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Outcomes of ROHs (runs of homozygosity)/ LCSHs (long contiguous stretches of homozygosity) spanning the imprinted loci of chromosomes 7, 11 and 15 among children with neurodevelopmental disorders

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Abstract

Background: Runs of homozygosity or long contiguous stretches of homozygosity (ROHs/LCSHs) are common in the human genome. ROHs/LCSHs spanning the imprinted loci have been previously associated with neurodevelopmental disorders. However, the outcomes of these epigenomic variations remain enigmatic. Accordingly, there is a need to evaluate the ROHs/LCSHs outcomes covering the imprinted loci. **The aim of the study:** To describe the outcomes of ROHs/LCSHs spanning the imprinted loci of chromosomes 7, 11 and 15 among children with neurodevelopmental disorders. **Materials and methods:** Using molecular karyotyping by high-resolution SNP array, we obtained data on ROHs/LCSHs from 772 children with neurodevelopmental disorders and congenital malformations. ROHs/LCSHs spanning the imprinted loci of chromosomes 7, 11 and 15 were additionally analyzed by original bioinformatic approaches to uncover the pathogenic value. **Results:** ROHs/LCSHs spanning the imprinted loci of chromosomes 7, 11 and 15 were detected in 67 (8.7%) individuals. Bioinformatic analyses demonstrated that ROHs/LCSHs affecting imprinted loci of chromosome 7 are not associated with clearly recognizable outcomes. Alternatively, ROHs/LCSHs affecting imprinted loci of chromosome 11 (11p15.5p15.4; Beckwith-Wiedemann syndrome) and chromosome 15 (15q11.2; Prader-Willi/Angelman syndromes) were associated with distinct outcomes as shown by bioinformatics approaches. Prader-Willi/Angelman syndrome loci were affected in 18 cases (2.3%), whereas Beckwith-Wiedemann syndrome loci were affected in 10 cases (1.3%). **Conclusion:** Analysis of the outcomes of ROHs/LCSHs spanning the imprinted loci of chromosomes 7, 11 and 15 has demonstrated that the epigenomic changes affecting 11p15.5p15.4, and 15q11.2 (28

cases; 3.6%) are associated with atypical forms of Beckwith-Wiedemann and Prader-Willi/Angelman syndromes, respectively. The outcomes of ROHs/LCSHs in chromosome 7 have not been found convincing for a definitive conclusion about the phenotypic effects. Molecular karyotyping by SNP array is a valuable diagnostic technique offering opportunities for detecting these common but underestimated epigenetic causes for neurodevelopmental disorders and congenital malformations.

Keywords: chromosome; runs of homozygosity; long contiguous stretches of homozygosity; neurodevelopmental disorders; SNP array; bioinformatics; cytogenomics

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Introduction. Runs of homozygosity or long contiguous stretches of homozygosity (ROHs/LCSHs) are losses of heterozygosity spanning more than 1 Mb at specific chromosomal loci (i.e. segmental uniparental disomy or a pair of homologous chromosomal loci larger than 1 Mb derived from a single parent). Currently, these epigenomic variations are intimately linked to parental consanguinity (the amount of large ROHs/LCSHs (>3 Mb) per individual genome is high) and autosomal recessive diseases (ROHs/LCSHs involve a locus containing a mutated gene associated with an autosomal recessive condition). ROHs/LCSHs may be occasionally associated with other pathological conditions. However, such reports are rare and irreproducible [1, 2]. Nonetheless, there is a type of ROHs/LCSHs clearly associated with congenital malformations and neurodevelopmental disorders detectable in at least 5% of the affected individuals. More precisely, these are ROHs/LCSHs spanning the loci containing imprinted gene clusters of chromosomes 7, 11 and 15 (alterations to these genes/gene clusters cause imprinting disorders) [3, 4]. These findings are reproducible in unrelated neurodevelopmental cohorts [5]. Epigenetic alterations within these imprinted gene clusters/genomic loci lead to an appreciable impact on molecular and cellular processes [6]. Accordingly, ROHs/LCSHs spanning chromosomal regions 7q21.11/7q21.3, 7q32.2, 11p15.5p15.4 and 15q11.2 containing diseases-associated imprinted genes are likely to cause deregulation of genomic imprinting and, thereby, to produce disease phenotypes [7].

Still, there are a number of unanswered questions surrounding the outcomes of ROHs/LCSHs spanning the imprinted loci of chromosomes 7, 11 and 15, which are generally related to phenotypic and molecular consequences of these epigenomic variations.

To answer these questions, applications of sophisticated methods of interpreting genomic or epigenomic variations are required. Recently, pathway-based classification of genomic variations to interpret the outcomes of alterations to genome has been proposed as a promising approach for medical genomics. The underlying basis for this bioinformatic technology is the analysis of genomic variations in the context of molecular and cellular pathways, which are able to be affected by the detected changes within an individual genome [8, 9, 10]. In the light of cytogenomic (chromosomal rearrangements and copy number variations) and (cyto)epigenomic (ROHs/LCSHs), the technology has repeatedly been found effective [7, 8, 11]. Our experience evidences that the most efficient way to define the effect of genetic/epigenetic changes on molecular and cellular pathways by the bioinformatic technology is to use systems analysis of the whole set of genes affected by (epi)genomic defects [12]. Thus, to succeed in studying the outcomes of ROHs/LCSHs spanning the imprinted loci of chromosomes 7, 11 and 15, this bioinformatic approach to interpretation of epicytogenomic variations should be applied.

Genomic imprinting disorders have been systematically studied by a variety of genomic,

epigenetic and cytogenetic/cytogenomic techniques. Apart from ROHs/LCSHs, numerous mechanisms for imprinting defects at 7q21.11/7q21.3, 7q32.2, 11p15.5p15.4 and 15q11.2 produced by genomic rearrangements, whole-chromosome uniparental disomy, and methylation defects are known [13, 14, 15]. Moreover, several studies highlight imprinted gene contribution to neurodevelopmental and neuropsychiatric diseases [16]. More specific defects (e.g. mosaic methylation patterns) are able to cause disease-associated alterations to imprinted genes mapped to 15q11.2 [17]. Imprinting defects at chromosomes 7q21.11/7q21.3/7q32.2, 11p15.5p15.4 and 15q11.2 are associated with Silver-Russell, Beckwith-Wiedemann and Prader-Willi/Angelman syndromes, respectively [13, 18, 19, 20]. Consequently, one may suggest that ROHs/LCSHs spanning these imprinted loci are likely to cause atypical forms of the syndromes and/or neurodevelopmental disorders.

The aim of the study. Our study is aimed at evaluating the outcomes of ROHs/LCSHs spanning imprinted loci at 7q21.11/7q21.3/7q32.2, 11p15.5p15.4 and 15q11.2 in a large cohort of children with neurodevelopmental diseases and congenital malformations. Additionally, we aimed at determining the occurrence of pathogenic ROHs/LCSHs spanning the aforementioned regions and the applicability of molecular karyotyping by SNP array for the molecular diagnosis.

Materials and methods. Molecular karyotyping by SNP array (CytoScan HD Arrays by Affymetrix (Santa Clara, CA); ~2.7 billion markers and ~750,000 SNPs for detecting copy number variations and losses of heterozygosity) was applied to uncover ROHs/LCSHs in the Russian cohort of children with neurodevelopmental disorders (intellectual disability, autism, epilepsy) and congenital anomalies (n=772). The cohort was repeatedly described previously [3, 4, 21, 22]; SNP array performance was presented in details previously [21, 22, 23]. Addressing the outcomes of

ROHs/LCSHs spanning imprinted loci at 7q21.11/7q21.3/7q32.2, 11p15.5p15.4 and 15q11.2 was carried out using original bioinformatic methods. Briefly, epigenetic, proteomic/interatomic and metabolomic profiling of imprinted genes of chromosomes 7, 11 and 15 was bioinformatically evaluated using systems analysis and data fusion, as described elsewhere [21, 24, 25]. Imprinted genes affected by ROHs/LCSHs were highlighted according to Geneimprint database (<https://www.geneimprint.com/site/genes-by-species.Homo+sapiens.imprinted-All>). Parental consanguinity was determined according to well-known protocol as reported previously [26].

Results and discussion. Molecular karyotyping using high-resolution SNP array was successfully applied for uncovering ROHs/LCSHs spanning imprinted loci at 7q21.11/7q21.3/7q32.2, 11p15.5p15.4 and 15q11.2 (Fig.1). Sixty seven out of 772 (8.7%) children from the neurodevelopmental cohort were found to exhibit ROHs/LCSHs spanning the loci mentioned previously. Parental consanguinity was uncovered in 11 cases (1.4%). Three cases of parental consanguinity demonstrated ROHs/LCSHs spanning imprinted genes at 11p15.5p15.4 (n=1) and 15q11.2 (n=2). The remaining cases of parental consanguinity were not associated with imprinting defects at the aforementioned loci of chromosome 7, 11 and 15. ROHs/LCSHs spanning imprinted genes of chromosome 7 were found in 39 cases (5%), chromosome 11 – 10 cases (1.3%), and chromosome 15 – 18 cases (2.3%). ROHs/LCSHs spanning the imprinted locus at 7q21.11/7q21.3 recurrently (i.e. more than 2 times) encompassed following genes: *MAGI2*, *TFPI2*, *SGCE*, *PEG10*, *PPP1R9A*, and *DLX5*; 7q32.2 – *CPA4* and *MEST*; 11p15.5p15.4 – *H19*, *IGF2*, *INS*, *KCNQ1*, *KCNQ1DN*, and *CDKN1C*; 15q11.2 – *MKRN3*, *MAGEL2*, *NDN*, *NPAP1*, *SNRPN*, and *UBE3A*. The data obtained correlates with previous reports on ROHs/LCSHs spanning shortly the imprinted loci in individuals with neurodevelopmental disorders and congenital malformations [3, 4].

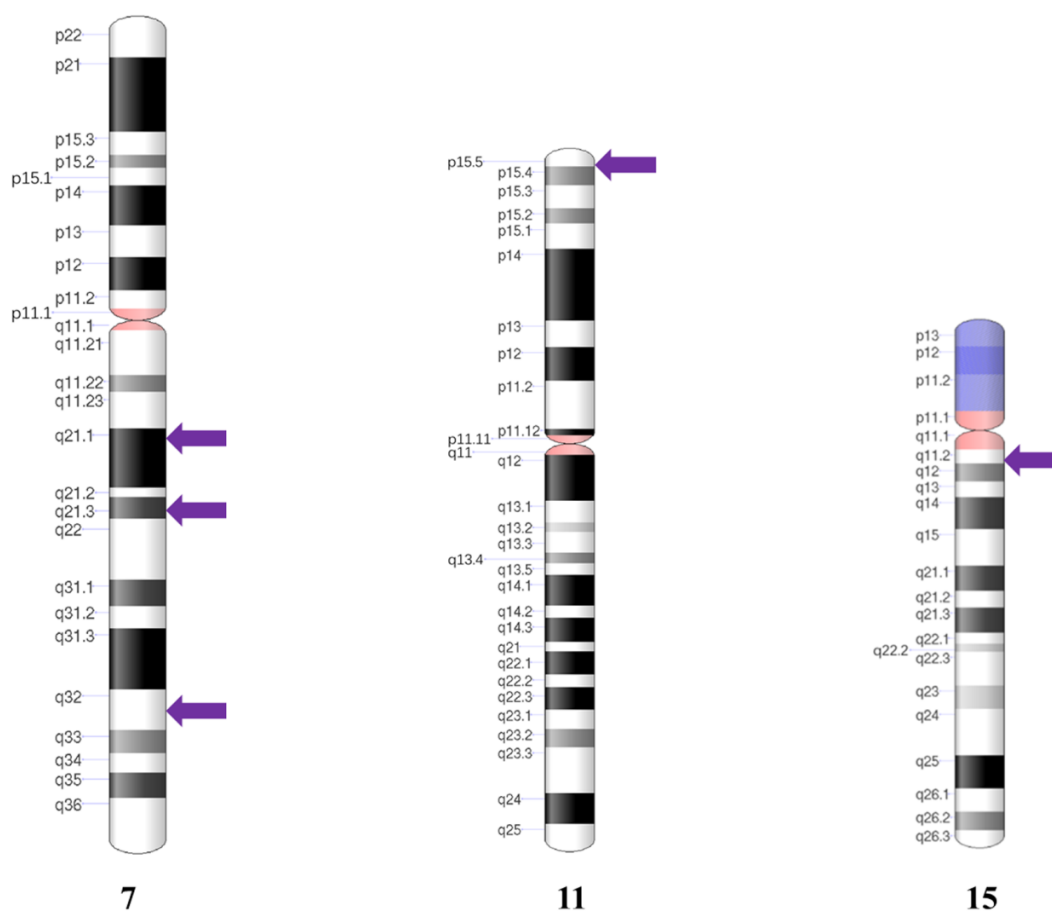


Fig. 1. Ideograms demonstrating the imprinted loci affected by ROHs/LCSHs investigated in the present study (7q21.11, 7q21.3, 7q32.2, 11p15.5p15.4, and 15q11.2).

Analysis of ROHs/LCSHs at 7q21.11, 7q21.3, and 7q32.2 has not allowed to determine direct outcomes of these epigenomic changes. Firstly, the overwhelming majority of these cases demonstrated pathogenic copy number variations ($n > 1$ per case) and chromosomal imbalances (deletions, duplications, aneuploidy) (data not shown). Secondly, bioinformatic analysis yielded contradictory results. Thirdly, phenotypic diversity of these cases hindered genotype-phenotype correlations. In other words, ROHs/LCSHs at these imprinted loci of chromosome 7 were not associated with specific clinical manifestations (e.g. Silver-Russell syndrome or another clinical entity). It is to note that there were only three genes (*SGCE*, *PEG10*, and *PPP1R9A*), which were systematically and concomitantly affected by ROHs/LCSHs at 7q21.3. In summary, we concluded that ROHs/LCSHs spanning imprinted regions 7q21.11, 7q21.3, and 7q32.2 are unlikely to cause a specific phenotype. Still, our

observations do not imply that these epigenomic changes lack any kind of phenotypic consequences

Focusing on 11p15.5p15.4, we found that ROHs/LCSHs at this chromosomal region affect imprinted genes in a recurrent manner. Furthermore, these imprinted genes are involved in a wide spectrum of shared pathways inasmuch as their transcripts form a common interactome. Ontologies of the imprinted genes are frequently shared, as well. Furthermore, all the cases demonstrating ROHs/LCSHs at the imprinted loci 11p15.5p15.4 presented with atypical forms of Beckwith-Wiedemann syndrome, which possesses phenotypically recognizable patterns of malformations and is repeatedly reported in the available literature [13, 15]. Figure 2 presents data on imprinted genes of chromosome 11 involved in ROHs/LCSHs.

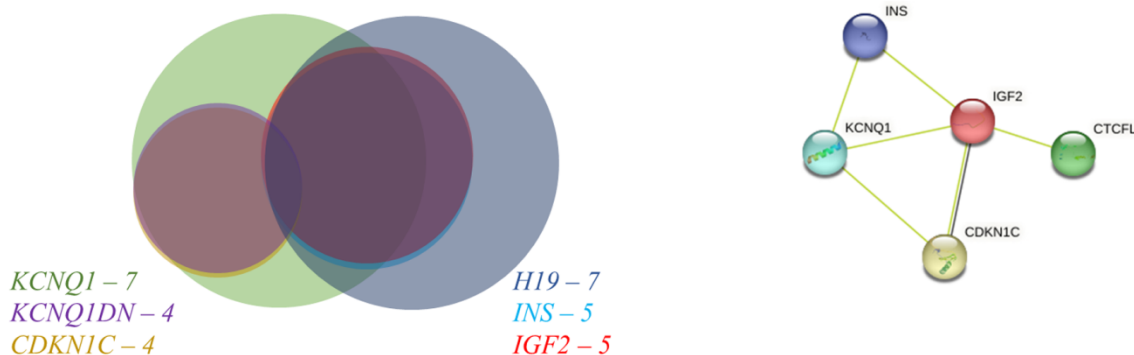


Fig. 2. Imprinted genes of chromosome 11 involved in ROHs/LCSHs: occurrence of ROHs/LCSHs spanning the gene (given in number of cases per gene and depicted by Euler circles) and interactome analysis.

Imprinting deregulation/defects at 15q11.2 are recognized causes of Angelman and Prader-Willi syndromes, which are well-known genetic neurodevelopmental disorders [7, 13-17, 19, 20]. Therefore, it is not surprising that ROHs/LCSHs within this imprinted region possess appreciable pathogenic consequences [3]. Still, the intrinsic outcomes of these epigenomic changes remains poorly understood. Our data indicate that ROHs/LCSHs at this chromosomal region affect imprinted genes in a recurrent manner as in the case of

chromosome 11. Transcripts of ROHs/LCSHs-affected genes within the imprinted locus of chromosome 15 form a common interactome. Shared ontologies between these imprinted genes are described, as well. Finally, similarity between ontologies of imprinted genes of chromosomes 11 and 15 confirms a hypothesis suggesting the existence of genomic imprinting-overlapping phenotypes and an imprinting network [15]. Figure 3 demonstrates data on imprinted genes of chromosome 15 involved in ROHs/LCSHs.

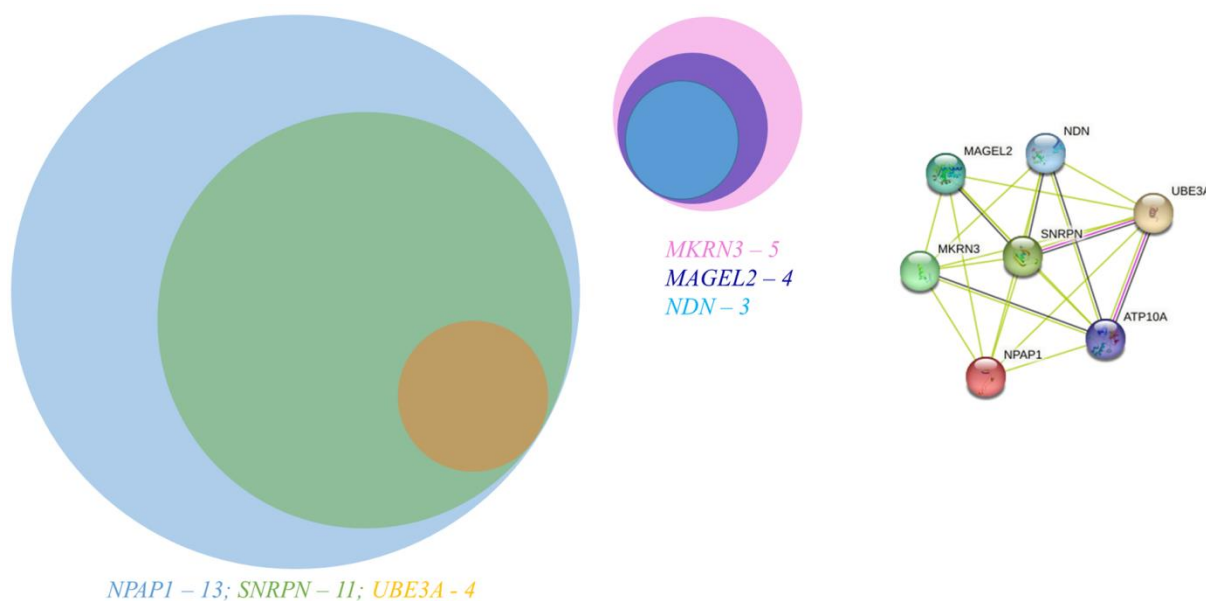


Fig. 3. Imprinted genes of chromosome 15 involved in ROHs/LCSHs: occurrence of ROHs/LCSHs spanning the gene (given in number of cases per gene and depicted by Euler circles) and interactome analysis.

As one may see, there are two distinct sets of genes concomitantly affected by ROHs/LCSHs (segmental uniparental disomy). The first gene set (*NPAPI*, *SNRPN*, and *UBE3A*) was more commonly associated with atypical Angelman syndrome phenotypes, whereas the second gene set (*MKRN3*, *MAGEL2*, and *NDN*) was more commonly associated with atypical Prader-Willi syndrome phenotypes. Unfortunately, parental origin of the segmental uniparental disomy (ROHs/LCSHs at these loci) was impossible to determine due to the impossibility of performing molecular karyotyping using both maternal and paternal DNA. These data would be intriguing for clinical description of these cases in light of the differences between Angelman and Prader-Willi syndromes.

ROHs/LCSHs at the imprinted loci 11p15.5p15.4 and 15q11.2 mimic uniparental disomy of chromosomes 11 and 15. However, regardless of the association between these epigenomic changes and neurodevelopmental disorders and congenital malformations [3, 4], guidelines on genetic diagnostic testing for uniparental disomy completely ignore ROHs/LCSHs or segmental uniparental disomies affecting the imprinted gene clusters [27]. This ignorance results into a major problem, which may be defined as underdiagnosing of epigenetic/epigenomic changes producing neurodevelopmental phenotypes or atypical forms of Beckwith-Wiedemann and Prader-Willi/Angelman syndrome. Additionally, there are numerous problems associated with molecular cytogenetic, cytogenomic and molecular genetic diagnosis of neurodevelopmental diseases associated with cytogenomic/epigenomic changes. These are basically referred to the impossibility of studying genomes and epigenomes at the chromosomal level by the majority of genomic techniques. For instance, SNP array is the only technique for cytogenomic detection of ROHs/LCSHs, whereas FISH is the only visual technique for detecting low-level mosaicism and parental origins of chromosomes in mosaic cases [7, 28, 29, 30]. All these technological aspects are to be taken into account during diagnosis of atypical forms

of Prader-Willi/Angelman and Beckwith-Wiedemann syndromes [30, 31]. To increase the efficiency of cytogenomic approaches to detecting ROHs/LCSHs and copy number variations, bioinformatic analysis (i.e. systems analysis, pathway-based classification etc.) is to be applied [8, 12]. Certainly, current medical genomics has technical potential to solve the diagnostic problems. In the light of uncovering ROHs/LCSHs at the imprinted loci and the outcomes, we may recommend to use molecular karyotyping using SNP array in combination with advanced bioinformatic techniques allowing defining pathogenic values of genomic and epigenomic variations.

Diverse epigenetic mechanisms have been described to regulate and to maintain genomic imprinting [32]. Recently, genomic imprinting has been addressed using profound theoretical and empirical analyses. As a result, the imprintome concept was proposed since regulation, deregulation and defects of imprinting are likely to form a complex system [33]. Unfortunately, chromosomal aspects of deregulation and defects (including occurrence of ROHs/LCSHs) have been totally left aside during the development of this concept. In this context, it is to mention that uniparental disomy is a chromosomal disorder in the first place [34]. Certainly, ROHs/LCSHs also do. To highlight this issue, we have introduced “cytoepigenomic variations” to describe cytogenetic/cytogenomic aspects of disease-associated ROHs/LCSHs during the work of the cytogenomic epileptology consortium. In this context, it is apposite to note that children exhibiting ROHs/LCSHs at the imprinted loci demonstrated epileptic conditions similar to the aforementioned imprinting disorders (Angelman syndrome is a recognized genetic cause of specific epilepsy types) [35]. Thus, theoretical issues related to definitions of ROHs/LCSHs reflect the analytical efforts to describe clinical outcomes of these disorders. To this end, using the data obtained and a review of current challenges and opportunities for cytogenetics and cytogenomics in the clinical context [35, 36], we concluded that sys-

tems analysis of cytogenomic and cytoepigenomic data [37] is the most promising way to uncover the outcomes of related genomic and epigenomic variations.

Conclusion. Cytoepigenomic variations manifesting as ROHs/LCSHs spanning the imprinted loci of chromosomes 7, 11 and 15 are common among children with neurodevelopmental disorders as detected by molecular karyotyping using SNP array. The incidence is estimated as 8.7%. Evaluations of the outcomes using advanced bioinformatic techniques addressing ontologies and interactomes of imprinted genes affected by ROHs/LCSHs have demonstrated that epigenomic changes affecting 11p15.5p15.4 and 15q11.2 (28 cases; 3.6%) are associated with definable cellular and clinical consequences in affected individuals. These mimic atypical forms of Beckwith-Wiedemann (ROHs/LCSHs spanning imprinted genes at 11p15.5p15.4) and Prader-Willi/Angelman syndromes (ROHs/LCSHs spanning imprinted genes at 15q11.2). Analysis of ROHs/LCSHs spanning imprinted genes chromosome 7 has not allowed us to determine apparent molecular/cellular and phenotypic consequences. Finally, we conclude that molecular karyotyping by SNP array followed by the application of advanced bioinformatic techniques represent a valuable diagnostic approach to uncover cytoepigenomic variations manifesting as ROHs/LCSHs spanning the imprinted loci, which are common but underappreciated sources for neurodevelopmental disorders.

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Conflict of interests

The authors have no conflict of interest to declare.

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