attié-Bitach T (2012) Antenatal spectrum of CHARGE syndrome in 40 fetuses with *CHD7* mutations. J Med Genet 49: 698–707.

Lennartsson A, Ekwall K (2009) Histone modification patterns and epigenetic codes. Biochim Biophys Acta 1790: 863–868.

Levenga J, de Vrij FM, Oostra BA, Willemsen R (2010) Potential therapeutic interventions for fragile X syndrome. Trends Mol Med 16: 516–527.

Li H, Yamagata T, Mori M, Yasuhara A, Momoi MY (2005) Mutation analysis of methyl–CpG binding protein family genes in autistic patients. Brain Dev 27: 321–325.

Lima FT, Brunoni D, Schwartzman JS, Pozzi MC, Kok F, Juliano Y, Pereira Lda V (2009) Genotype-phenotype correlation in Brazillian Rett syndrome patients. Arq Neuropsiquiatr 67: 577–584.

Lin C, Franco B, Rosner MR (2005) CDKL5/Stk9 kinase inactivation is associated with neuronal developmental disorders. Hum Mol Genet 14: 3775–3786.

Lubin FD (2012) Epileptogenesis: can the science of epigenetics give us answers? Epilepsy Curr 12: 105–110.

Mackay DJ, Temple IK (2010) Transient neonatal diabetes mellitus type 1. Am J Med Genet C Semin Med Genet. 154C: 335–342.

Manipalviratn S, DeCherney A, Segars J (2009) Imprinting disorders and assisted reproductive technology. Fertil Steril 91: 305–315.

Mari F, Azimonti S, Bertani I, Bolognese F, Colombo E, Caselli R, Scala E, Longo I, Grosso S, Pescucci C, Ariani F, Hayek G, Balestri P, Bergo A, Badaracco G, Zappella M, Broccoli V, Renieri A, Kilstrup-Nielsen C, Landsberger N (2005) CDKL5 belongs to the same molecular pathway of MeCP2 and it is responsible for the early-onset seizure variant of Rett syndrome. Hum Mol Genet 14: 1935–1946.

Miremadi A, Oestergaard MZ, Pharoah PD, Caldas C (2007) Cancer genetics of epigenetic genes. Hum Mol Genet 16: R28–49.

Mogi M, Harada M, Narabayashi H, Inagaki H, Minami M, Nagatsu T (1996) Interleukin (IL)-1 beta, IL-2, IL-4, IL-6 and transforming growth factor-alpha levels are elevated in ventricular cerebrospinal fluid in juvenile parkinsonism and Parkinson's disease. Neurosci Lett 211: 13–16.

van Montfoort AP, Hanssen LL, de Sutter P, Viville S, Geraedts JP, de Boer P (2012) Assisted reproduction treatment and epigenetic inheritance. Hum Reprod Update 18: 171–197.

Neumann LC, Markaki Y, Mladenov E, Hoffmann D, Buiting K, Horsthemke B (2012) The imprinted NPAP1/C15orf2 gene in the Prader-Willi syndrome region encodes a nuclear pore complex associated protein. Hum Mol Genet 21: 4038–4048.

Nimura K, Ura K, Kaneda Y (2010) Histone methyltransferases: regulation of transcription and contribution to human disease. J Mol Med (Berl) 88: 1213–1220.

Ohhata T, Wutz A (2012) Reactivation of the inactive X chromosome in development and reprogramming. Cell Mol Life Sci [Epub ahead of print].

Oostra BA, Willemsen R (2009) FMR1: a gene with three faces. Biochim Biophys Acta 1790: 467–477.

O'Roak BJ, Vives L, Fu W, Egertson JD, Stanaway IB, Phelps IG, Carvill G, Kumar A, Lee C, Ankenman K, Munson J, Hiatt JB, Turner EH, Levy R, O'Day DR, Krumm N, Coe BP, Martin BK, Borenstein E, Nickerson DA, Mefford HC, Doherty D, Akey JM, Bernier R, Eichler EE, Shendure J (2012) Multiplex targeted sequencing identifies recurrently mutated genes in Autism spectrum disorders. Science 338: 1619–1622.

Owen CM, Segars JH Jr (2009) Imprinting disorders and assisted reproductive technology. Semin Reprod Med 27: 417–428.

Pereira PM, Schneider A, Pannetier S, Heron D, Hanauer A (2010) Coffin-Lowry syndrome. Eur J Hum Genet 18: 627–633.

Pfeiffer BE, Huber KM (2009) The state of synapses in fragile X syndrome. Neuroscientist. 15: 549–567.

Plenge RM, Stevenson RA, Lubs HA, Schwartz CE, Willard HF (2002) Skewed X-chromosome inactivation is a common feature of X-linked mental retardation disorders. Am J Hum Genet 71: 168–173.

Portela A, Esteller M (2010) Epigenetic modifications and human disease. Nat Biotechnol 28: 1057–1068.

Psoni S, Sofocleous C, Traeger-Synodinos J, Kitsiou-Tzeli S, Kanavakis E, Fryssira-Kanioura H (2010) Phenotypic and genotypic variability in four males with MECP2 gene sequence aberrations including a novel deletion. Pediatr Res 67: 551–556.

Qiu J, Shi G, Jia Y, Li J, Wu M, Li J, Dong S, Wong J (2010) The X-linked mental retardation gene PHF8 is a histone demethylase involved in neuronal differentiation. Cell Res 20: 908–918.

Qureshi IA, Mehler MF (2012) Emerging roles of non-coding RNAs in brain evolution, development, plasticity and disease. Nat Rev Neurosci 13: 528–541.

Qureshi IA, Mehler MF (2010) Epigenetic mechanisms underlying human epileptic disorders and the process of epileptogenesis. Neurobiol Dis 39: 53–60.

Ramocki MB, Tavyev YJ, Peters SU (2010) The MECP2 duplication syndrome. Am J Med Genet A 152A: 1079–1088.

Ravn K, Roende G, Duno M, Fuglsang K, Eiklid KL, Tümer Z, Nielsen JB, Skjeldal OH (2011) Two new Rett syndrome families and review of the literature: expanding the knowledge of MECP2 frameshift mutations. Orphanet J Rare Dis 6: 58.

Razin A, Kantor B (2005) DNA methylation in epigenetic control of gene expression. Prog Mol Subcell Biol 38: 151–167.

Rejeb I, Ben Jemaa L, Chaabouni H (2009) X linked mental retardation. Tunis Med 87: 311–318.

Ricciardi S, Kilstrup-Nielsen C, Bienvenu T, Jacquette A, Landsberger N, Broccoli V (2009) CDKL5 influences RNA splicing activity by its association to the nuclear speckle molecular machinery. Hum Mol Genet 18: 4590–4602.

Riday TT, Dankoski EC, Krouse MC, Fish EW, Walsh PL, Han JE, Hodge CW, Wightman RM, Philpot BD, Malanga CJ (2012) Pathway-specific dopaminergic deficits in a mouse model of Angelman syndrome. J Clin Invest 122: 4544–4554.

Rio M, Clech L, Amiel J, Faivre L, Lyonnet S, Le Merrer M, Odent S, Lacombe D, Edery P, Brauner R, Raoul O, Gosset P, Prieur M, Vekemans M, Munnich A, Colleaux L, Cormier-Daire V (2003) Spectrum of *NSD1* mutations in Sotos and Weaver syndromes. J Med Genet 40: 436–440.

Roche-Martinez A, Gerotina E, Armstrong-Moron J, Sans-Capdevila O, Pineda M (2011) *FOXG1*, a new gene responsible for the congenital form of Rett syndrome – in Spanish. Rev Neurol 52: 597–602.

Roelfsema JH, Peters DJ (2007) Rubinstein-Taybi syndrome: clinical and molecular overview. Expert Rev Mol Med 9: 1–16.

Rzońca SO, Gos M (2012) Role of FMRP protein: function and role in pathogenesis of Fragile X Syndrome (in Polish). Postępy Biologii Komórki 39: 459–476.

Sahoo T, del Gaudio D, German JR, Shinawi M, Peters SU, Person RE, Garnica A, Cheung SW, Beaudet AL (2008) Prader-Willi phenotype caused by paternal deficiency for the HBII-85 C/D box small nucleolar RNA cluster. Nat Genet 40: 719–721.

Santos-Rebouças CB, Fintelman-Rodrigues N, Jensen LR, Kuss AW, Ribeiro MG, Campos M Jr, Santos JM, Pimentel MM (2011) A novel nonsense mutation in *KDM5C/JARID1C* gene causing intellectual disability, short stature and speech delay. Neurosci Lett 498: 67–71.

Saul RA, Tarleton JC (2012) *FMR1*-related disorders. In: GeneReviews™ [Internet] (Pagon RA, Bird TD, Dolan CR, et al., Eds). University of Washington, Seattle, WA [Available at http://www.ncbi.nlm.nih.gov/books/NBK1384/]

Savage T, Peek J, Hofman PL, Cutfield WS (2011) Childhood outcomes of assisted reproductive technology. Hum Reprod 26: 2392–2400.

Schwartzman JS, Bernardino A, Nishimura A, Gomes RR, Zatz M (2001) Rett syndrome in a boy with a 47,XXY karyotype confirmed by a rare mutation in the *MECP2* gene. Neuropediatrics 32: 162–164.

Shorvon SD (2011) The etiologic classification of epilepsy. Epilepsia 52: 1052–1057.

Smith FM, Garfield AS, Ward A (2006) Regulation of growth and metabolism by imprinted genes. Cytogenet Genome Res 113: 279–291.

Stuss DP, Boyd JD, Levin DB, Delaney KR (2012) *MeCP2* mutation results in compartment-specific reductions in dendritic branching and spine density in layer 5 motor cortical neurons of YFP-H mice. PLoS One 7: e31896.

Tan WH, Bacino CA, Skinner SA, Anselm I, Barbieri-Welge R, Bauer-Carlin A, Beaudet AL, Bichell TJ, Gentile JK, Glaze DG, Horowitz LT, Kothare SV, Lee HS, Nespeca MP, Peters SU, Sahoo T, Sarco D, Waisbren SE, Bird LM (2011) Angelman syndrome: Mutations influence features in early childhood. Am J Med Genet A 155A: 81–90.

Temudo T, Santos M, Ramos E, Dias K, Vieira JP, Moreira A, Calado E, Carrilho I, Oliveira G, Levy A, Barbot C, Fonseca M, Cabral A, Cabral P, Monteiro J, Borges L, Gomes R, Mira G, Pereira SA, Santos M, Fernandes A, Epplen JT, Sequeiros J, Maciel P (2011) Rett syndrome with and without detected *MECP2* mutations: an attempt to redefine phenotypes. Brain Dev 33: 69–76.

Tran S, Wang L, Le J, Guan J, Wu L, Zou J, Wang Z, Wang J, Wang F, Chen X, Cai L, Lu X, Zhao H, Guo J, Bao Y, Zheng X, Zhang T (2012) Altered methylation of the DNA repair gene MGMT is associated with neural tube defects. J Mol Neurosci 47: 42–51.

Tsurusaki Y, Okamoto N, Ohashi H, Kosho T, Imai Y, Hibi-Ko Y, Kaname T, Naritomi K, Kawame H, Wakui K, Fukushima Y, Homma T, Kato M, Hiraki Y, Yamagata T, Yano S, Mizuno S, Sakazume S, Ishii T, Nagai T, Shiina M, Ogata K, Ohta T, Niikawa N, Miyatake S, Okada I, Mizuguchi T, Doi H, Saitsu H, Miyake N, Matsumoto N (2012) Mutations affecting components of the SWI/SNF complex cause Coffin-Siris syndrome. Nat Genet 44: 376–378.

Urdinguio RG, Sanchez-Mut JV, Esteller M (2009) Epigenetic mechanisms in neurological diseases: genes, syndromes, and therapies. Lancet Neurol 8: 1056–1072.

van Bokhoven H, Kramer JM (2010) Disruption of the epigenetic code: an emerging mechanism in mental retardation. Neurobiol Dis 39: 3–12.

Van der Aa N, Van den Bergh M, Ponomarenko N, Verstraete L, Ceulemans B, Storm K (2011) Analysis of *FOXG1* is highly recommended in male and female patients with Rett syndrome. Mol Syndromol 1: 290–293.

Van Esch H (2010) *MECP2* duplication syndrome. In: GeneReviews™ [Internet] (Pagon RA, Bird TD, Dolan CR, et al., Eds) University of Washington, Seattle, WA [Available at: http://www.ncbi.nlm.nih.gov/books/NBK1284/]

Van Houdt JK, Nowakowska BA, Sousa SB, van Schaik BD, Seuntjens E, Avonce N, Sifrim A, Abdul-Rahman OA,

van den Boogaard MJ, Bottani A, Castori M, Cormier-Daire V, Deardorff MA, Filges I, Fryer A, Fryns JP, Gana S, Garavelli L, Gillessen-Kaesbach G, Hall BD, Horn D, Huylebroeck D, Klapecki J, Krajewska-Walasek M, Kuechler A, Lines MA, Maas S, Macdermot KD, McKee S, Magee A, de Man SA, Moreau Y, Morice-Picard F, Obersztyn E, Pilch J, Rosser E, Shannon N, Stolte-Dijkstra I, Van Dijck P, Vilain C, Vogels A, Wakeling E, Wieczorek D, Wilson L, Zuffardi O, van Kampen AH, Devriendt K, Hennekam R, Vermeesch JR (2012) Heterozygous missense mutations in *SMARCA2* cause Nicolaides-Baraitser syndrome. Nat Genet 44: 445–449.

Vinueza Veloz MF, Buijsen RA, Willemsen R, Cupido A, Bosman LW, Koekkoek SK, Potters JW, Oostra BA, De Zeeuw CI (2012) The effect of an mGluR5 inhibitor on procedural memory and avoidance discrimination impairments in *Fmr1* KO mice. Genes Brain Behav 11: 325–331.

Wang L, Wang F, Guan J, Le J, Wu L, Zou J, Zhao H, Pei L, Zheng X, Zhang T (2010) Relation between hypomethylation of long interspersed nucleotide elements and risk of neural tube defects. Am J Clin Nutr 91: 1359–1367.

Weng MK, Zimmer B, Pöltl D, Broeg MP, Ivanova V, Gaspar JA, Sachinidis A, Wüllner U, Waldmann T, Leist M (2012) Extensive transcriptional regulation of chroma-tin modifiers during human neurodevelopment. PLoS One. 7: e36708.

Willemsen R, Levenga J, Oostra BA (2011) CGG repeat in the *FMR1* gene: size matters. Clin Genet 80: 214–225.

Williams CA, Driscoll DJ, Dagli AI (2010) Clinical and genetic aspects of Angelman syndrome. Genet Med 12: 385–395.

Williams SR, Aldred MA, Der Kaloustian VM, Halal F, Gowans G, McLeod DR, Zondag S, Toriello HV, Magenis RE, Elsea SH (2010) Haploinsufficiency of HDAC4 causes brachydactyly mental retardation syndrome, with brachydactyly type E, developmental delays, and behavioral problems. Am J Hum Genet 87: 219–228.

Yamazawa K, Ogata T, Ferguson-Smith AC (2010) Uniparental disomy and human disease: an overview. Am J Med Genet C Semin Med Genet 154C: 329–334.

Yonath H, Marek–Yagel D, Resnik-Wolf H, Abu-Horvitz A, Baris HN, Shohat M, Frydman M, Pras E (2011) X inactivation testing for identifying a non-syndromic X-linked mental retardation gene. J Appl Genet 52: 437–441.

Zhang Q, Bouma GJ, McClellan K, Tobet S (2012) Hypothalamic expression of snoRNA Snord116 is consistent with a link to the hyperphagia and obesity symptoms of Prader-Willi syndrome. Int J Dev Neurosci 30: 479–485.