Molecular Genetics and Metabolism xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Minireview

The role of epigenetics in lysosomal storage disorders: Uncharted territory

Shahzeb Hassan, Ellen Sidransky*, Nahid Tayebi

Medical Genetics Branch, NHGRI, NIH, Bethesda, MD, United States

ARTICLE INFO

Keywords:
Lysosomal storage disorders
Epigenetics
DNA methylation
Histone modifications
microRNAs
Genotype/phenotype correlation

ABSTRACT

The study of the contribution of epigenetic mechanisms, including DNA methylation, histone modifications, and microRNAs, to human disease has enhanced our understanding of different cellular processes and diseased states, as well as the effect of environmental factors on phenotypic outcomes. Epigenetic studies may be particularly relevant in evaluating the clinical heterogeneity observed in monogenic disorders. The lysosomal storage disorders are Mendelian disorders characterized by a wide spectrum of associated phenotypes, ranging from neonatal presentations to symptoms that develop in late adulthood. Some lack a tight genotype/phenotype correlation. While epigenetics may explain some of the discordant phenotypes encountered in patients with the same lysosomal storage disorder, especially among patients sharing the same genotype, to date, few studies have focused on these mechanisms. We review three common epigenetic mechanisms, DNA methylation, histone modifications, and microRNAs, and highlight their applications to phenotypic variation and therapeutics. Three specific lysosomal storage diseases, Gaucher disease, Fabry disease, and Niemann-Pick type C disease are presented as prototypical disorders with vast clinical heterogeneity that may be impacted by epigenetics. Our goal is to motivate researchers to consider epigenetics as a mechanism to explain the complexities of biological functions and pathologies of these rare disorders.

1. Introduction

In 1942, the British scientist and philosopher Conrad Waddington first introduced the term “epigenotype”, suggesting that the relationship between genotype and phenotype might be more complex than previously appreciated. The term was derived from “epigenesis,” which describes an interactive embryological growth process [1]. In his paper, “The epigenotype” Waddington explained it as “concatenations of processes” through which genes affect phenotypic expression. As an experimental embryologist, Waddington focused on abnormalities in *Drosophila melanogaster* wing development, and observed that certain defects were a result of more than just genes [2]. He further developed the concept of an “epigenetic landscape” in his book “Strategy of Genes” [3] where he proposed that a developing embryonic cell resembles a ball rolling down a slope with various hills and valleys, and that it has a number of developmental pathways or “chreodes” that it can “choose” before reaching the mature state. He emphasized the importance of gene regulation, and noted that many different genetic and environmental factors can influence the cell's path as it moves through this diverse developmental “landscape” [3].

Today, epigenetics extends far beyond the fields of embryology and developmental biology. Epigenetics is now defined as “mitotically and meiotically heritable changes in gene expression not caused by changes in the primary DNA sequence.” These changes are influenced by different events that occur throughout a lifetime, beginning at conception. Different epigenetic factors are closely interconnected, with multiple levels of feedback. For example, genomic stability is essential for proper gene expression. Changes to the cell's DNA repair system, which preserves genomic stability, and reduction-oxidation (redox) reactions, which cause major interruptions to DNA stability during development, would be both considered epigenetic alterations [4]. Fahrner and Bjornsson identified more than 25 genes directly involved in the epigenetic machinery, describing the Mendelian inheritance of mutations in these genes [5]. Thus, the field of epigenetics has evolved from an “in addition to genetics” phenomenon, to a widely explored scientific discipline. Most Mendelian disorders and inherited complex disease are caused by primary gene(s) with a major impact; however, phenotypic expression of these disorders varies from population to population, and

Abbreviations: GD, Gaucher disease; LSDs, lysosomal storage disorders; GLD, globoid cell leukodystrophy; IDS, iduronate-2-sulfatase; MPS IVA, Mucopolysaccharidosis type IVA; NPC, Niemann-Pick disease type C; GALNS, *N*-acetylgalactosamine-6-sulfate sulfatase; AGU, Aspartylglucosaminuria; FD, Fabry disease; PD, Parkinson's disease; RISC, RNA induced silencing complex; HDACs, histone deacetylases; HATs, histone acetyltransferases; miRNAs, microRNAs; HDACi, histone deacetylase inhibitor; CpG, Cytosine-phosphate-Guanine; DNMT, DNA methyltransferase; MBD, methyl CpG binding domain

* Corresponding author at: Section on Molecular Neurogenetics, Medical Genetics Branch, National Human Genome Research Institute, NIH, Building 35, Room 1E623, 35 Convent Drive, MSC 3708, Bethesda, MD 20892-3708, United States.
E-mail address: sidranse@mail.nih.gov (E. Sidransky).

http://dx.doi.org/10.1016/j.ymgme.2017.07.012
Received 26 May 2017; Received in revised form 30 July 2017; Accepted 31 July 2017

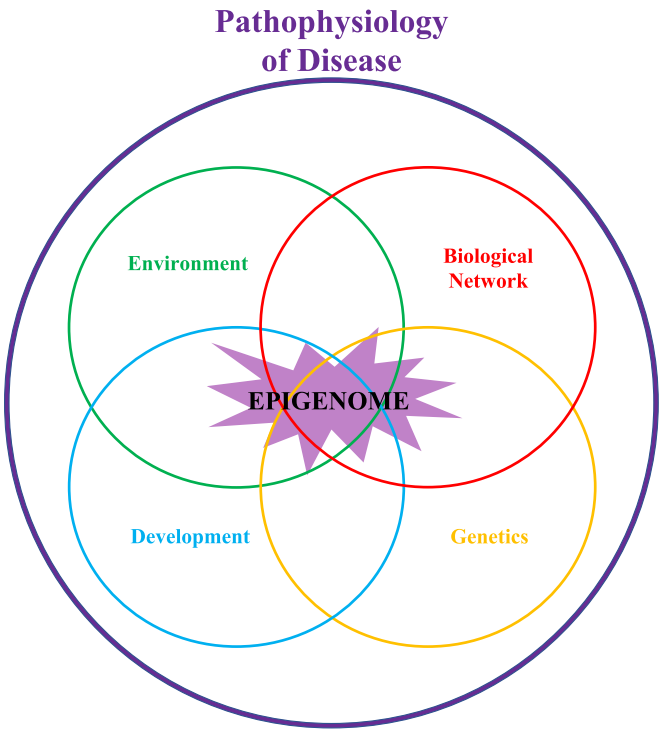

Fig. 1. Four key factors impact the epigenome and contribute to the phenotypic variation in a given disease. These four factors include genetics, environment, biological networks (relationships between humans and other organisms), and development (including embryonic, early childhood, adolescence, adulthood and old age). The effect of each factor on the pathophysiology of the disease is not scaled in this figure.

in some cases from individual to individual. Fig. 1 illustrates four different categories that may contribute to phenotypic variation in a given disease; genetics, biological networks, development and environment, each of which is impacted by epigenetics (Fig. 1).

In order to catalyze basic biology and disease-oriented research, and to enhance public dissemination of human epigenomic data through an online database, the NIH Roadmap Epigenetics Mapping Consortium was established in 2008. Its goal is to map epigenetic marks, such as DNA methylation, histone modifications, and small RNA transcripts in different cell and tissue types and is a resource for work in this field [6,7].

One field where epigenetics merits increased consideration is in unraveling the complexity encountered in Mendelian disorders. Often in such disorders, the correlation between genotype and phenotype is limited, and patients with the same genetic mutations can exhibit variability in disease severity and diverse symptoms, as seen in achondroplasia, ferroportin disease, cystic fibrosis, hemophilia, and Huntington disease [8–13]. Multiple factors contributing to the discordant phenotypes have been considered. In discordant affected siblings, either environmental or unlinked genetic factors may play a role. Epigenetic studies often focus on identical twins discordant for certain disease manifestations, which can provide mechanistic insights.

The potential role of epigenetics specifically in the lysosomal storage disorders (LSDs), a group of over 50 rare Mendelian disorders, particularly merits increased attention. Since LSDs have significant phenotypic heterogeneity [14], epigenetic mechanisms, reviewed here, may contribute to the spectrum of clinical variability encountered.

2. Epigenetic mechanisms

Epigenetic modifications occur by three basic mechanisms, DNA methylation, histone modifications, and microRNAs.

2.1. DNA methylation

DNA methylation is one of the most widely studied epigenetic modifications involving the transfer of a methyl group to the fifth position of a cytosine nucleotide. While DNA methylation has been appreciated since DNA was discovered as the genetic material [15], in the past two decades, studies of DNA methylation have expanded because of its role in gene regulation. Methylation of Cytosine-phosphate-Guanine (CpG) dinucleotides, particularly in gene promoter regions and other regulatory elements, can directly block the binding of transcription factors [16,17], and can recruit methyl CpG binding domain (MBD) proteins, further attracting histone deacetylases and possibly other factors involved in altering chromatin architecture [18,19]. The family of DNA methyltransferases (DNMTs) catalyze the transfer of a methyl group from the donor *S*-adenosylmethionine (SAM) to cytosine residues [19]. DNMT1 is involved in post-replicative maintenance of methylation by binding with proliferating cell nuclear antigen (PCNA) [20,21]. DNMT3a and DNMT3b are responsible for *de novo* methylation and the initial establishment of global methylation patterns during early mammalian development [22,23].

CpG sites occur at one-fifth of their expected frequency, most likely due to the mutagenic properties of 5-methylcytosine and its tendency to spontaneously deaminate into thymidine [24,25]. Approximately 70% of all CpG dinucleotides in the genome are methylated. CpG-nucleotides in GC-rich regions, known as CpG islands, are usually located within promoter regions, and have relatively no DNA methylation [26]. Exceptions occur during X-inactivation [27] and genomic imprinting [28]. DNA methylation is critical in marking the parental origin of alleles, and certain imprinted genes are influenced by epigenetic processes from parental germ cells, resulting in expression of only one of the parental alleles [29]. However, additional processes, including transcription, histone modifications and higher order chromatin, may also be important in marking imprinted loci [30].

CpG islands tend to occur near the 5′ end of housekeeping genes, where they play a role in the regulation of transcription. In the human genome, 72% of promoters have been classified as being high in CpG content, while the remaining 28% have low CpG content [31]. Aberrant methylation of CpG islands has been implicated in diverse diseases including cancer, schizophrenia, congenital heart disease, amyotrophic lateral sclerosis, Alzheimer disease, and atherosclerosis [26,32–40]. CpG methylation patterns are critical for proper development, and some have been conserved evolutionarily, such as differences in CpG methylation between neuronal and glial cells, conserved in mice and humans [41].

2.2. Histone modifications

Another class of epigenetic marks includes histone modifications, such as acetylation, phosphorylation, methylation, β-*N*-acetylglucosamine deamination, ADP ribosylation, ubiquitination, sumoylation, histone tail clipping, and histone proline isomerization [42]. These marks execute their effects either by directly restructuring the DNA-protein complex and/or chromatin, or by controlling the binding of chromatin remodeling factors. Histone acetylation is the most extensively studied of these epigenetic modifications. Histone acetyltransferases (HATs) catalyze the transfer of an acetyl group to the epsilon-amino groups of lysine residues, located within the N-terminal tails of the H2A, H2B, H3, and H4 core histones [43,44], and histone deacytelases (HDACs) remove the acetyl group. An optimal balance between these enzymes is required for proper functioning of critical nuclear processes [45]. Reversible histone acetylation facilitates transcriptional activation [46,47]. It is thought that the acetyl moiety added by HAT neutralizes the positive charge on the lysine residue, thereby decreasing DNA-histone interaction and allowing the more relaxed chromatin state to be accessed by regulatory molecules [42,48]. Moreover, HAT can directly interact with transactivator proteins to

regulate transcription. For example, the HAT hGCN5 acetylates the HIV transactivator TAT to enhance Tat-dependent transcription of the HIV-1 long terminal repeat [49]. Histone acetylation acts downstream of the promoter region to enhance transcriptional elongation [50], as well as DNA repair [51,52].

An additional important post-translational modification that acts on nucleosomal histone tails is histone phosphorylation. Serine, threonine, and tyrosine residues on histones can either be phosphorylated by kinases, or have their phosphate group removed by phosphatases. Particular phosphorylation sites have been shown to contribute to the compacted state of chromatin. For example, histone 3 serine 10 plays a role in chromosome condensation during mitosis [53]. Interestingly, this same phosphorylation site has also been shown to facilitate transcription and the expression of genes [54,55]. Histone phosphorylation has also been implicated in DNA damage repair, meiosis, and apoptosis [56–58].

Histone methylation is a more complex epigenetic modification, since amino acid residues can either be mono-, di-, or trimethylated, leading to varied functional effects. For example, di- and trimethylation of histone 3 lysine 4 has been linked to promoter activation [59], while monomethylation of the same site restricts access to chromatin-remodeling enzymes, leading to gene repression [60]. Histone methyltransferases vary the levels of methylation between the histone proteins [61]. Moreover, histone methylation has been associated with DNA methylation in imprinting control regions [62].

The various histone modifications are very interconnected, with substantial “crosstalk” signaling as they regulate each other's functions [63]. For example, phosphorylation of histone 3 serine 10 can potentially preserve methylation patterns by blocking the access of histone 3 lysine 9 in HeLA cells [64]. Covalent posttranslational modifications act in combination through a ‘histone code’ [65,66], operating synergistically or antagonistically to modulate chromatin structure [65], and serving as ‘binding sites’ for protein complexes to further regulate downstream cellular processes [66].

2.3. MicroRNAs

MicroRNAs (miRNAs), noncoding RNA strands, also play a pivotal role in monitoring gene expression. These epigenetic marks were first identified in *Caenorhabditis elegans* when Lee, Feinbaum, and Ambros observed two lin-4 strands, 22 and 61 nucleotides in length, that exhibited antisense complementarity to the 3′ translated region of the mRNA transcript of lin-14 [67]. Subsequently, over two thousand novel miRNAs have been identified in humans, in part due to the advent of next-generation sequencing and advanced bioinformatics tools [68,69]. In the latest update for miRBase (version 21, June 2014), the primary reference database for miRNA sequences and annotation [70], 28,645 entries characterize hairpin precursor miRNAs, which express 35,828 mature miRNA products in 223 species. The miRBase includes 4196 new hairpin sequences and 5441 new mature products (ftp://mirbase.org/pub/mirbase/CURRENT/README) [70]. Each miRNA recognizes the 3’UTR of multiple mRNA transcripts [71] and many miRNAs can recognize the same mRNA sequence [72]. Though only approximately 1% of all genes encode miRNAs [73], they collectively regulate over 60% of the mammalian genes [74], and are implicated in different cellular processes, including the determination of cell fate, differentiation, developmental timing, proliferation, and apoptosis [75–79]. These short RNA molecules play a role in a number of diseases, including myocardial infarction, cardiac hypertrophy, Alzheimer disease, Fragile X syndrome, rheumatoid arthritis, hepatitis C virus infection, and cancer [80–86].

Understanding the diverse processes of miRNA biogenesis has been critical for recognizing the role of these small regulatory molecules. In the nucleus, primary transcripts known as pri-miRNAs are first transcribed either by RNA polymerase II or III [87,88]. These pri-miRNAs are then processed by a Microprocessor complex, consisting of the RNase III Drosha and DiGeorge syndrome chromosomal region 8 (DGCR8) protein [89–91]. After the pri-miRNAs have been processed into pre-miRNA, they are exported by Exportin-5, in the presence of Ran-GTP, into the cytoplasm [92]. The RNase III Dicer cleaves these pre-miRNA hairpins into ~22 nucleotide complexes [93–95]. These double-stranded miRNAs are then loaded onto Argonaute proteins to form the RNA induced silencing complex (RISC) [96]. The miRNA duplex subsequently unwinds in the RISC, leaving a single guide strand, which typically has weaker 5′ base pairing than its complement [97]. The new mature miRNAs repress gene expression at specific target sites, which is dependent on the complementarity between the miRNA and the target sites. In animals, if the miRNA resembles the target mRNA sequence, then gene silencing is induced by translational repression. However, if the miRNA perfectly or near-perfectly matches the mRNA transcript, then the mRNA will be cleaved [98,99]. The Argonaute 2 protein of the RISC is mainly responsible for the degradation of miRNA, and is the only protein required for RISC activity [99,100].

3. Therapeutic applications of epigenetics

The epigenetics of cancer, studied for decades, has generated a large amount of information regarding the accumulation of genetic material and epigenetic modification. The increased knowledge of epigenetic machinery, pathways and genes has led to new insights regarding the potential use of DNA methylation, histone modifications, and microRNAs for therapeutic applications. DNMT inhibitors, such as 5-azacytidine and 5-aza-2′-deoxycytidine have shown considerable potential as cancer therapies [101–103]. Targeting histone methyltransferases and demethylases is also becoming a new treatment strategy in cancer [104,105]. Additionally, the use of anti-miRNA oligonucleotides (AMOs) to inhibit miRNA expression is the source of increased interest. These short deoxyribonucleotide analogues hybridize to complementary miRNA strands and repress their function through their steric-blocking mechanism [106]. The broader category of antisense oligonucleotides (ASOs) also modify gene expression by complementarily binding to mRNA strands. These diverse therapeutic applications highlight the importance and implications of studies of epigenetics.

4. The lysosomal storage disorders: diseases with vast clinical heterogeneity

The lysosomal storage diseases (LSDs) are monogenic disorders mainly characterized by deficient lysosomal proteins, usually enzymes, leading to the accumulation of specific macromolecule substrates [107]. This definition has extended to defects in integral membrane proteins, transporters and/or the post-translational modification processes of acid hydrolases [108]. LSDs encompass more than 50 disorders, occurring at a frequency of about 1 in 5000 live births [109]. Though there are considerable variations in organ involvement and prognosis among the different LSDs, most are characterized by a broad range in clinical symptoms [14], and incomplete genotype-phenotype correlation. We highlight the genotypic and phenotypic variability in three specific LSDs and emphasize why epigenetics might play a role.

4.1. Gaucher disease

Gaucher disease (GD) [110] is an autosomal recessive disorder characterized by a deficiency in glucocerebrosidase, leading to lysosomal accumulation of its substrate, glucosylceramide. Approximately 300 mutations in *GBA1*, the gene encoding glucocerebrosidase, have been identified in patients with GD [111]. Glucosylceramide accumulation, particularly evident in Gaucher macrophages, is a key characteristic of this disease [112]. These macrophages, known as “Gaucher cells” are about 20–100 μm in diameter, and have small, often eccentrically placed nuclei, while the cytoplasm has characteristic “crinkles”

or striations [113].

GD has been classified into three main types. Type 1 is defined as the non-neuronopathic form, manifesting with hepatosplenomegaly, anemia, thrombocytopenia, and bone involvement. Both types 2 and 3 have central nervous system involvement and have generally been distinguished by the rate and progression of neurological symptoms. Patients with type 2 GD experience rapid neurological deterioration during infancy and do not live past the first few years of life, whereas patients with type 3 present with visceral involvement and specific nervous system deficits, that are more gradual than in type 2 [114,115]. One subgroup with type 3 GD has slowed horizontal saccadic eye-movements as their primary neurologic manifestation.

The contribution of lysosomal glucosylceramide to the various GD phenotypes is not fully established. One possible explanation is that in macrophages, glucosylceramide interferes with other biological processes, such as cellular trafficking [116]. Additionally, aberrant macrophage activation and higher levels of macrophage-derived cytokines might contribute to phenotype [117]. A few modifiers have been identified that may contribute to phenotype in some cases. LIMP-2, a membrane receptor for glucocerebrosidase encoded by *SCARB2*, was shown to influence the GD phenotype in one family [118]. Another possible modifier is *PSAP*, the gene, which encodes four saposins including saposin-C, the activator of glucocerebrosidase [119].

GD has been characterized by considerable genotypic and phenotypic heterogeneity, even among infants with the most severe symptoms. Choy reported variance in hematological, orthopedic, and neurological symptoms among members of a French-Canadian family [120]. Amaral et al. found that among a subset of Portuguese patients with GD, a correlation between genotype and phenotype could not be established, with different phenotypes even among siblings [121]. Additionally, Elstein et al. noted significant phenotypic discordance among a group of 18 patients with the N370S/V394 L (p.N409S/P433L) genotype [122]. Goker-Alpan et al. described a range of phenotypes "from mildly symptomatic young adults exhibiting slowed saccades to young children with brain stem involvement" in 32 children, who were all homozygous for the point mutation L444P (p.L483P). Furthermore, they noted differences between children of various ethnic backgrounds, where African-American patients exhibited more neurological manifestations, while Hispanic patients had more developmental defects. They suggested that modifiers and environmental factors could contribute to this heterogeneity [123]. Gupta et al. noted differing pulmonary, visceral, hematological, neurological, and ophthalmological manifestations in infants with different forms of type 2 GD (perinatal lethal, non-perinatal lethal, and intermediate), further highlighting the "wide phenotypic spectrum" of GD [124].

Particularly valuable in demonstrating limited genotype-phenotype correlation in this disease are reports of monozygotic twins with discordant Gaucher phenotypes. In a pair of Moroccan monozygotic (confirmed by DNA fingerprinting) twin sisters with genotype N188S/N188S (p.N227S/p.N227S), one twin had prominent organomegaly, hematological and neurological manifestations, absent in the other [125]. In another report, monozygotic and dizygotic twin pairs with GD were clinically assessed. In the monozygotic pair, one twin displayed clear GD symptoms, while the other showed no significant signs of the disease. Among the dizygotic twins, both had splenomegaly, though one twin had more other disease manifestations [126].

Adding to the complexity and variability of GD is its association with Parkinson disease (PD). Multiple studies have revealed a genetic link between *GBA1* mutations and PD [127–132] although the exact mechanism underlying this association has yet to be determined. *GBA1* mutations are likely to be a" susceptibility factor" rather than a Mendelian cause of Parkinson disease [133], as only a fraction of *GBA1* carriers and GD patients develop PD [134]. Epigenetic analyses might potentially help to identify other genes that work in concert to cause parkinsonism in the subset of patients with GD, considering the role of epigenetics in PD [135].

4.2. Fabry disease

Fabry disease (FD) also is characterized by genotypic heterogeniety and phenotypic variation. This X-linked disorder results from the deficiency of the enzyme alpha-galactosidase A, leading to lysosomal accumulation of globotriaosylceramide. Classic disease manifestations include angiokeratoma, neuropathic pain, renal, cardiac, and cerebrovascular involvement [136]. Patients typically begin exhibiting symptoms at approximately 4–8 years of age with an average age at death of 41 years [137]. Atypical clinical presentations with later onset of cardiac and renal manifestations, have been sub-classified into "cardiac variant" and "renal variant" groups, respectively [138]. Additionally, heterozygous female carriers of FD can exhibit a spectrum of phenotypes, ranging from those with severe manifestations to asymptomatic adults [139]. Much of the variability in clinical symptoms among the female population is related to X-inactivation [140].

Both the phenotypic variability encountered and the identification of hundreds of different mutant alleles in FD make it difficult to establish a clear genotype-phenotype correlation. Clinical variability both among patients within the same family, and among those from unrelated families with the same mutation, has been reported. In a group of 96 Dutch patients with FD, Vedder et al. described differences in glomerular filtration rate, microalbuminuria, left ventricular hypertrophy, and cerebral complications between males and females [141]. Rigoldi et al. reported significant intrafamilial phenotypic heterogeneity in target-organs affected and disease severity among 16 hemizygous males from four families, [142]. More recently, Cammarata et al. further emphasized the intrafamilial phenotypic variability of FD encountered among 15 members of an Italian family. Two of the males had no detectable alpha-galactosidase A activity, although one had relatively severe symptoms, while the second was asymptomatic. Redonnet-Vernhet et al. described female twin sisters discordant for Fabry disease, where one showed symptoms of the disease, and the other did not [143]. Though the likely explanation for this discrepancy is lyonization, environmental factors might still influence the variance in phenotypes. The persistent finding of widespread variability in clinical manifestations and the lack of tight genotype-phenotype correlation in FD suggest that epigenetic studies may help to elucidate the mechanisms behind the pathology of this complex disorder.

4.3. Niemann-Pick C disease

Niemann-Pick disease type C (NPC) is a third group of LSDs exhibiting significant clinical heterogeneity. Types C1 and C2 are characterized by mutations in either the *NPC1* or *NPC2* gene, respectively, which leads to deficiencies in transporting cholesterol and other lipids. Although the exact mechanism of action remains unknown, the NPC1 and NPC2 proteins have been implicated in the efflux of cholesterol in the late-endosomal/lysosomal pathway [144,145].

NPC has an approximate incidence of 1:150,000 in Western Europe [146] NPC has been classified as a neurovisceral disorder manifesting with hepatosplenomegaly, cerebellar ataxia, dysarthria, dysphagia, dementia, seizures, dystonia, and vertical supranuclear gaze palsy. It is often associated with lethality in the second to fourth decade [147].

Patients with NPC also display wide phenotypic heterogeneity, even within subgroups. Vanier et al. reported genetic variability among patients with NPC by establishing two complementation groups of 27 and 5 individuals, based on fluorescent pattern analyses after filipin staining. Patients from each group exhibited considerable variability in disease severity, including three individuals with severe pulmonary complications [148]. Prasad et al. reported three cases with marked phenotypic differences including prominent neurological manifestations, megaloblastic anemia, and pulmonary involvement. Further clinical variability in age of onset, presenting signs, pattern of organ system involvement, and natural history have been described in small cohorts with NPC [149,150]. More recently, Stampfer et al. reported

heterogeneous neurological symptoms in a group of 42 patients from Germany and Switzerland [151]. Benussi et al. examined a pair of monozygotic twins, in which one was described with “inferior limb clumsiness, dysphagia and dysarthria” and “broad-based ataxic gait, limb dysmetria, downward vertical gaze palsy, brisk lower limb reflexes and ankle clonus,” while the other remained fairly asymptomatic with only “mild neurological impairment.” They further mention the implication of “epigenetic differences” as a possible contributor to the discordant phenotypes [152].

5. Epigenetic analyses in LSDs

Epigenetics has been considered in patients with LSDs in relatively few reports when compared to other disease, such as cancer. There have been a limited number of studies investigating DNA methylation in LSDs. In 1993, Enomma et al., studying the LSD Aspartylglucosaminuria (AGU), performed DNA methylation analysis of the *Aspartylglucosaminidase* (*AGA*) gene in both patients with AGU and normal individuals. The methylation patterns were not significantly different, and they concluded that regulation of *AGA* was at the translational, not transcriptional, level. Although their study did not include extensive epigenetic examination of DNA methylation, it still provided valuable insight [153]. Tomatsu et al. carried out a methylation study of the *N-acetylgalactosamine-6-sulfate sulfatase* (*GALNS*) gene, in which mutations lead to deficiency of the lysosomal enzyme in patients with Mucopolysaccharidosis type IVA (MPS IVA). They reported a “correlation between methylation status of CpG sites and distribution of transitional mutations.” This transitional change of a cytosine to thymine (or guanine to adenine) is a result of deamination of 5-methylcytosine. Among patients with MPS IV, 29.1% of point mutations in the coding region of *GALNS* resulted from transitional mutations at CpG dinucleotides. This study showed that methylation at CpG dinucleotides increased the mutability at these sites, subsequently influencing disease expression in MPS IVA [154]. In 2006, Tomatsu et al. observed a difference in methylation patterns of the *iduronate-2-sulfatase* (*IDS*) gene when comparing 11 patients with Hunter syndrome with five healthy controls. Using bisulfite genomic sequencing analysis, they determined that the portion of the *IDS* gene between exon 2 to intron 3 was more methylated in patients than in normal individuals [155]. Moreover, Kennedy et al. identified changes in amino acid metabolism and methylation patterns in the cerebellum of presymptomatic NPC-1 deficient mice. Specifically, they noted decreased expression of DNMT3A and methyl-CpG-domain-binding proteins, along with hypermethylation of specific promoter regions of single copy genes in NPC1-deficient cerebellum at early stages of the disease. Such epigenetic changes could play a role in the neuropathology of NPC-1, especially since they were noted in pre-symptomatic mice [156].

Methylation can also be useful for diagnostics, as observed in several studies in Fabry disease. Evaluating plasma and urine samples of patients with FD, Auray-Blais et al. identified methylated isoforms of the globotriaosylceramide (Gb3) [157]. In another study, Abaoui et al. found seven methylated Gb3 isoforms in urine samples from 150 patients FD not seen in controls [158]. Additionally, Hübner et al. reported methylation at position 78,504 in the promoter region (CpG island) of calcitonin receptor in patients with FD on enzyme replacement therapy, suggesting that this modification could be used as a biomarker for either treatment or disease severity, as more critical patients tend to be on enzyme replacement therapy [159]. Overall, these studies highlight the diagnostic potential of DNA methylation in FD.

Genomic imprinting can also be considered an epigenetic process, especially when one of the parental alleles is silenced through methylation. Simonaro et al. investigated the *SMPD1* gene, which encodes acid sphingomyelinase, deficient in type A and B Niemann-Pick disease. They found this gene to be paternally imprinted in patients with Niemann-Pick disease. They found the clinical presentations reflected acid sphingomyelinase expression from the maternal allele. This study emphasizes how epigenetics can play an important role in modulating LSD phenotypes [160].

Other epigenetic marks have also been studied in LSDs, including acetylation and miRNAs. De Mello et al. studied inflammatory parameters and histone H4 acetylation levels of a cohort of 10 patients with type 1 GD and 11 controls. They noted lower global Histone H4 acetylation levels in the patients with GD compared to the controls. The authors proposed that this could be related to the decrease in brain-derived neurotrophic factors also observed in the GD type 1 [161]. Queiroz et al. presented a comprehensive overview on the current work on non-coding RNAs and LSDs, specifically highlighting the research done on miRNAs [162]. Frankel et al. evaluated how the miRNA, miR-95, regulates sulfatase-modifying factor 1 activity and lysosomal processing. They concluded that miR-95 lowers sulfatase protein levels and activity, which subsequently leads to disrupted proteoglycan catabolism and impaired autophagy-mediated degradation [163]. These studies demonstrate how targeting an epigenetic mark, miRNA, can expand our understanding of lysosomal processing and serve as a potential treatment strategy for patients with LSDs.

Three reports have studied the relationship between miRNAs and GD. Dasgupta et al. evaluated miRNA levels in a mouse model of neuronopathic GD. They found differentially expressed miRNAs in multiple brain regions, with the highest number in the midbrain. The authors also noted how after treatment of the mice with isofagomine, a drug that helps to chaperone glucocerebrosidase (GCase), the number of differentially methylated miRNAs was lowered by 50–60%, which further changed the expression of a number of differentially expressed mRNAs. These miRNAs play a role in important neurological processes, such as axonal guidance and mitochondrial function, and could impact biological mechanisms contributing to neuropathic GD [164]. Siebert et al. investigated miRNAs and their effect on GCase activity and function. After screening 875 different miRNA mimics in GD fibroblasts, they observed several miRNAs that increased and decreased GCase activity. Particularly, one miRNA, miR-127–5p, decreased GCase activity by lowering the expression of LIMP-2 [165]. Ginns et al. studied neurological changes in GD mouse models to further understand the connection between GD and Parkinson disease. They found changes in the miRNA profile of the ventral mesencephalon when the mice were treated with a GCase inhibitor, conduritol B epoxide. The authors noted how functions of certain miRNAs were related to synaptic plasticity and neuroinflammation [166]. These three studies emphasize the important function of miRNAs in GD pathogenesis.

Other studies have explored the potential therapeutic efficacy of epigenetic modifications in LSDs. Four reports examined the use of histone deacetylase inhibitors (HDACi)s in NPC. Maceyka et al. describe the therapeutic potential of HDACis, showing how these drugs could repair lysosomal storage buildup of cholesterol and sphingolipids by increasing expression of the low activity mutant NPC1 protein [167]. Pipalia et al. tested the efficacy of the HDACi, panobinostat, in mutant NPC1 fibroblasts, showing the ability of the drug to restore proper cholesterol homeostasis in the cells [168]. Munkacsi et al., found that a large proportion of the histone deacetylase genes were up-regulated in NPC fibroblasts. Subsequent treatment with the HDACi, suberoylanilide hydroxamic acid corrected cholesterol homeostasis and lysosomal accumulation of sphingolipids [169]. Additionally, Wehrmann et al. showed significant reductions in intracellular cholesterol accumulation after treating NPC cells with the HDACis, vorinostat and panobinostat [170].

The efficacy of HDACi in GD has also been investigated. Lu et al. showed that the HDACis, SAHA and LB-205, rescued the function of mutant glucocerebrosidase by increasing its catalytic activity in fibroblasts from patients with mutations N370S (p.N409S) and L444P (p.L483P) approximately two-fold [171]. It was later shown that HDACs hyperacetylate the molecular chaperone Hsp90β, changing its function and increasing glucocerebrosidase levels [172]. These studies

demonstrate the therapeutic potential of epigenetic modifications in different LSDs, emphasizing the need for further studies in this field.

6. Conclusions

Epigenetics is an emerging field with tremendous potential for furthering our understanding of the pathology underlying many diseases. Recently, there has been an improved understanding of regulators of epigenetic mechanisms, such as the redox environment [4]. Increased focus on DNA alterations related to methylation, histone modifications and miRNAs has led to new therapeutic applications in the field of cancer. Future research into epigenetics will aid in the treatment, prognosis, and prevention of other diseases. A more recent appreciation of the role of genes involved in the epigenetic machinery opens new directions in this field [5].

Additionally, epigenetic studies may aid in identifying factors contributing to heterogeneity in LSDs. Over 14 years ago, Beutler challenged the scientific community to investigate additional factors contributing to the phenotypes of so-called “single-gene” diseases [173]. Future studies should focus on the evaluation of monozygotic twins with LSDs with discordant phenotypes. Such studies are invaluable for unraveling genetic and environmental contributions, as suggested as well by Beutler [173].

Moreover, further epigenetic studies in the LSDs can provide insight into much more prevalent disorders. The association of GD with Parkinson disease, and the implications of mutations in *NPC1* and/or *NPC2* in Alzheimer, HIV, and cardiovascular disease are just two examples of how studying relatively rare disorders can advance our understanding of more common disorders [174-177].

The field of epigenetics, while relatively new, has proven to be vital in understanding and potentially treating a growing number of diseases. Among the different LSDs, consideration of the contribution of epigenetic modifications to patient phenotypes may enhance our knowledge of the complexity of these diseases.

Acknowledgements

This work was supported by the Intramural Research Programs of the NHGRI and NIH.

The authors thank Mr. Ozhan B. Kazempour for his help in preparing the figure.

References

[1] L. Speybroeck, From epigenesis to epigenetics, Ann. N. Y. Acad. Sci. 981 (2006) 61–81, http://dx.doi.org/10.1111/j.1749-6632.2002.tb04912.x.
[2] C.H. Waddington, The epigenotype, Endeavour 1 (1942) 18–20.
[3] C.H. Waddington, The Strategy of the Genes, George Allen & Unwin, London, 1957.
[4] Y. Mikhed, A. Görlach, U.G. Knaus, A. Daiber, Redox regulation of genome stability by effects on gene expression, epigenetic pathways and DNA damage/repair, Redox Biol. 5 (2015) 275–289, http://dx.doi.org/10.1016/j.redox.2015.05.008.
[5] J.A. Fahrner, H.T. Bjornsson, Mendelian disorders of the epigenetic machinery: tipping the balance of chromatin states, Annu. Rev. Genomics Hum. Genet. 15 (2014) 269–293, http://dx.doi.org/10.1146/annurev-genom-090613-094245.
[6] B.E. Bernstein, J.A. Stamatoyannopoulos, J.F. Costello, B. Ren, A. Milosavljevic, A. Meissner, et al., The NIH roadmap epigenomics mapping consortium, Nat. Biotechnol. 28 (2010) 1045–1048, http://dx.doi.org/10.1038/nbt1010-1045.
[7] L.H. Chadwick, The NIH roadmap epigenomics program data resource, Epigenomics 4 (2012) 317–324, http://dx.doi.org/10.2217/epi.12.18.
[8] D.L. Rimoin, Clinical variability in achondroplasia, Basic Life Sci. 48 (1988) 123–127.
[9] L. Cremonesi, L. Cemonesi, G.L. Forni, N. Soriani, M. Lamagna, I. Fermo, et al., Genetic and clinical heterogeneity of ferroportin disease, Br. J. Haematol. 131 (2005) 663–670, http://dx.doi.org/10.1111/j.1365-2141.2005.05815.x.
[10] J. Zielenski, L.C. Tsui, Cystic fibrosis: genotypic and phenotypic variations, Annu. Rev. Genet. 29 (1995) 777–807, http://dx.doi.org/10.1146/annurev.ge.29.120195.004021.
[11] K. van Dijk, K. Fischer, J.G. van der Bom, D.E. Grobbee, H.M. van den Berg, Variability in clinical phenotype of severe haemophilia: the role of the first joint bleed, Haemophilia 11 (2005) 438–443, http://dx.doi.org/10.1111/j.1365-2516.2005.01124.x.
[12] H.M. van den Berg, P.H.G. De Groot, K. Fischer, Phenotypic heterogeneity in severe hemophilia, J. Thromb. Haemost. 5 (Suppl. 1) (2007) 151–156, http://dx.doi.org/10.1111/j.1538-7836.2007.02503.x.
[13] S.E. Folstein, M.H. Abbott, M.L. Franz, S. Huang, G.A. Chase, M.F. Folstein, Phenotypic heterogeneity in Huntington disease, J. Neurogenet. 1 (1984) 175–184.
[14] V. Gieselmann, What can cell biology tell us about heterogeneity in lysosomal storage diseases? Acta Paediatr. Suppl. 94 (2005) 80–86 (discussion 79).
[15] L.D. Moore, T. Le, G. Fan, DNA methylation and its basic function, Neuropsychopharmacology 38 (2012) 23–38, http://dx.doi.org/10.1038/npp.2012.112.
[16] F. Watt, P.L. Molloy, Cytosine methylation prevents binding to DNA of a HeLa cell transcription factor required for optimal expression of the adenovirus major late promoter, Genes Dev. 2 (1988) 1136–1143.
[17] D.N. Mancini, S.M. Singh, T.K. Archer, D.I. Rodenhiser, Site-specific DNA methylation in the neurofibromatosis (NF1) promoter interferes with binding of CREB and SP1 transcription factors, Oncogene 18 (1999) 4108–4119, http://dx.doi.org/10.1038/sj.onc.1202764.
[18] P.A. Wade, Methyl CpG binding proteins: coupling chromatin architecture to gene regulation, Oncogene 20 (2001) 3166–3173, http://dx.doi.org/10.1038/sj.onc.1204340.
[19] P.A. Wade, Methyl CpG-binding proteins and transcriptional repression, BioEssays 23 (2001) 1131–1137, http://dx.doi.org/10.1002/bies.10008.
[20] M.-F. Robert, S. Morin, N. Beaulieu, F. Gauthier, I.C. Chute, A. Barsalou, et al., DNMT1 is required to maintain CpG methylation and aberrant gene silencing in human cancer cells, Nat. Genet. 33 (2003) 61–65, http://dx.doi.org/10.1038/ng1068.
[21] R. Pacaud, E. Brocard, L. Lalier, E. Hervouet, F.M. Vallette, P.-F. Cartron, The DNMT1/PCNA/UHRF1 disruption induces tumorigenesis characterized by similar genetic and epigenetic signatures, Sci Rep 4 (2014) 4230, http://dx.doi.org/10.1038/srep04230.
[22] M. Okano, D.W. Bell, D.A. Haber, E. Li, DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development, Cell 99 (1999) 247–257.
[23] T. Chen, Y. Ueda, J.E. Dodge, Z. Wang, E. Li, Establishment and maintenance of genomic methylation patterns in mouse embryonic stem cells by Dnmt3a and Dnmt3b, Mol. Cell. Biol. 23 (2003) 5594–5605.
[24] X. Zhang, C.K. Mathews, Effect of DNA cytosine methylation upon deamination-induced mutagenesis in a natural target sequence in duplex DNA, J. Biol. Chem. 269 (1994) 7066–7069.
[25] A.P. Bird, DNA methylation and the frequency of CpG in animal DNA, Nucleic Acids Res. 8 (1980) 1499–1504.
[26] A.M. Deaton, A. Bird, CpG islands and the regulation of transcription, Genes Dev. 25 (2011) 1010–1022, http://dx.doi.org/10.1101/gad.2037511.
[27] P.H. Yen, P. Patel, A.C. Chinault, T. Mohandas, L.J. Shapiro, Differential methylation of hypoxanthine phosphoribosyltransferase genes on active and inactive human X chromosomes, Proc. Natl. Acad. Sci. U. S. A. 81 (1984) 1759–1763.
[28] A. Razin, H. Cedar, DNA methylation and genomic imprinting, Cell 77 (1994) 473–476.
[29] W. Reik, J. Walter, Genomic imprinting: parental influence on the genome, Nat. Rev. Genet. 2 (2001) 21–32, http://dx.doi.org/10.1038/35047554.
[30] L.K. Abramowitz, M.S. Bartolomei, Genomic imprinting: recognition and marking of imprinted loci, Curr. Opin. Genet. Dev. 22 (2012) 72–78, http://dx.doi.org/10.1016/j.gde.2011.12.001.
[31] S. Saxonov, P. Berg, D.L. Brutlag, A genome-wide analysis of CpG dinucleotides in the human genome distinguishes two distinct classes of promoters, Proc. Natl. Acad. Sci. 103 (2006) 1412–1417, http://dx.doi.org/10.1073/pnas.0510310103.
[32] K.D. Robertson, DNA methylation and human disease, Nat. Rev. Genet. 6 (2005) 597–610, http://dx.doi.org/10.1038/nrg1655.
[33] M. Esteller, CpG island hypermethylation and tumor suppressor genes: a booming present, a brighter future, Oncogene 21 (2002) 5427–5440, http://dx.doi.org/10.1038/sj.onc.1205600.
[34] T. Maehata, H. Taniguchi, H. Yamamoto, K. Nosho, Y. Adachi, N. Miyamoto, et al., Transcriptional silencing of Dickkopf gene family by CpG island hypermethylation in human gastrointestinal cancer, World J. Gastroenterol. 14 (2008) 2702–2714.
[35] K.-O. Uhm, E.S. Lee, Y.M. Lee, H.S. Kim, Y.-N. Park, S.-H. Park, Aberrant promoter CpG islands methylation of tumor suppressor genes in cholangiocarcinoma, Oncol. Res. 17 (2008) 151–157.
[36] T.L. Roth, F.D. Lubin, M. Sodhi, J.E. Kleinman, Epigenetic mechanisms in schizophrenia, Biochim. Biophys. Acta 1790 (2009) 869–877, http://dx.doi.org/10.1016/j.bbagen.2009.06.009.
[37] C. Serra-Juhé, I. Cuscó, A. Homs, R. Flores, N. Torán, L.A. Pérez-Jurado, DNA methylation abnormalities in congenital heart disease, Epigenetics 10 (2015) 167–177, http://dx.doi.org/10.1080/15592294.2014.998536.
[38] L.J. Martin, M. Wong, Aberrant regulation of DNA methylation in amyotrophic lateral sclerosis: a new target of disease mechanisms, Neurotherapeutics 10 (2013) 722–733, http://dx.doi.org/10.1007/s13311-013-0205-6.
[39] P.L. De Jager, G. Srivastava, K. Lunnon, J. Burgess, L.C. Schalkwyk, L. Yu, et al., Alzheimer's disease: early alterations in brain DNA methylation at ANK1, BIN1, RHBDF2 and other loci, Nat. Neurosci. 17 (2014) 1156–1163, http://dx.doi.org/10.1038/nn.3786.
[40] C. Dong, W. Yoon, P.J. Goldschmidt-Clermont, DNA methylation and atherosclerosis, J. Nutr. 132 (2002) 2406S–2409S.
[41] N.J. Kessler, T.E. Van Baak, M.S. Baker, E. Laritsky, C. Coarfa, R.A. Waterland, CpG methylation differences between neurons and glia are highly conserved from mouse to human, Hum. Mol. Genet. 25 (2016) 223–232, http://dx.doi.org/10.

1093/hmg/ddv459.
[42] A.J. Bannister, T. Kouzarides, Regulation of chromatin by histone modifications, Cell Res. 21 (2011) 381–395, http://dx.doi.org/10.1038/cr.2011.22.
[43] M.H. Kuo, C.D. Allis, Roles of histone acetyltransferases and deacetylases in gene regulation, BioEssays 20 (1998) 615–626, http://dx.doi.org/10.1002/(SICI)1521-1878(199808)20:8<615::AID-BIES4>3.0.CO;2-H.
[44] K. Luger, A.W. Mäder, R.K. Richmond, D.F. Sargent, T.J. Richmond, Crystal structure of the nucleosome core particle at 2.8 A resolution, Nature 389 (1997) 251–260, http://dx.doi.org/10.1038/38444.
[45] S. Legartová, L. Stixová, H. Strnad, S. Kozubek, N. Martinet, F.J. Dekker, et al., Basic nuclear processes affected by histone acetyltransferases and histone deacetylase inhibitors, Epigenomics 5 (2013) 379–396, http://dx.doi.org/10.2217/epi.13.38.
[46] R. Sternglanz, Histone acetylation: a gateway to transcriptional activation, Trends Biochem. Sci. 21 (1996) 357–358.
[47] T.R. Hebbes, A.W. Thorne, C. Crane-Robinson, A direct link between core histone acetylation and transcriptionally active chromatin, EMBO J. 7 (1988) 1395–1402.
[48] D.Y. Lee, J.J. Hayes, D. Pruss, A.P. Wolffe, A positive role for histone acetylation in transcription factor access to nucleosomal DNA, Cell 72 (1993) 73–84.
[49] E. Col, C. Caron, D. Seigneurin-Berny, J. Gracia, A. Favier, S. Khochbin, The histone acetyltransferase, hGCN5, interacts with and acetylates the HIV transactivator, Tat, J. Biol. Chem. 276 (2001) 28179–28184, http://dx.doi.org/10.1074/jbc.M101385200.
[50] Y. Zhao, J. Lu, H. Sun, X. Chen, W. Huang, D. Tao, et al., Histone acetylation regulates both transcription initiation and elongation of hsp22 gene in *Drosophila*, Biochem. Biophys. Res. Commun. 326 (2005) 811–816, http://dx.doi.org/10.1016/j.bbrc.2004.11.118.
[51] F. Gong, K.M. Miller, Mammalian DNA repair: HATs and HDACs make their mark through histone acetylation, Mutat. Res. 750 (2013) 23–30, http://dx.doi.org/10.1016/j.mrfmmm.2013.07.002.
[52] M.-R. Duan, M.J. Smerdon, Histone H3 lysine 14 (H3K14) acetylation facilitates DNA repair in a positioned nucleosome by stabilizing the binding of the chromatin Remodeler RSC (Remodels Structure of Chromatin), J. Biol. Chem. 289 (2014) 8353–8363, http://dx.doi.org/10.1074/jbc.M113.540732.
[53] Y. Wei, C.A. Mizzen, R.G. Cook, M.A. Gorovsky, C.D. Allis, Phosphorylation of histone H3 at serine 10 is correlated with chromosome condensation during mitosis and meiosis in *Tetrahymena*, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 7480–7484.
[54] H.-G. Kim, K.W. Lee, Y.-Y. Cho, N.J. Kang, S.-M. Oh, A.M. Bode, et al., Mitogen- and stress-activated kinase 1-mediated histone H3 phosphorylation is crucial for cell transformation, Cancer Res. 68 (2008) 2538–2547, http://dx.doi.org/10.1158/0008-5472.CAN-07-6597.
[55] H. Kurita, M. Schnekenburger, J.L. Ovesen, Y. Xia, A. Puga, The Ah receptor recruits IKKα to its target binding motifs to phosphorylate serine-10 in histone H3 required for transcriptional activation, Toxicol. Sci. 139 (2014) 121–132, http://dx.doi.org/10.1093/toxsci/kfu027.
[56] E.R. Foster, J.A. Downs, Histone H2A phosphorylation in DNA double-strand break repair, FEBS J. 272 (2005) 3231–3240, http://dx.doi.org/10.1111/j.1742-4658.2005.04741.x.
[57] Q. Dong, F. Han, Phosphorylation of histone H2A is associated with centromere function and maintenance in meiosis, Plant J. 71 (2012) 800–809, http://dx.doi.org/10.1111/j.1365-313X.2012.05029.x.
[58] P.J. Hurd, A.J. Bannister, K. Halls, M.A. Dawson, M. Vermeulen, J.V. Olsen, et al., Phosphorylation of histone H3 Thr-45 is linked to apoptosis, J. Biol. Chem. 284 (2009) 16575–16583, http://dx.doi.org/10.1074/jbc.M109.005421.
[59] M. Pinskaya, S. Gourvennec, A. Morillon, H3 lysine 4 di- and tri-methylation deposited by cryptic transcription attenuates promoter activation, EMBO J. 28 (2009) 1697–1707, http://dx.doi.org/10.1038/emboj.2009.108.
[60] J. Cheng, R. Blum, C. Bowman, D. Hu, A. Shilatifard, S. Shen, et al., A role for H3K4 monomethylation in gene repression and partitioning of chromatin readers, Mol. Cell 53 (2014) 979–992, http://dx.doi.org/10.1016/j.molcel.2014.02.032.
[61] J.C. Rice, S.D. Briggs, B. Ueberheide, C.M. Barber, J. Shabanowitz, D.F. Hunt, et al., Histone methyltransferases direct different degrees of methylation to define distinct chromatin domains, Mol. Cell 12 (2003) 1591–1598.
[62] A. Henckel, K. Nakabayashi, L.A. Sanz, R. Feil, K. Hata, P. Arnaud, Histone methylation is mechanistically linked to DNA methylation at imprinting control regions in mammals, Hum. Mol. Genet. 18 (2009) 3375–3383, http://dx.doi.org/10.1093/hmg/ddp277.
[63] T. Suganuma, J.L. Workman, Crosstalk among histone modifications, Cell 135 (2008) 604–607, http://dx.doi.org/10.1016/j.cell.2008.10.036.
[64] Q. Duan, H. Chen, M. Costa, W. Dai, Phosphorylation of H3S10 blocks the access of H3K9 by specific antibodies and histone methyltransferase. Implication in regulating chromatin dynamics and epigenetic inheritance during mitosis, J. Biol. Chem. 283 (2008) 33585–33590, http://dx.doi.org/10.1074/jbc.M803312200.
[65] T. Jenuwein, C.D. Allis, Translating the histone code, Science 293 (2001) 1074–1080, http://dx.doi.org/10.1126/science.1063127.
[66] B.D. Strahl, C.D. Allis, The language of covalent histone modifications, Nature 403 (2000) 41–45, http://dx.doi.org/10.1038/47412.
[67] R.C. Lee, R.L. Feinbaum, V. Ambros, The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14, Cell 75 (1993) 843–854.
[68] M.R. Friedländer, E. Lizano, A.J.S. Houben, D. Bezdan, M. Báñez-Coronel, G. Kudla, et al., Evidence for the biogenesis of more than 1,000 novel human microRNAs, Genome Biol. 15 (2014) R57, http://dx.doi.org/10.1186/gb-2014-15-4-r57.
[69] C.P.C. Gomes, J.-H. Cho, L. Hood, O.L. Franco, R.W. Pereira, K. Wang, A review of computational tools in microRNA discovery, Front. Genet. 4 (2013) 81, http://dx.doi.org/10.3389/fgene.2013.00081.
[70] A. Kozomara, S. Griffiths-Jones, miRBase: integrating microRNA annotation and deep-sequencing data, Nucleic Acids Res. 39 (2011) D152–7, http://dx.doi.org/10.1093/nar/gkq1027.
[71] D. Bonci, V. Coppola, M. Musumeci, A. Addario, R. Giuffrida, L. Memeo, et al., The miR-15a-miR-16-1 cluster controls prostate cancer by targeting multiple oncogenic activities, Nat. Med. 14 (2008) 1271–1277, http://dx.doi.org/10.1038/nm.1880.
[72] S. Wu, S. Huang, J. Ding, Y. Zhao, L. Liang, T. Liu, et al., Multiple microRNAs modulate p21Cip1/Waf1 expression by directly targeting its 3′ untranslated region, Oncogene 29 (2010) 2302–2308, http://dx.doi.org/10.1038/onc.2010.34.
[73] B. John, A.J. Enright, A. Aravin, T. Tuschl, C. Sander, D.S. Marks, Human microRNA targets, PLoS Biol. 2 (2004) e363, , http://dx.doi.org/10.1371/journal.pbio.0020363.
[74] M. Hafner, S. Lianoglou, T. Tuschl, D. Betel, Genome-wide identification of miRNA targets by PAR-CLIP, Methods 58 (2012) 94–105, http://dx.doi.org/10.1016/j.ymeth.2012.08.006.
[75] M. Lizé, A. Klimke, M. Dobbelstein, MicroRNA-449 in cell fate determination, Cell Cycle 10 (2011) 2874–2882.
[76] M.T.N. Le, H. Xie, B. Zhou, P.H. Chia, P. Rizk, M. Um, et al., MicroRNA-125b promotes neuronal differentiation in human cells by repressing multiple targets, Mol. Cell. Biol. 29 (2009) 5290–5305, http://dx.doi.org/10.1128/MCB.01694-08.
[77] V. Ambros, MicroRNAs and developmental timing, Curr. Opin. Genet. Dev. 21 (2011) 511–517, http://dx.doi.org/10.1016/j.gde.2011.04.003.
[78] D. Lenkala, B. LaCroix, E.R. Gamazon, P. Geeleher, H.K. Im, R.S. Huang, The impact of microRNA expression on cellular proliferation, Hum. Genet. 133 (2014) 931–938, http://dx.doi.org/10.1007/s00439-014-1434-4.
[79] M. Jovanovic, M.O. Hengartner, miRNAs and apoptosis: RNAs to die for, Oncogene 25 (2006) 6176–6187, http://dx.doi.org/10.1038/sj.onc.1209912.
[80] J. Fiedler, T. Thum, MicroRNAs in myocardial infarction, Arterioscler. Thromb. Vasc. Biol. 33 (2013) 201–205, http://dx.doi.org/10.1161/ATVBAHA.112.300137.
[81] J. Wang, X. Yang, The function of miRNA in cardiac hypertrophy, Cell. Mol. Life Sci. 69 (2012) 3561–3570, http://dx.doi.org/10.1007/s00018-012-1126-y.
[82] O.C. Maes, H.M. Chertkow, E. Wang, H.M. Schipper, MicroRNA: implications for Alzheimer disease and other human CNS disorders, Curr. Genomics 10 (2009) 154–168, http://dx.doi.org/10.2174/138920209788185252.
[83] Y. Li, L. Lin, P. Jin, The microRNA pathway and fragile X mental retardation protein, Biochim. Biophys. Acta 1779 (2008) 702–705, http://dx.doi.org/10.1016/j.bbagrm.2008.07.003.
[84] V. Furer, J.D. Greenberg, M. Attur, S.B. Abramson, M.H. Pillinger, The role of microRNA in rheumatoid arthritis and other autoimmune diseases, Clin. Immunol. 136 (2010) 1–15, http://dx.doi.org/10.1016/j.clim.2010.02.005.
[85] S. Shrivastava, A. Mukherjee, R.B. Ray, Hepatitis C virus infection, microRNA and liver disease progression, World J. Hepatol. 5 (2013) 479–486, http://dx.doi.org/10.4254/wjh.v5.i9.479.
[86] G.A. Calin, C.M. Croce, MicroRNA signatures in human cancers, Nat. Rev. Cancer 6 (2006) 857–866, http://dx.doi.org/10.1038/nrc1997.
[87] Y. Lee, M. Kim, J. Han, K.-H. Yeom, S. Lee, S.H. Baek, et al., MicroRNA genes are transcribed by RNA polymerase II, EMBO J. 23 (2004) 4051–4060, http://dx.doi.org/10.1038/sj.emboj.7600385.
[88] G.M. Borchert, W. Lanier, B.L. Davidson, RNA polymerase III transcribes human microRNAs, Nat. Struct. Mol. Biol. 13 (2006) 1097–1101, http://dx.doi.org/10.1038/nsmb1167.
[89] A.M. Denli, B.B.J. Tops, R.H.A. Plasterk, R.F. Ketting, G.J. Hannon, Processing of primary microRNAs by the microprocessor complex, Nature 432 (2004) 231–235, http://dx.doi.org/10.1038/nature03049.
[90] R.I. Gregory, K.-P. Yan, G. Amuthan, T. Chendrimada, B. Doratotaj, N. Cooch, et al., The Microprocessor complex mediates the genesis of microRNAs, Nature 432 (2004) 235–240, http://dx.doi.org/10.1038/nature03120.
[91] N.M. Williams, Molecular mechanisms in 22q11 deletion syndrome, Schizophr. Bull. 37 (2011) 882–889, http://dx.doi.org/10.1093/schbul/sbr095.
[92] R. Yi, Y. Qin, I.G. Macara, B.R. Cullen, Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs, Genes Dev. 17 (2003) 3011–3016, http://dx.doi.org/10.1101/gad.1158803.
[93] Y. Feng, X. Zhang, P. Graves, Y. Zeng, A comprehensive analysis of precursor microRNA cleavage by human Dicer, RNA 18 (2012) 2083–2092, http://dx.doi.org/10.1261/rna.033688.112.
[94] E. Bernstein, A.A. Caudy, S.M. Hammond, G.J. Hannon, Role for a bidentate ribonuclease in the initiation step of RNA interference, Nature 409 (2001) 363–366, http://dx.doi.org/10.1038/35053110.
[95] G. Hutvágner, J. McLachlan, A.E. Pasquinelli, E. Bálint, T. Tuschl, P.D. Zamore, A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA, Science 293 (2001) 834–838, http://dx.doi.org/10.1126/science.1062961.
[96] A.J. Pratt, I.J. MacRae, The RNA-induced silencing complex: a versatile gene-silencing machine, J. Biol. Chem. 284 (2009) 17897–17901, http://dx.doi.org/10.1074/jbc.R900012200.
[97] D.P. Bartel, MicroRNAs: genomics, biogenesis, mechanism, and function, Cell 116 (2004) 281–297.
[98] R.W. Carthew, E.J. Sontheimer, Origins and mechanisms of miRNAs and siRNAs, Cell 136 (2009) 642–655, http://dx.doi.org/10.1016/j.cell.2009.01.035.
[99] G. Meister, M. Landthaler, A. Patkaniowska, Y. Dorsett, G. Teng, T. Tuschl, Human Argonaute2 mediates RNA cleavage targeted by miRNAs and siRNAs, Mol. Cell 15 (2004) 185–197, http://dx.doi.org/10.1016/j.molcel.2004.07.007.

[100] T.A. Rand, K. Ginalski, N.V. Grishin, X. Wang, Biochemical identification of Argonaute 2 as the sole protein required for RNA-induced silencing complex activity, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 14385–14389, http://dx.doi.org/10.1073/pnas.0405913101.
[101] J.K. Christman, 5-Azacytidine and 5-aza-2′-deoxycytidine as inhibitors of DNA methylation: mechanistic studies and their implications for cancer therapy, Oncogene 21 (2002) 5483–5495, http://dx.doi.org/10.1038/sj.onc.1205699.
[102] A. Borodovsky, V. Salmasi, S. Turcan, A.W.M. Fabius, G.S. Baia, C.G. Eberhart, et al., 5-azacytidine reduces methylation, promotes differentiation and induces tumor regression in a patient-derived IDH1 mutant glioma xenograft, Oncotarget 4 (2013) 1737–1747, http://dx.doi.org/10.18632/oncotarget.1408.
[103] E. Kaminskas, A.T. Farrell, Y.-C. Wang, R. Sridhara, R. Pazdur, FDA drug approval summary: azacitidine (5-azacytidine, Vidaza) for injectable suspension, Oncologist 10 (2005) 176–182, http://dx.doi.org/10.1634/theoncologist.10-3-176.
[104] L. Morera, M. Lübbert, M. Jung, Targeting histone methyltransferases and demethylases in clinical trials for cancer therapy, Clin. Epigenetics 8 (2016) 57, http://dx.doi.org/10.1186/s13148-016-0223-4.
[105] A. Spannhoff, A.-T. Hauser, R. Heinke, W. Sippl, M. Jung, The emerging therapeutic potential of histone methyltransferase and demethylase inhibitors, ChemMedChem 4 (2009) 1568–1582, http://dx.doi.org/10.1002/cmdc.200900301.
[106] A.G. Torres, M.M. Fabani, E. Vigorito, M.J. Gait, MicroRNA fate upon targeting with anti-miRNA oligonucleotides as revealed by an improved Northern-blot-based method for miRNA detection, RNA 17 (2011) 933–943, http://dx.doi.org/10.1261/rna.2533811.
[107] F.M. Platt, B. Boland, A.C. van der Spoel, The cell biology of disease: lysosomal storage disorders: the cellular impact of lysosomal dysfunction, J. Cell Biol. 199 (2012) 723–734, http://dx.doi.org/10.1083/jcb.201208152.
[108] M.L. Schultz, L. Tecedor, M. Chang, B.L. Davidson, Clarifying lysosomal storage diseases, Trends Neurosci. 34 (2011) 401–410, http://dx.doi.org/10.1016/j.tins.2011.05.006.
[109] M. Fuller, P.J. Meikle, J.J. Hopwood, Epidemiology of lysosomal storage diseases: an overview, in: A. Mehta, M. Beck, G. Sunder-Plassmann (Eds.), Fabry Disease: Perspectives from 5 years of FOS, Oxford PharmaGenesis, Oxford, 2006(Chapter 2).
[110] A. Zimran, T. Gelbart, B. Westwood, G.A. Grabowski, E. Beutler, High frequency of the Gaucher disease mutation at nucleotide 1226 among Ashkenazi Jews, Am. J. Hum. Genet. 49 (1991) 855–859.
[111] A. Dandana, S. Ben Khelifa, H. Chahed, A. Miled, S. Ferchichi, Gaucher disease: clinical, biological and therapeutic aspects, Pathobiology 83 (2015) 13–23, http://dx.doi.org/10.1159/000440865.
[112] A.P. Bussink, M. van Eijk, G.H. Renkema, J.M. Aerts, R.G. Boot, The biology of the Gaucher cell: the cradle of human chitinases, Int. Rev. Cytol. 252 (2006) 71–128, http://dx.doi.org/10.1016/S0074-7696(06)52001-7.
[113] M. Jmoudiak, A.H. Futerman, Gaucher disease: pathological mechanisms and modern management, Br. J. Haematol. 129 (2005) 178–188, http://dx.doi.org/10.1111/j.1365-2141.2004.05351.x.
[114] J. Charrow, H.C. Andersson, P. Kaplan, E.H. Kolodny, P. Mistry, G. Pastores, et al., The Gaucher registry, Arch. Intern. Med. 160 (2000) 2835, http://dx.doi.org/10.1001/archinte.160.18.2835.
[115] V. Bohra, V. Nair, Gaucher's disease, Indian J. Endocrinol. Metab. 15 (2011) 182–186, http://dx.doi.org/10.4103/2230-8210.83402.
[116] L.K. Hein, P.J. Meikle, J.J. Hopwood, M. Fuller, Secondary sphingolipid accumulation in a macrophage model of Gaucher disease, Mol. Genet. Metab. 92 (2007) 336–345, http://dx.doi.org/10.1016/j.ymgme.2007.08.001.
[117] C.E. Hollak, L. Evers, J.M. Aerts, M.H. van Oers, Elevated levels of M-CSF, sCD14 and IL8 in type 1 Gaucher disease, Blood Cells Mol. Dis. 23 (1997) 201–212, http://dx.doi.org/10.1006/bcmd.1997.0137.
[118] A. Velayati, J. DePaolo, N. Gupta, J.H. Choi, N. Moaven, W. Westbroek, et al., A mutation in SCARB2 is a modifier in Gaucher disease, Hum. Mutat. 32 (2011) 1232–1238, http://dx.doi.org/10.1002/humu.21566.
[119] R.J. Tamargo, A. Velayati, E. Goldin, E. Sidransky, The role of saposin C in Gaucher disease, Mol. Genet. Metab. 106 (2012) 257–263, http://dx.doi.org/10.1016/j.ymgme.2012.04.024.
[120] F.Y. Choy, Intrafamilial clinical variability of type 1 Gaucher disease in a French-Canadian family, J. Med. Genet. 25 (1988) 322–325.
[121] O. Amaral, A.M. Fortuna, L. Lacerda, R. Pinto, M.C. Sa Miranda, Molecular characterisation of type 1 Gaucher disease families and patients: intrafamilial heterogeneity at the clinical level, J. Med. Genet. 31 (1994) 401–404.
[122] D. Elstein, C.R. Scott, M. Zeigler, A. Abrahamov, A. Zimran, Phenotypic heterogeneity in patients with Gaucher disease and the N370S/V394L genotype, Genet. Test. 9 (2005) 26–29, http://dx.doi.org/10.1089/gte.2005.9.26.
[123] O. Goker-Alpan, K.S. Hruska, E. Orvisky, P.S. Kishnani, B.K. Stubblefield, R. Schiffmann, et al., Divergent phenotypes in Gaucher disease implicate the role of modifiers, J. Med. Genet. 42 (2005) e37, , http://dx.doi.org/10.1136/jmg.2004.028019.
[124] N. Gupta, I.M. Oppenheim, E.F. Kauvar, N. Tayebi, E. Sidransky, Type 2 Gaucher disease: phenotypic variation and genotypic heterogeneity, Blood Cells Mol. Dis. 46 (2011) 75–84, http://dx.doi.org/10.1016/j.bcmd.2010.08.012.
[125] M. Biegstraaten, I.N. van Schaik, J.M.F.G. Aerts, M. Langeveld, M.M.A.M. Mannens, L.J. Bour, et al., A monozygotic twin pair with highly discordant Gaucher phenotypes, Blood Cells Mol. Dis. 46 (2011) 39–41, http://dx.doi.org/10.1016/j.bcmd.2010.10.007.
[126] R.H. Lachmann, I.R. Grant, D. Halsall, T.M. Cox, Twin pairs showing discordance of phenotype in adult Gaucher's disease, QJM 97 (2004) 199–204, http://dx.doi.org/10.1093/qjmed/hch036.
[127] A. Lwin, Glucocerebrosidase mutations in subjects with parkinsonism, Mol. Genet. Metab. 81 (2004) 70–73, http://dx.doi.org/10.1016/j.ymgme.2003.11.004.
[128] J. Simón-Sánchez, C. Schulte, J.M. Bras, M. Sharma, J.R. Gibbs, D. Berg, et al., Genome-wide association study reveals genetic risk underlying Parkinson's disease, Nat. Genet. 41 (2009) 1308–1312, http://dx.doi.org/10.1038/ng.487.
[129] W.C. Nichols, N. Pankratz, D.K. Marek, M.W. Pauciulo, V.E. Elsaesser, C.A. Halter, et al., Mutations in GBA are associated with familial Parkinson disease susceptibility and age at onset, Neurology 72 (2009) 310–316, http://dx.doi.org/10.1212/01.wnl.0000327823.81237.d1.
[130] J.G. Becker, G.M. Pastores, A. Di Rocco, M. Ferraris, J.J. Graber, S. Sathe, Parkinson's disease in patients and obligate carriers of Gaucher disease, Parkinsonism Relat. Disord. 19 (2013) 129–131, http://dx.doi.org/10.1016/j.parkreldis.2012.06.023.
[131] O. Goker-Alpan, R. Schiffmann, M.E. LaMarca, R.L. Nussbaum, A. McInerney-Leo, E. Sidransky, Parkinsonism among Gaucher disease carriers, J. Med. Genet. 41 (2004) 937–940, http://dx.doi.org/10.1136/jmg.2004.024455.
[132] J. Mitsui, I. Mizuta, A. Toyoda, R. Ashida, Y. Takahashi, J. Goto, et al., Mutations for Gaucher disease confer high susceptibility to Parkinson disease, Arch. Neurol. 66 (2009) 571–576, http://dx.doi.org/10.1001/archneurol.2009.72.
[133] E. Sidransky, M.A. Nalls, J.O. Aasly, J. Aharon-Peretz, G. Annesi, E.R. Barbosa, et al., Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease, N. Engl. J. Med. 361 (2009) 1651–1661, http://dx.doi.org/10.1056/NEJMoa0901281.
[134] W. Westbroek, A.M. Gustafson, E. Sidransky, Exploring the link between glucocerebrosidase mutations and parkinsonism, Trends Mol. Med. 17 (2011) 485–493, http://dx.doi.org/10.1016/j.molmed.2011.05.003.
[135] C. Labbé, O. Lorenzo-Betancor, O.A. Ross, Epigenetic regulation in Parkinson's disease, Acta Neuropathol. 132 (2016) 515–530, http://dx.doi.org/10.1007/s00401-016-1590-9.
[136] D.P. Germain, Fabry disease, Orphanet J. Rare Dis. 5 (2010) 30, http://dx.doi.org/10.1186/1750-1172-5-30.
[137] A. Mehta, D.A. Hughes, Fabry disease. 2002 Aug 5 [updated 2017 Jan 5], in: R.A. Pagon, M.P. Adam, H.H. Ardinger, et al. (Eds.), GeneReviews® [Internet], University of Washington, Seattle, Seattle (WA), 1993–2017.
[138] S. Nakao, C. Kodama, T. Takenaka, A. Tanaka, Y. Yasumoto, A. Yoshida, et al., Fabry disease: detection of undiagnosed hemodialysis patients and identification of a “renal variant” phenotype, Kidney Int. 64 (2003) 801–807, http://dx.doi.org/10.1046/j.1523-1755.2003.00160.x.
[139] R.Y. Wang, A. Lelis, J. Mirocha, W.R. Wilcox, Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life, Genet. Med. 9 (2007) 34–45, http://dx.doi.org/10.1097/GIM.0b013e31802d8321.
[140] R. Torra, A. Ortíz, Fabry disease: the many faces of a single disorder, Clin. Kidney J. 5 (2012) 379–382, http://dx.doi.org/10.1093/ckj/sfs124.
[141] A.C. Vedder, G.E. Linthorst, M.J. van Breemen, J.E.M. Groener, F.J. Bemelman, A. Strijland, et al., The Dutch Fabry cohort: diversity of clinical manifestations and Gb3 levels, J. Inherit. Metab. Dis. 30 (2007) 68–78, http://dx.doi.org/10.1007/s10545-006-0484-8.
[142] M. Rigoldi, D. Concolino, A. Morrone, F. Pieruzzi, R. Ravaglia, F. Furlan, et al., Intrafamilial phenotypic variability in four families with Anderson-Fabry disease, Clin. Genet. 86 (2014) 258–263, http://dx.doi.org/10.1111/cge.12261.
[143] I. Redonnet-Vernhet, J.K. Ploos van Amstel, R.P. Jansen, R.A. Wevers, R. Salvayre, T. Levade, Uneven X inactivation in a female monozygotic twin pair with Fabry disease and discordant expression of a novel mutation in the alpha-galactosidase A gene, J. Med. Genet. 33 (1996) 682–688.
[144] M.T. Vanier, Complex lipid trafficking in Niemann-Pick disease type C, J. Inherit. Metab. Dis. 38 (2015) 187–199, http://dx.doi.org/10.1007/s10545-014-9794-4.
[145] A.I. Rosenbaum, F.R. Maxfield, Niemann-Pick type C disease: molecular mechanisms and potential therapeutic approaches, J. Neurochem. 116 (2011) 789–795, http://dx.doi.org/10.1111/j.1471-4159.2010.06976.x.
[146] M. Patterson, Niemann-Pick Disease Type C. 2000 Jan 26 [updated 2013 Jul 18], in: R.A. Pagon, M.P. Adam, H.H. Ardinger, et al. (Eds.), GeneReviews® [Internet], University of Washington, Seattle, Seattle (WA), 1993–2017.
[147] M.T. Vanier, Niemann-Pick disease type C, Orphanet J. Rare Dis. 5 (2010) 16, http://dx.doi.org/10.1186/1750-1172-5-16.
[148] M.T. Vanier, S. Duthel, C. Rodriguez-Lafrasse, P. Pentchev, E.D. Carstea, Genetic heterogeneity in Niemann-Pick C disease: a study using somatic cell hybridization and linkage analysis, Am. J. Hum. Genet. 58 (1996) 118–125.
[149] C. Prasad, C. Pushpanathan, R. Morris, A. Davis, F. Dougherty, Spectrum of phenotypic variability in Niemann-Pick type C disease: a cause of delayed diagnosis, Paediatr. Child Health 3 (1998) 329–333.
[150] M.R. Natowicz, J.M. Stoler, E.M. Prence, L. Liscum, Marked heterogeneity in Niemann-Pick disease, type C. Clinical and ultrastructural findings, Clin. Pediatr. 34 (1995) 190–197.
[151] M. Stampfer, S. Theiss, Y. Amraoui, X. Jiang, S. Keller, D.S. Ory, et al., Niemann-Pick disease type C clinical database: cognitive and coordination deficits are early disease indicators, Orphanet J. Rare Dis. 8 (2013) 35, http://dx.doi.org/10.1186/1750-1172-8-35.
[152] A. Benussi, A. Alberici, E. Premi, V. Bertasi, M.S. Cotelli, M. Turla, et al., Phenotypic heterogeneity of Niemann-Pick disease type C in monozygotic twins, J. Neurol. 262 (2015) 642–647, http://dx.doi.org/10.1007/s00415-014-7619-x.
[153] N.E. Enomaa, P.L. Lukinmaa, E.M. Ikonen, J.C. Waltimo, A. Palotie, A.E. Paetau, et al., Expression of aspartylglucosaminidase in human tissues from normal individuals and aspartylglucosaminuria patients, J. Histochem. Cytochem. 41 (1993) 981–989.
[154] S. Tomatsu, T. Nishioka, A.M. Montaño, M.A. Gutierrez, O.S. Pena, K.O. Orii, et al.,

Mucopolysaccharidosis IVA: identification of mutations and methylation study in GALNS gene, J. Med. Genet. 41 (2004) e98.
[155] S. Tomatsu, K. Sukegawa, G.G. Trandafirescu, M.A. Gutierrez, T. Nishioka, S. Yamaguchi, et al., Differences in methylation patterns in the methylation boundary region of IDS gene in Hunter syndrome patients: implications for CpG hot spot mutations, Eur. J. Hum. Genet. 14 (2006) 838–845, http://dx.doi.org/10.1038/sj.ejhg.5201615.
[156] B.E. Kennedy, A.S. Hundert, D. Goguen, I.C.G. Weaver, B. Karten, Presymptomatic alterations in amino acid metabolism and DNA methylation in the cerebellum of a murine model of Niemann-Pick type C disease, Am. J. Pathol. 186 (2016) 1582–1597, http://dx.doi.org/10.1016/j.ajpath.2016.02.012.
[157] C. Auray-Blais, M. Boutin, Novel gb(3) isoforms detected in urine of fabry disease patients: a metabolomic study, Curr. Med. Chem. 19 (2012) 3241–3252.
[158] M. Abaoui, M. Boutin, P. Lavoie, C. Auray-Blais, Tandem mass spectrometry multiplex analysis of methylated and non-methylated urinary Gb3 isoforms in Fabry disease patients, Clin. Chim. Acta 452 (2016) 191–198, http://dx.doi.org/10.1016/j.cca.2015.11.018.
[159] A. Hübner, T. Metz, A. Schanzer, S. Greber-Platzer, C.B. Item, Aberrant DNA methylation of calcitonin receptor in Fabry patients treated with enzyme replacement therapy, Mol. Genet. Metab. Rep. 5 (2015) 1–2, http://dx.doi.org/10.1016/j.ymgmr.2015.08.002.
[160] C.M. Simonaro, J.-H. Park, E. Eliyahu, N. Shtraizent, M.M. McGovern, E.H. Schuchman, Imprinting at the SMPD1 locus: implications for acid sphingomyelinase-deficient Niemann-Pick disease, Am. J. Hum. Genet. 78 (2006) 865–870, http://dx.doi.org/10.1086/503750.
[161] A.S. de Mello, I.R.V. da Silva, G.P. Reinaldo, G.P. Dorneles, J. Cé, P.D. Lago, et al., The modulation of inflammatory parameters, brain-derived neurotrophic factor levels and global histone H4 acetylation status in peripheral blood of patients with Gaucher disease type 1, Clin. Biochem. 50 (2017) 228–233, http://dx.doi.org/10.1016/j.clinbiochem.2016.11.014.
[162] M.T. Queiroz, V.G. Pereira, C.C. do Nascimento, V. D'Almeida, The underexploited role of non-coding RNAs in lysosomal storage diseases, Front. Endocrinol. 7 (2016) 133, http://dx.doi.org/10.3389/fendo.2016.00133.
[163] L.B. Frankel, C. Di Malta, J. Wen, E.-L. Eskelinen, A. Ballabio, A.H. Lund, A non-conserved miRNA regulates lysosomal function and impacts on a human lysosomal storage disorder, Nat. Commun. 5 (2014) 5840, http://dx.doi.org/10.1038/ncomms6840.
[164] N. Dasgupta, Y.-H. Xu, R. Li, Y. Peng, M.K. Pandey, S.L. Tinch, et al., Neuronopathic Gaucher disease: dysregulated mRNAs and miRNAs in brain pathogenesis and effects of pharmacologic chaperone treatment in a mouse model, Hum. Mol. Genet. 24 (2015) 7031–7048, http://dx.doi.org/10.1093/hmg/ddv404.
[165] M. Siebert, W. Westbroek, Y.-C. Chen, N. Moaven, Y. Li, A. Velayati, et al., Identification of miRNAs that modulate glucocerebrosidase activity in Gaucher disease cells, RNA Biol. 11 (2014) 1291–1300, http://dx.doi.org/10.1080/15476286.2014.996085.
[166] E.I. Ginns, S.K.-K. Mak, N. Ko, J. Karlgren, S. Akbarian, V.P. Chou, et al., Neuroinflammation and α-synuclein accumulation in response to glucocerebrosidase deficiency are accompanied by synaptic dysfunction, Mol. Genet. Metab. 111 (2014) 152–162, http://dx.doi.org/10.1016/j.ymgme.2013.12.003.
[167] M. Maceyka, S. Milstien, S. Spiegel, The potential of histone deacetylase inhibitors in Niemann-Pick type C disease, FEBS J. 280 (2013) 6367–6372, http://dx.doi.org/10.1111/febs.12505.
[168] N.H. Pipalia, C.C. Cosner, A. Huang, A. Chatterjee, P. Bourbon, N. Farley, et al., Histone deacetylase inhibitor treatment dramatically reduces cholesterol accumulation in Niemann-Pick type C1 mutant human fibroblasts, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 5620–5625, http://dx.doi.org/10.1073/pnas.1014890108.
[169] A.B. Munkacsi, F.W. Chen, M.A. Brinkman, K. Higaki, G.D. Gutiérrez, J. Chaudhari, et al., An “exacerbate-reverse” strategy in yeast identifies histone deacetylase inhibition as a correction for cholesterol and sphingolipid transport defects in human Niemann-Pick type C disease, J. Biol. Chem. 286 (2011) 23842–23851, http://dx.doi.org/10.1074/jbc.M111.227645.
[170] Z.T. Wehrmann, T.W. Hulett, K.L. Huegel, K.T. Vaughan, O. Wiest, P. Helquist, et al., Quantitative comparison of the efficacy of various compounds in lowering intracellular cholesterol levels in Niemann-Pick type C fibroblasts, PLoS One 7 (2012) e48561, , http://dx.doi.org/10.1371/journal.pone.0048561.
[171] J. Lu, C. Yang, M. Chen, D.Y. Ye, R.R. Lonser, R.O. Brady, et al., Histone deacetylase inhibitors prevent the degradation and restore the activity of glucocerebrosidase in Gaucher disease, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 21200–21205, http://dx.doi.org/10.1073/pnas.1119181109.
[172] C. Yang, S. Rahimpour, J. Lu, K. Pacak, B. Ikejiri, R.O. Brady, et al., Histone deacetylase inhibitors increase glucocerebrosidase activity in Gaucher disease by modulation of molecular chaperones, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 966–971, http://dx.doi.org/10.1073/pnas.1221046110.
[173] E. Beutler, Discrepancies between genotype and phenotype in hematology: an important frontier, Blood 98 (2001) 2597–2602, http://dx.doi.org/10.1182/blood.V98.9.2597.
[174] M. Malnar, S. Hecimovic, N. Mattsson, H. Zetterberg, Bidirectional links between Alzheimer's disease and Niemann-Pick type C disease, Neurobiol. Dis. 72 (Pt A) (2014) 37–47, http://dx.doi.org/10.1016/j.nbd.2014.05.033.
[175] E.M. Coleman, T.N. Walker, J.E. Hildreth, Loss of Niemann Pick type C proteins 1 and 2 greatly enhances HIV infectivity and is associated with accumulation of HIV Gag and cholesterol in late endosomes/lysosomes, Virol. J. 9 (2012) 31, http://dx.doi.org/10.1186/1743-422X-9-31.
[176] M. Afzali, A. Nakhaee, S.P. Tabatabaei, K. Tirgar-Fakheri, M. Hashemi, Aberrant promoter methylation profile of Niemann-Pick type C1 gene in cardiovascular disease, Iran. Biomed. J. 17 (2013) 77–83.
[177] Y. Li, P. Li, H. Liang, Z. Zhao, M. Hashimoto, J. Wei, Gaucher-associated Parkinsonism, Cell. Mol. Neurobiol. 35 (2015) 755–761, http://dx.doi.org/10.1007/s10571-015-0176-8.