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Article *in* Russian Journal of Genetics · October 2017

DOI: 10.1134/S1022795417100106

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ISSN 1022-7954, Russian Journal of Genetics, 2017, Vol. 53, No. 10, pp. 1072–1079. © Pleiades Publishing, Inc., 2017.
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REVIEWS
AND THEORETICAL ARTICLES

Epigenetic Silencing of Genomic Structural Variations

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Received December 7, 2016; in final form, March 1, 2017

Abstract—A great amount of copy number variations (CNVs) are identified in the human genome. Most of them are neutral; nevertheless, the role of CNVs in the pathogenesis of hereditary diseases is still significant. Especially, this is important for neuropsychiatric disorders, such as intellectual disability and autism. When analyzing the CNV-associated diseases, the controversial question is to distinguish the pathogenic CNVs among common polymorphic variants and to predict the disease risk in other children of the family. Unfortunately, the mechanisms of phenotypic expression and incomplete penetrance of CNVs remain largely unknown. Currently, incomplete penetrance and variable expressivity of CNVs are attributed mainly to allelic interaction of different genetic variations. However, epigenetic mechanisms of gene expression regulation in the context of structural variation of the genome are poorly explored. It is possible that epigenetic modifications of the genome regions with CNVs may underlie the understanding of ways of phenotypic manifestations of structural variations in the human genome.

Keywords: meiotic silencing, genomic structural variations, incomplete penetrance, paramutations, DNA methylation, intellectual disability, autism

DOI: 10.1134/S1022795417100106

The development of the microarray-based technology made it possible to identify many DNA copy number variations (CNVs) in the human genome. About 90% of the CNVs overlap with the coding regions, indicating their possible role in the regulation of expression through the effect of the dose or gene position. The exact number of hereditary diseases caused by CNVs remains unknown, but it is clear that it can be very significant. It was shown that CNVs causes 15–25% of cases of undifferentiated intellectual disability [1]. Another frequent disease associated with CNVs is autism. In different countries, the prevalence of autism varies and reaches up to 1 per 68 children in the United States [2]. In the Russian Federation, according to official statistics of the Scientific Center for Mental Health from 1999, the incidence of autism was 1 per 385 individuals (more recent statistics are extremely incomplete because of the lack of officially approved national principles for such recording) [3]. From 6 to 10% of cases of autism and autism spectrum disorders are associated with CNVs [4].

It should be noted that a significant proportion of CNVs identified in patients with intellectual disability are inherited [5]. Taking into consideration this fact, as well as the presence of a significant number of CNVs in the genome of healthy individuals, an important problem is the assessment of the potential pathogenetic significance of various CNVs. The aforementioned facts indicate that a significant part of the structural variations of the genome have incomplete penetrance. However, currently there are almost no data explaining the mechanisms for implementing the incomplete penetrance of CNVs, which in turn causes an underestimation of the pathogenetic significance of CNVs. This leads to difficulties in detecting pathogenetically significant chromosomal rearrangements in patients, as well as uncertainty in the prognosis of the inheritance of such disorders.

On the other hand, CNVs can potentially lead to changes in the expression activity of genes localized on an intact homolog without changing the nucleotide sequence. Cases with a similar type of inheritance have recently been described in families with children with autism and autism spectrum disorders [6], as well as in families with hereditary forms of cancer [7]. The explanation of the mechanisms of incomplete penetrance of CNVs will lead to a more complete understanding of the mechanisms of their inheritance, which will significantly improve the medical genetic counseling of patients with CNV-associated diseases. In this review, a hypothesis is proposed that explains the incomplete penetrance of CNVs owing to the origin of inherited epigenetic modifications of the genome in the sites of localization of CNVs.

Table 1. Penetrance of microduplications and microdeletions (according to [10–12])

Chromosomal region with aberration	Type of aberration	CNV penetrance in patients with intellectual disability and ASD, % (95% CI)		CNV penetrance in patients with schizophrenia, % (95% CI)	
Reference		[10]	[11]	[11]	[12]
1q21.1	Deletion	36.9 (23.0–55.0)	35.0 (18.0–67.0)	5.2 (2.5–11.0)	6.1 (3.0–12.0)
1q21.1	Duplication	29.1 (16.9–46.8)	18.0 (10.0–33.0)	2.9 (1.3–6.3)	–
2p16.3	Deletion	–	26.0 (16.0–80.0)	6.4 (2.5–8.3)	2.0 (1.0–4.0)
3q29	Deletion	–	53.0 (15.0–100.0)	18 (4.7–67.0)	–
7q11.23	Duplication	–	44.0 (13.0–100.0)	6 (1.4–20.0)	–
15q11.2	Deletion	10.4 (8.45–12.7)	11.0 (8.2–14.0)	2.0 (1.4–2.7)	2.0 (1.0–3.0)
15q11-q13 (Prader-Willi/ Angelman syndrome)	Duplication	–	54.0 (25.0–100.0)	4.2 (1.4–12.0)	–
15q13.3	Deletion	–	35.0 (19.0–62.0)	4.7 (2.2–9.9)	7.4 (3.0–16.0)
16p13.11	Duplication	–	8.4 (5.7–13.0)	2.2 (1.3–3.7)	2.4 (1.0–4.0)
16p11.2	Deletion	46.8 (31.5–64.2)	23.0 (8.4–63.0)	2.6 (0.8–9.2)	
16p11.2	Duplication	27.2 (17.4–40.7)	26.0 (18.0–43.0)	8.0 (4.3–14.0)	6.9 (3.0–14.0)
16p12.1	Deletion	12.3 (7.91–18.8)	–	–	–
16p13.11	Deletion	13.1 (7.91–21.3)	–	–	–
17q12	Deletion	34.4 (13.7–70.0)	39.0 (13.0–100.0)	4.0 (0.8–18.0)	6.7 (3.0–17.0)
17q12	Duplication	21.1 (10.6–39.5)	–	–	–
22q11.2 (DiGeorge syndrome)	Deletion	–	88.0 (53.0–100.0)	12 (6.5–18.0)	55.3 (18.0–97.0)
22q11.21	Duplication	21.9 (14.7–31.8)	–	–	–

INCOMPLETE PENETRANCE OF CNV AND PARAMUTATIONS

The human genome is characterized by high variability in CNVs, the sizes of which vary from several thousand to one million base pairs. A significant part (about 7 million CNVs) is currently interpreted as polymorphic variants [8], whereas only 27000 CNVs (0.4%) have been shown to have pathogenetic significance [9]. More impressive are the results of mapping of polymorphic CNVs—they cover 78% of the human genome and about 95% of all transcripts in the sample of healthy individuals. The figures cited indicate the existence of systemic mechanisms that ensure the incomplete penetrance of CNV.

The availability of such mechanisms is also evidenced by data on the evaluation of the penetrance of pathogenetically significant frequent CNVs, which is about 30% on average in patients with intellectual disability [10, 11] and only 8% in individuals with schizophrenia [11, 12] (Table 1).

Earlier, we also described cases of inheritance of pathogenetically significant duplications in children with intellectual disability from clinically healthy fathers. In total, two families with such duplications were identified. In the first case, a 351 kb microduplication at 18p11.32 was inherited from a healthy father. The duplication included the *METTL4*, *NDC80*, *CBX3P2*, and *SMCHD1* genes [13]. In the second case, the microduplication included the single *CNTN6* gene (3p26.3) and was also inherited from the father [14].

Currently, the incomplete penetrance of CNVs is explained mainly by the allelic interactions of various genetic variations [15, 16]. In particular, such variants of interaction as CNV–point mutations and CNV–CNV are considered. For example, the phenotypic manifestation of the Bard–Biddle syndrome, a disease with an autosomal recessive type of inheritance, may be due to a combination of microdeletions in the *NPHP1* gene on one allele and a point mutation on another (c.14G>T (p.Arg5Leu) in the *NPHP1* gene) [17]. CNV–CNV allelic interactions were identified in the analysis of the epistatic interaction of genes localized in regions of two different CNVs [18]. The initial analysis was carried out by comparing the databases of protein-protein interactions with the databases of CNVs. Thus, 37 paired CNVs with pairs of genes localized within them with the possibility of protein-protein interactions were identified. In a further study, a CNV–CNV interaction associated with the regulation of the expression of the *TP53TG3* gene by the *TP53* gene was identified. This study shows the possi-

bility of formation of incomplete penetrance through the epistatic regulation of genes caused by the CNV–CNV interaction. However, the fact that this mechanism is stochastic and rather rare indicates that incomplete penetrance caused by allelic interactions is the exception rather than the rule.

Another explanation for the incomplete penetrance of CNVs can be the epigenetic mechanisms. One of these pathways is known in plants, where it leads to the appearance of paramutations. Paramutations are the interaction between homologous DNA sequences localized on different chromosomes, leading to a change in the expression activity of the gene on one of the homologs without changing the nucleotide sequence and transmitted through mitosis and meiosis [19]. For the first time, paramutations were discovered in maize, in which the trans-interaction of homologous chromosomes and the inhibition of the expression of one of the alleles of the *red1* locus (paramutable) by another allele (paramutagenic) was identified [20, 21]. Subsequently, paramutations were also found in other organisms, including insects and nematodes [22]. The connection between the structural variations of the genome and the appearance of paramutations is indicated by the fact that all known examples of loci subject to paramutation have in their composition or in the immediate environment repeated DNA sequences or inverted duplications [23]. Traditionally, meiotic silencing due to RNA interference, using transcripts from repeated DNA sequences, is considered as the molecular mechanism underlying the paramutations. To ensure the expression of these sequences, it seems that it is necessary to form a specific conformation of chromatin containing repeats [23]. Such chromatin conformation can potentially be provided by the looping of unpaired DNA segments on one of the homologs. Mechanisms for maintaining transcriptional silencing during the next generation are associated with DNA methylation. In plants, the origin of paramutations directly depends on the RNA-dependent DNA methylation mechanism [24, 25], which plays an important role in establishing methylation of repeated DNA sequences, especially near genes [26, 27]. In addition to paramutations, methylation is the main mechanism for suppressing the transcriptional activity of transposons and unpaired DNA sequences, as well as regulating the dose of genes localized on sex chromosomes.

MEIOTIC SILENCING

In meiosis, both in female and in male germ cells, the mechanism of meiotic silencing by unpaired DNA (MSUD) is described, which is the repression of unpaired DNA sequences with the help of small interfering RNA (siRNA) in meiosis prophase I [28, 29]. Currently, the exact mechanism for detecting of unpaired genomic regions is not fully understood. However, it is assumed that RNA transcribed from an unpaired homolog during meiosis triggers a gene suppression mechanism by RNA interference, followed by methylation of CG dinucleotides in an unpaired region and next to it [5]. Genes involved in meiotic silencing are homologs of genes involved in RNA interference in plants, fungi, and animals. These genes include *Sad-1* (encodes a protein that has significant homology with RNA-dependent RNA polymerases), *dcl-1/sms-3* (Dicer-like exonuclease), *sms-2* (Argonaute homolog), *qip* (converts RNA duplexes of siRNA), etc. The Yizhou Wang group [30] identified meiotic-silencing-associated small interfering RNAs (masiRNAs), and their relationship to meiotic silencing of unpaired DNA segments was demonstrated.

Further fixation of this state via methylation of CpG sites depends on the type of gametogenesis. It seems that the differential nature of the establishment of DNA methylation in female and male germ cells can lead to the transmission of epigenetic modifications established in female meiosis to the next generation.

In addition to the inactivation of transposons, a similar mechanism functions also in the meiotic sex chromosome inactivation (MSCI) [31]. In meiosis prophase I, together with conjugation of autosomes, the conjugation of pseudoautosomal regions of sex chromosomes occurs. All unpaired sections of the sex chromosomes undergo meiotic silencing by a mechanism analogous to the mechanism of inactivation of retrotransposons.

A similar mechanism works also in germ cells with Robertsonian translocations [32]. The formation of a trivalent leads to a disruption of the chromosome conjugation involved in translocation, which in turn leads to the silencing of significant regions of DNA on these chromosomes. This creates a deficit of proteins involved in RNA interference and causes a decrease in the effectiveness of inactivation of sex chromosomes. These observations support the fact that the mechanisms of inactivation of unpaired DNA segments are, apparently, universal and do not depend on targets for inactivation by meiotic silencing.

MEIOTIC SILENCING OF CNV

The idea of the possible role of DNA methylation in inheritance of deletions in humans was first expressed by Pembrey et al. [6] when analyzing the phenomenon of reverse discordance. The authors analyzed the pedigrees described by Ceroni et al. [33], in which families of children with CAS syndrome (childhood apraxia of speech) and a 21.3 kb deletion in the *ZNF277* gene were studied. This microdeletion affects the so-called autism susceptibility locus (AUTS1), which is associated with autism, but its frequency in patients with CAS syndrome was almost three times higher than in children with ASD. The peculiarities in the pedigree, noted by the Pembrey

group [6], consisted in the inheritance of this microdeletion: in some families, cases of the CAS-syndrome phenotype were revealed not only in the proband with the deletion but also in the siblings without it. Such a mismatch of genotypes with a similar phenotype the authors called a reverse discordance. They hypothesized meiosis mismatch methylation (3M). This hypothesis suggests that, in prophase I of the oogenesis, the conjugation of the chromosome carrying the microdeletion with the normal homolog increases the chance of abnormal methylation owing to the looping of the intact sequence on the normal homolog. This, in turn, leads to suppression of the functional activity of genes localized on an intact chromosome. In fact, the phenomenon of reverse discordance, described by Pembrey et al. [6], corresponds to paramutations, but in the format of interaction of homologous chromosomes. In the case of paramutations, in their classical definition, the interaction between homologous DNA sequences localized on different chromosomes causes the change in expression activity of genes on the homolog without changing the nucleotide sequence, and the change in expression on the intact homolog is transmitted through mitosis and meiosis [19].

On the basis of the results of a study of the pedigrees of patients with ASD who were carriers of homozygous microdeletion of the *ZNF277* gene, Pembrey et al. [6] identified several families in which the phenomenon of reverse discordance was observed and suggested that the presence of the disease in the absence of a deletion in a patient is due to methylation of the intact homolog. In addition, similar observations were made in patients with ASD [34]. A family was identified in which the presence of the paramutation phenomenon associated with deletion of the *OXTR* gene was also shown. Two children had an ASD phenotype: one inherited a microdeletion from the mother, and the second child had methylation of the gene on a normal homolog also inherited from the mother [34].

Methylation of unpaired DNA regions in maternal germ cells is confirmed by studies on the methylation status in balanced translocations and inversions of maternal origin in the Beckwith–Wiedemann syndrome [35]. It is shown that the transfer of chromosomes with rearrangements through oogenesis leads to local hypermethylation of DNA in the region with aberrations. DNA methylation is observed not only directly in the regions with translocations and inversions but also in adjacent areas of chromosomes. The fact that meiotic silencing is observed not only in deletions but also in other cases of nonhomologous binding of DNA segments, in particular, in the case of small inversions and translocations, suggests that the 3M hypothesis does not describe all cases associated with meiotic silencing; it does not take into account the probable role of meiotic silencing of microduplications.

In addition, sex differences in the meiotic silencing mechanism should be taken into account, since DNA methylation is established differently in female and male gametogenesis [36]. In oogenesis, DNA methylation occurs in meiosis prophase I, after conjugation of homologous chromosomes, during the long arrest of meiosis from the embryonic period of development and up to puberty. If there is a deletion on one of the homologous chromosomes when a synaptonemal complex is formed, then a region of DNA without a deletion, localized on a normal homologous chromosome, is looped and suppressed by noncoding RNA. Then, in oocytes during the arrest of meiosis, the repression of these sequences can potentially be fixed during the establishment of DNA methylation. The biological meaning of such a process can be the protection from new inserts of active retrotransposons and restriction of their expression during the long arrest of meiosis. At the completion of meiosis, this leads to the formation of two types of gametes—with deletion and without deletion; on the chromosome without deletion, the region homologous to the deleted sequence will be hypermethylated. If the expression of genes localized in such a hypermethylated region is regulated by DNA methylation, then this epigenetic modification may have certain phenotypic consequences. The origin of such hypermethylated regions can be considered as a paramutation, where the deletion on one homolog is a paramutagen, and the hypermethylated region on another homolog is a paramutable allele.

In the presence of duplication in the germ line during meiosis prophase I in oocytes, a duplicated region of DNA is looped and methylated. Later in meiosis, two types of gametes are formed, carrying a normal or duplicated allele. In this case, the expression of genes localized in the duplicated DNA region can be suppressed by hypermethylation of their promoters. This mechanism can explain the incomplete penetrance and variable expressivity of some CNVs, represented by an increase in the copy number of DNA regions.

If the methylation of unpaired DNA occurs in the oocytes, the question remains as to how much it is maintained during the epigenetic reprogramming wave in the blastocyst. It was previously believed that both reprogramming waves demethylate most of the CpG sites in the genome, but a group of Chinese scientists headed by Tang and Qiao [37, 38] recently measured the average level of cell methylation in a human blastocyst. They found that DNA is not fully demethylated—43% of CpG sites remain methylated. These data were obtained using massive parallel sequencing technology, while the previous conclusions were mainly made by analyzing fluorescently labeled antibodies to 5-methylcytosine. The method for estimating the amount of 5-methylcytosine mainly reflects the methylation of recurring sequences that represent the greater part of the human genome, such

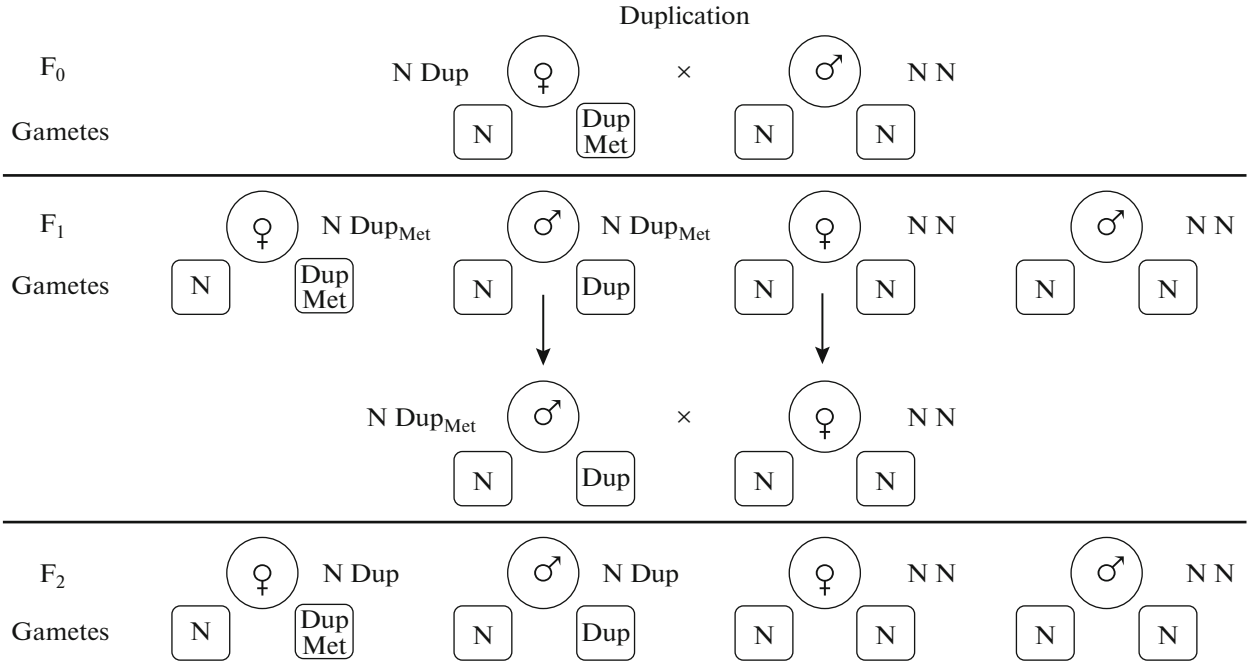

Fig. 1. The scheme of the influence of methylation of unpaired DNA regions in male and female meiosis on the phenotype when chromosomal microduplications are inherited. N—intact allele, Dup—allele with duplication, Dup_{Met}—methylated allele with duplication.

as LINE and SINE. It is possible that unique DNA sequences may not be affected during the reprogramming of blastocyst cells or that they are affected but not to such a global extent as repeated DNA sequences. This suggests that, at least for some genes, methylation of unpaired DNA established in female meiosis can be inherited without being reprogrammed in the zygote and during the first cleavage divisions.

In the male germ line, demethylation occurs during mitotic divisions of primordial cells in embryogenesis, during which almost all previously established epigenetic modifications are removed (residual methylation is about 7.8%), followed by DNA hypermethylation and the establishment of a specific *de novo* methylation profile [38]. As in oocytes, in male meiosis, apparently, unpaired regions are looped during the conjugation of homologous chromosomes and their repression by noncoding RNAs occurs. However, no further methylation of the DNA of these sequences occurs. In particular, this can lead to demethylation of DNA in regions with duplications on chromosomes of paternal origin and phenotypic manifestation of chromosomal imbalance in the next generation. This type of inheritance was observed in the family with 3p26.3 microduplication, which involves the single *CNTN6* gene: the microduplication in a patient with intellectual disability and developmental anomalies was inherited from a clinically healthy father, who, in turn, received it from his healthy mother [14].

INHERITANCE AND PENETRANCE OF CNVs IN LIGHT OF CNV MEIOTIC SILENCING HYPOTHESIS

The hypothesis of meiotic silencing of the CNV proposed in this paper makes it possible to evaluate the inheritance and penetrance of various CNVs depending on the parental origin of the anomaly. If the CNV is a duplication of chromosomal material, then the duplicated part is absent on the second homolog and remains unpaired. This potentially leads to its suppression owing to the mechanism of meiotic silencing, which acts in the meiosis of both female and male germ cells. The following wave of methylation in female germ cells can lead to the fixation of the repression of duplicated sequences by DNA methylation. As a result, two types of gametes are formed in female meiosis: (1) normal and (2) containing duplication with increased DNA methylation level (Fig. 1). Thus, in the next generation, genes in the regions of duplications inherited from the mother can (1) have the same methylation status as in the mother's cells if she received this duplication from her mother or (2) be hypermethylated relative to the somatic cells of the mother if she inherited this duplication from her father, or this aberration appeared *de novo* in the germ line after meiosis.

In male meiosis, the methylation wave occurs long before the formation of the synaptonemal complex and, apparently, does not affect the sequences suppressed by meiotic silencing. Therefore, genes in the region of unpaired duplications hypomethylated ear-

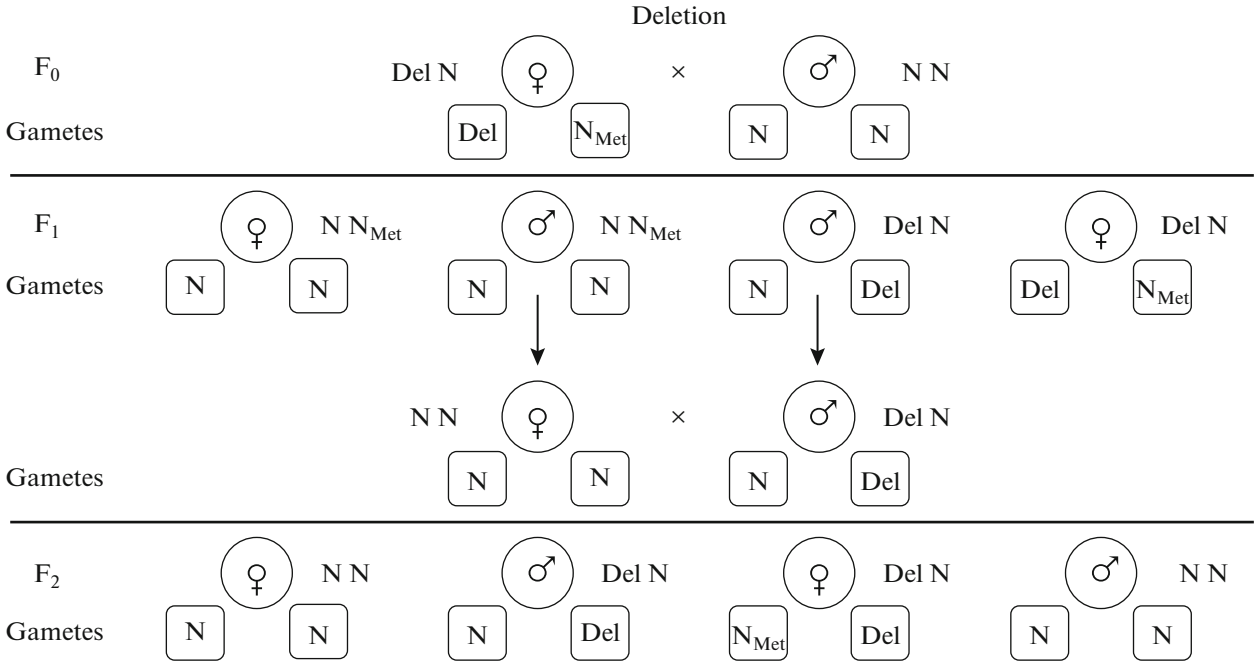

Fig. 2. The scheme of the influence of methylation of unpaired DNA regions in male and female meiosis on the phenotype when chromosomal microdeletions are inherited. N—intact allele, N_{Met}—intact methylated allele, Del—allele with deletion.

lier during the reprogramming of the genome of male germ cells remain unmethylated. This should lead to the situation where in genes of offspring located in the regions of duplications inherited from the father, the level of methylation of genes should be lower compared to that in the somatic cells of the father (if he, in turn, inherited this duplication from his mother) or comparable with it (if he inherited it from his father). All in all, such a mechanism should lead to an increase in the level of DNA methylation in regions with duplications inherited from the mother and to their incomplete penetrance. The same duplications inherited from the father can lead to the formation of a pathological phenotype by demethylation in paternal meiosis.

In the case of deletion, during the formation of the synaptonemal complex, on the contrary, the normal sequence on the second intact homolog remains unpaired. In female meiosis, this leads to its methylation and the formation of gametes of two types: (1) with a deletion and (2) with a homologous region with an increased level of DNA methylation (Fig. 2). In accordance with the proposed hypothesis, it is expected that, in the presence of a deletion in the mother, but not in the offspring, the level of DNA methylation of the genes located in the region of deletions inherited from the mother will be increased. On the contrary, if the deletion is present in the somatic cells of the offspring, the methylation level in its region will be determined by the DNA sequences obtained from the father and will not differ from them in the degree of methylation. The same will be observed for genes in the region of deletions inherited from the father. Thus, differences in the methylation index should be observed for genes in the region of deletions inherited from the mother.

In general, when inheriting deletions of maternal origin, such a mechanism should lead to the origin of paramutations in the next generation: a part of the offspring may have a pathological phenotype owing to the presence of an inherited deletion; in other offspring, a similar phenotype may be due to disturbance of the gene function in the deletion owing to hypermethylation without the inheritance of the deletion itself.

Most likely, the proposed hypothesis is not universal, and the phenotypic manifestation of a part of the inherited CNVs will not follow the described model. First, we must not forget that the expression of not all genes is regulated by methylation. Also, theoretically, the possible reasons for the discrepancy may be changes in the epigenetic status of the genes under consideration during one of the reprogramming waves: (1) during the active demethylation of the predominantly paternal genome in the zygote immediately after fertilization; (2) during the passive demethylation of both genomes during the first cleavage divisions; (3) when establishing the tissue-specific pattern of methylation during the following tissue differentiation. In addition, the exceptions may be due to the pattern of methylation during meiotic silencing, namely, that it is random. The random methylation of CpG sites may result in the methylation of the promoter region not being sufficient to inhibit the expression of genes in the CNV region.

The proposed model can explain the effects observed during the inheritance of genomic structural variations—the incomplete penetrance of CNV and the phenomenon of paramutations that may be caused by the meiotic silencing of unpaired DNA. Further work on clarifying the mechanisms for the implementation of incomplete penetrance and paramutations will allow more accurate prediction of the phenotypic manifestations of CNV in the offspring, which is a critical moment in medical genetic counseling under the increasing application of methods of whole genome analysis in medicine.

ACKNOWLEDGMENTS

This work was supported by Russian Science Foundation, project no. 16-15-10229.

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Translated by A. Kashevarova