Review

Genomics of neurodevelopmental disorders

Genómica de los trastornos del desarrollo neurológico

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ABSTRACT

Introduction: Neurodevelopmental disorders (NDD) are featured by a delay in the acquisition of motor functions, cognitive abilities and speech, or combined deficits in these areas with the onset before the age of 5 years. Genetic causes account for approximately a half of all NDD cases.

Objective: to describe alterations of the genome implied in neurodevelopmental disorders and some aspects of their genetic counseling.

Methods: Bibliographic search in Medline, Pubmed, Scielo, LILACS and Cochrane, emphasizing in the last five years, the relationship between the various genetic factors that may be involved in neurodevelopmental disorders.

Results: Multiple genetic factors are involved in neurodevelopmental disorders, from gross ones such as chromosomal aneuploidies to more subtle ones such as variations in the number of copies in the genome. Special emphasis is placed on microdeletion-micro duplication syndromes as a relatively frequent cause of NDDs and their probable mechanisms of formation are explained.

Final Considerations: Genetic aberrations are found in at least 30-50% of children with NDD. Conventional karyotyping allows the detection of chromosomal aberrations encompassing more than 5-7 Mb, which represent 5-10% of causative genome rearrangements in NDD. Molecular karyotyping (e.g. SNP array/array CGH) can significantly improve the yield in patients with NDD and congenital malformations.

Keywords: CNV; chromosomal abnormalities; genome; genomic aberrations; microdeletions; microduplications; neurodevelopmental disorders.

RESUMEN

Introducción: Los trastornos del neurodesarrollo están caracterizados por retardo en la adquisición de las funciones motoras, habilidades cognitivas para el habla o el déficit combinado en estas áreas; se presenta en niños menores de 5 años de edad. Las causas genéticas están implicadas en más de la mitad de los pacientes con estos trastornos

Objetivo: Examinar las alteraciones del genoma implicados en los trastornos del neurodesarrollo y algunos aspectos de su asesoramiento genético.

Métodos: Búsqueda bibliográfica en Medline, Pubmed, Scielo, LILACS y Cochrane con énfasis en los últimos cinco años, acerca de la relación entre los variados factores genéticos que pueden estar involucrados en los trastornos del neurodesarrollo.

Resultados: Los factores genéticos involucrados pueden ser groseros como las aneuploidías cromosómicas hasta los más sutiles como las variaciones en el número de copias en el genoma. Se describen los síndromes de microdeleción-micro duplicación como una causa relativamente frecuente de los trastornos del neurodesarrollo y se explican sus probables

mecanismos de formación. Se relacionan las aneuploidías cromosómicas y las variaciones en el número de copia como causas de estos trastornos.

Consideraciones finales. Las aberraciones genéticas se encuentran en 30-50 % de los niños con trastornos del neurodesarrollo. El cariotipo convencional permite la detección de aberraciones cromosómicas que abarcan más de 5-7 Mb, lo que representa 5-10 % de los reordenamientos genómicos causales en estos trastornos. El cariotipo molecular (por ejemplo, una matriz de SNP/ CGH de matriz) puede mejorar significativamente la certeza del diagnóstico en pacientes con trastornos del neurodesarrollo y malformaciones congénitas.

Palabras clave: variaciones en el número de copias (CNV); anomalías cromosómicas; genoma; aberraciones del genoma; microdeleciones; microduplicaciones; desordenes del neurodesarrollo.

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Introduction

Neurodevelopmental disorders (NDD) are featured by a delay in the acquisition of motor functions, cognitive abilities and speech, or combined deficits in these areas with the onset before the age of 5 years. The prevalence may reach 1-3 %, according to different studies[1,2]. Genetic causes account for approximately a half of all NDD cases; chromosomal aberrations (CA) account for 5-10%of cases[3,4]. However, the extensive variability of causal genetic defects hinders the etiological diagnosis. The phenotypic effect of CA depends on the type, origin, and length of aberrations. Additionally, gene density and functional aspects of genes and their interactions with other genes and environmental modulating significantly contributes to the phenotype, as well.[5,6]The aim of this work is to describe some alterations of the genome implied in neurodevelopmental disorders.

Methods

Bibliographic search in Medline, Pubmed, Scielo, LILACS and Cochrane, emphasizing in the last five years, the relationship between the various genetic factors that may be involved in neurodevelopmental disorders.

Results

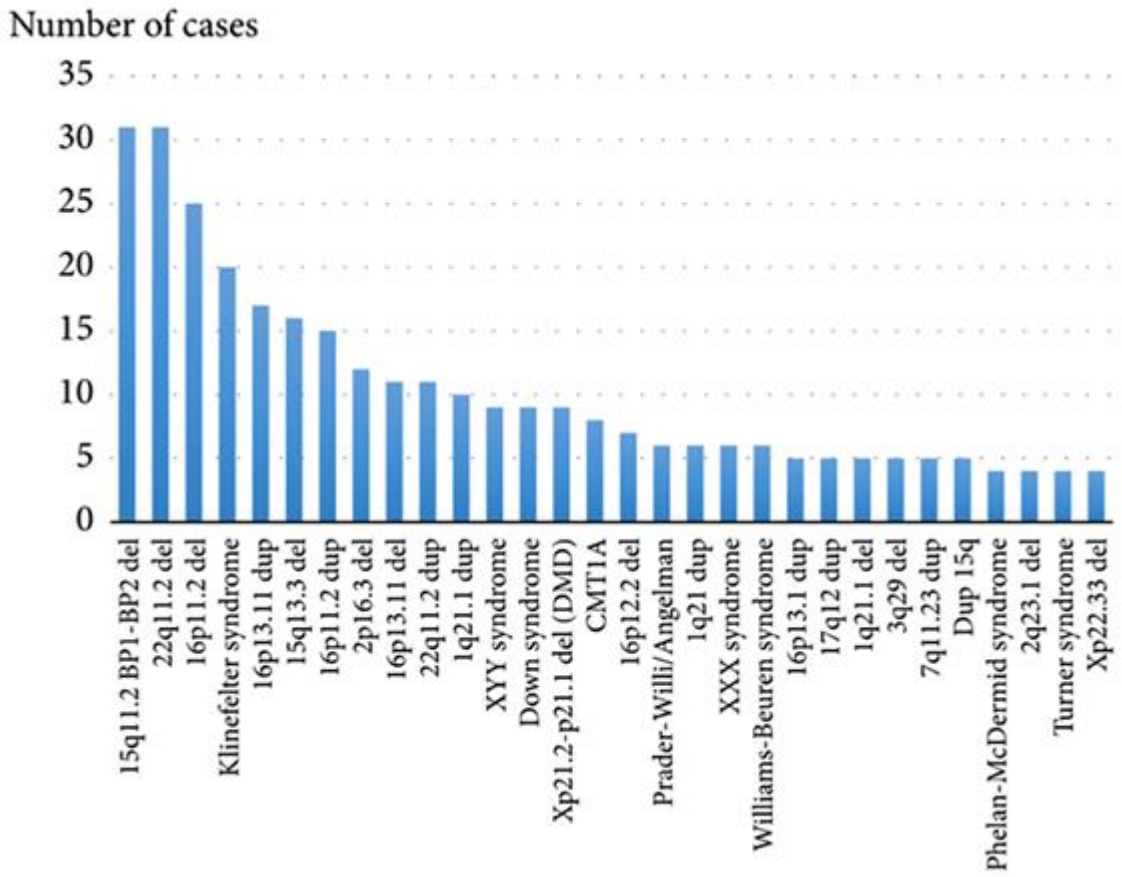
Multiple genetic factors are involved in neurodevelopmental disorders, from gross ones such as chromosomal aneuploidies to subtler ones such as variations in the number of copies in the genome. Special emphasis is placed on microdeletion-micro duplication syndromes as a relatively frequent cause of NDDs and their probable mechanisms of formation are explained.

Microdeletion and microduplication syndromes

During the last decades an increasing number of so-called contiguous gene syndromes (CGSs) have been identified in patients with intellectual disability. CGSs are caused by an aberrant copy number (gain or loss) of specific chromosomal regions. Originally, CGSs were considered to encompass critical regions of two or more genes, located in a close proximity to each other. Some of these regions affect many genes but a limited number of genes may be dosage-sensitive and, thereby, causative for specific manifestations. Thus, the denomination "CGS" has been replaced by the designation "microdeletion or microduplication syndromes" (MMSs).[7] The common molecular cause of recurrent MMSs is a non-allelic homologous recombination. Repetitive elements are prone to illegitimate intra- or interchromosomal/chromatide recombination during meiosis and mitosis. The expected number of MMS is suggested to be higher than is currently known, because many of these events have a deleterious intrauterine effect.[8,9]

Theoretically, there should be a reciprocal microduplication syndrome for each microdeletion syndrome. However, microdeletion syndromes are more common according to current molecular cytogenetic studies (Fig.1). The main reason for this inequality is that microduplications are supposed to have a lower clinical impact than microdeletions.

Subsequently, the patients with microduplications are less commonly addressed by molecular (cyto)genetic techniques due to less severe phenotypic manifestations.[9,10]



Source: ref. 7.

Fig. - Most common pathogenic findings on 5487 chromosomal microarrays.

Additional causes for MMSs recurrence

Human non-homologous DNA recombination and end joining may occur due to double stranded breaks, which serve as a repair mechanism. This cause is less frequent and is not directly mediated by the features of the genome sequence.[11]In addition, MMSs can be a result of meiotic recombination when one parent carries a polymorphic inversion (e.g., a heterochromatic region of chromosome 9), which leads to a recombinant gamete with a deletion or duplication in this regiondue aninverted loop formation.[9]

Chromosomal aneuploidies

The most frequent cause of chromosomal syndromes is aneuploidy, which affects no less than 0.5% of newborns.[12,13] Almost all of these conditions are associated with brain dysfunction [14] The most frequent aneuploidies among newborns are trisomy of chromosomes 21, 18, 13 and aneuploidy of sex chromosomes (gonosomes). Mosaic trisomy of chromosomes 8 and 9 (there are two cell populations (normal/trisomic) in an affected individual) are relatively common, as well (Tabla). [14,15]

Table - Genetic syndromes associated with different kinds of brain dysfunction

Disease	Aneuploidy	Neurodevelopmental abnormalities	Incidence
Down syndrome	Trisomy of chromosome 21	IQ: 25-50; neuropathological changes	~1:800
Edwards syndrome	Trisomy of chromosome 18	Severe intellectual disability; malformations usually incompatible with life	~1:7000
Patau syndrome	Trisomy of chromosome 13	Severe intellectual disability; malformations usuallyincompatible with life	1:6000-1:29000
Trisomy 8	Trisomy of chromosome 8 (mosaic)	Various (non-specific) neurodevelopmental abnormalities, intellectual disability	More than 100 reported cases
Trisomy 9	Trisomy of chromosome 9 (mosaic)	Intellectual disability and motor delay	More than 40 reported cases
Trisomy 22	Trisomy of chromosome22 (mosaic)	Severe intellectual disability	More than 20 reported cases
Turner syndrome	Monosomy of chromosome X	IQ: ~90. Behavioral and cognitive disabilities/psychiatric disorders	>1:2000 (females)
Klinefelter syndrome	Additional chromosome X in a male karyotype	IQ: 85-90. Psychiatric disorders and behavioral phenotypes	~1:500 (males)
Trisomy X syndrome	Trisomy of chromosome X	IQ:85-90. Psychiatric disorders may occur. Rare cases with intellectual disability	~1:1000 (females)
XYY syndrome	An additional Y chromosome	Aggressive behavior in childhood and adolescence. Psychiatric disorders and behavioral phenotypes	~1:800 (males)

Copy number variations

Numerous human genome loci are prone to submicroscopic copy number variations (CNVs). These CNVs are located in euchromatic regions and dispersed over the entire human genome. CNVs(gain/loss of submicroscopic regions) can either lead to clinical manifestations or lack detectable phenotypic consequences.[7,16] Several features of CNVs support their role in disease pathogenesis. Although less abundant than SNPs, they account for a larger nucleotide variation than SNPs because encompassing larger DNA sequences in the absolute size.[17] Spanning thousands of nucleotide bases, CNVs often encompass and disrupt functional DNA sequences. Moreover, there appears to be enrichment in CNVs affecting "environmental sensor" genes, i.e. genes that are not necessarily critical for early embryonic development, but

are involved in perceiving and interacting with the environment.[18,19] he way how CNVs change their size when passed from one generation to the next, i.e. how specific DNA-regions are lost or amplified within a CNV, is not as yet completely understood. This may result from unequal crossing-over events in low copy repeat regions [5, 16], or from altered reparation after DNA-break and/or replication stress (e.g. non-allelic homologous recombination, microhomology-mediated break-induced replication, or chromothripsis).[7,20,21,22,23,24] The most known disease-causing CNVs are 17q21.31microdeletions (Koolen-De Vries syndrome.[25] reciprocal 17q21.31 microduplications,[26,27] 17q23.1q23.2 microdeletions[28] and 3q13 microdeletions.[29] Some microdeletion and microduplication syndromes are not caused by recurrent CNVs, but individuals witht he aberrations present with similar phenotypes,[30] which allows for the definition of smallest regions of overlap, or critical regions, for the syndrome, which are likely to contain disease-causing genes (e.g. 1q43q44, 1q41q42 and 1q24q25 microdeletions).[31,32,33]

Genetic counseling

Genetic counseling in cases of CNVs with reduced penetrance and variable expressivity can be particularly difficult.[34] If a parent carries the CNV, there is a 50% -inheritance-chance for off spring, but the establishment of additional risk factors in the family as well as the likelihood of having another affected childr equires more sophisticated (bioinformatics) analysis. For at least some recurrent CNVs, there are estimates either for penetrance, for any clinical phenotype or for psychiatric disorders, such as schizophrenia.[35-36] The penetrance analysis shows that not all CNVs confer equal risk. steimates for the requency of carriers with significantly abnormal phenotypes range from ~10% for 15q11.2 BP1-BP2 microdeletion syndrome to~60% for distal 16p11.2 microdeletions.[35] Unfortunately, it remains difficult to predict the severity of phenotypic outcomes, although some researchers suggest that there may be protective actors (e.g. gender)[37].Furthermore, it is important to note that “penetrance” is quite relative; there may still be negative CNV effects among the so-called healthy parents or controls. This is supported by recent studies of general populations reporting negative effects of the CNVs, including cognitive impairments, other neuropsychiatric features, alterations in body weight, and reduced fertility.[38,39] Therefore, it is likely that most of these CNV shave some type of negative impact on an individual’s development and neurologic functioning, although these impacts may not be always evident. Another notable feature of recurrent CNVs

is variable expressivity. Same CNVs may be identified in populations of patients with intellectual disability, autism, and schizophrenia. Such effects may indicate that there are shared etiologies among NDD.[40,41,42,43] Several studies have demonstrated the applicability of this assumption by comparing parental neurocognitive function to their children with *de novo* risk factor CNVs, showing a correlation between lower levels of parental functioning in specific domains (such as IQ and social responsiveness) scores and more significant impairments in those domains among their off spring.[44,45.46]

Final considerations

Genetic aberrations are found in at least 30-50% of children with NDD. Conventional karyotyping allows the detection of chromosomal aberrations en compassing more than 5-7 Mb, which represent 5-10% of causative genome rearrangements in NDD. Molecular karyotyping (e.g. SNP array/array CGH) can significantly improve the yield in patients with NDD and congenital malformations, which is repeatedly shown by systematic cohort studies. Recommendation: Cuban NDD cohorts have not yet been studied by these high-resolution techniques. The application of molecular karyotyping to the cohort can help in revealing new genetic aberrations and can provide effective genetic counseling.

References

1. Patel DR, Merrick J. Neurodevelopmental and neurobehavioral disorders. Transl Pediatr. 2020;9 (1):S1-S2

2. Vorsanova SG, Yurov YB, Soloviev IV, Iourov IY. Molecular cytogenetic diagnosis and somatic genome variations. Curr Genom. 2010;11(6):440-6.

3. Patel DR, Merrick J. Neurodevelopmental disabilities: Introduction and epidemiology. In: Patel D, Greydanus D, Omar H,Merrick J, editors. Neurodevelopmental Disabilities. Dordrecht: Springer; 2011.

4. Iourov IY, Vorsanova SG, Yurov YB. Single cell genomics of the brain: focus on neuronal diversity and neuropsychiatric diseases. Curr Genom. 2012;13(6):477-88.

5. Guo H, Bttella E, Marcogliese PC, Zhao R, Andrews JC, Nowakowski TJ. *et al.* Disruptive mutation in TANC2 define a neurodevelopmental syndrome associate with psychiatric disorders. Nat Commun. 2019;10(1):4679.

6. Naseer MI, Chaudhary AG, Rasool M, Kalamegan G, Ashgan FT, Assidi M, *et al.* Copy number variations in Saudi family with intellectual disability and epilepsia. BMC Genomics. 2016;17:757.

7. Weise A, Mrasek K, Klein E, Mulatinho M, Llerena JrJC, Hardekopf D, *et al*. Microdeletion and microduplication syndromes. J Histoch Cytochem. 2012;60(5):346-58.

8. Gu W, Zhang F, Lupski JR. Mechanisms for human genomic Rearrangements. Pathogenet. 2008;1(1): 4.

9. Gardner RM, Amor DJ. Part Two: Parent or child with a chromosomal abnormality. Chromosome Abnormalities and Genetic Counseling. Fifth edition. Oxford, New York: Oxford University Press; 2018.

10. Méndez-Rosado LA, García D, Molina-Gamboa O, García A, de León N, Lantigua-Cruz A, *et al.* Algorithm for the diagnosis of patients with neurodevelopmental disorders and suspicion of a genetic syndrome. Arch Argent Pediatr. 2020;118(1):47-60.

11. Lieber MR. The mechanism of human non homologous DNA end joining. J Biol Chem. 2008;283(1):1-5.

12. Méndez-Rosado LA, Hechavarría-Estenoz D, de la Torre ME, Pimentel-Benitez H, Hernández-Gil J, Perez B, *et al.* Current status of prenatal diagnosis in Cuba: causes of low prevalence of Down syndrome. Prenatal Diagnosis. 2014;34: –6.

13. Hernández G, González N, Méndez Rosado LA. Genetic and non-genetic risk factors in pregnant women with prenatal diagnosis. Mayabeque. 2010-2012. The Cuban J. Communit Genet. 2015;(3):23-7.

14. Iourov IY, Vorsanova SG, Yurov YB. Chromosomal variation in mammalian neuronal cells: known facts and attractive hypotheses. Internat Rev Cytol. 2006;249:143-91.

15. Wang JCC. Autosomal aneuploidy. In: Gersen SL, Keagle MB, ediors. The Principles of Clinical Cytogenetics (2nd ed.). Totowa (NJ): Humana Press; 2005. p. 133-14.

16. Liehr T. Benign and Pathological Chromosomal Imbalances: Microscopic and Submicroscopic Copy Number Variations (CNVs) in Genetics and Counseling. San Diego, CA: Academic Press of Elsevie; 2014.

17. Tuzun E, Sharp AJ, Bailey JA, Kaul R, Morrison VA, Pertz LM, *et al.* Fine-scale structural variation of the human genome. Nat Genet. 2005;37(7):727.

18. Iourov IY, VorsanovaSG, Yurov YB. Somatic cell genomics of brain disorders: a new opportunity to clarify genetic-environmental interactions. Cytogenet Genome Research. 2013; 139(3):181-8.

19. Vorsanova SG, Yurov YB, Iourov IY. Neurogenomic pathway of autism spectrum disorders: linking germline and somatic mutations to genetic-environmental interactions. Curr Bioinformat. 2017;12(1):19-26.

20. Girirajan S, Dennis MY, Baker C, Malig M, Coe BP, Campbell CD, *et al.* Refinement and discovery of new hotspots of copy-number variation associated with autism spectrum disorder. Am J Hum Genet. 2013;92:221-37.

21. Levinson G, Gutman GA. Slipped-strand mispairing: a major mechanism for DNA sequence evolution. Mol Biol Evol. 1987;4:203-21.

22. Liu P, Carvalho CM, Hastings PJ, Lupski JR. Mechanisms for recurrent and complex human genomic rearrangements. Curr Opin Genet Dev. 2012;22:211-20.

23. Arlt MF, Wilson TE, Glover TW. Replication stress and mechanisms of CNV formation. Curr Opin Genet Dev. 2012;22:204-10.

24. Liehr T, Schreyer I, Kuechler A, Manolakos E, Singer S, Dufke A, *et al.* Parental origin of deletions and duplications–about the necessity to check for cryptic inversions. Mol Cytogenet. 2018;11(1):20-7.

25. Koolen DA, Pfundt R, Linda K, Beunders G, Veenstra-Knol He, Conta JH, *et al.* The Koolen-de Vries syndrome: a phenotypic comparison of patients with a 17q21.31 microdeletion versus a KANSsl1 sequence variant. Eur J Hum Genet. 2016;24 (5):652-9.

26. Natacci F, Alfei E, Tarara LD, Arrigo S, Zuffardi O, Gentilin B, *et al.* Chromosome 17q21.31 duplication syndrome: description of a new familiar case and further delination of the clinical spectrum. Eur J Paediatr Neurol. 2016;20(1):183-7.

27. Sharp AJ, Hansen S, Selzer RR, Cheng Z, Regan R, Hurst JA, *et al.* Discovery of previously unidentified genomic disorders from the duplication architecture of the human genome. Nat Genet. 2006;38(9):1038-42.

28. Ballif BC, Theisen A, Rosenfeld JA, Traylor RN, Gastier-Foster J, Thrush DL, *et al.* Identification of a recurrent microdeletion at 17q23.1q23.2 flanked by segmental duplications associated with heart defects and limb abnormalities. Am J Hum Genet. 2010; 86(3):454-61.

29. Shuvarikov A, Campbell IM, Dittwald P, Neill NJ, Bialer MG, Moore C, *et al.* Recurrent HERV-Hmediated 3q13.2-q13.31 deletions cause a syndrome of hypotonia and motor, language, and cognitive delays. Hum Mutat 2013; 34(10):1415–1423

30. Iourov IY, Vorsanova SG, Kurinnaia OS, Zelenova MA, Silvanovich AP, Yurov YB. Molecular karyotyping by array CGH in a Russian cohort of children with intellectual disability, autism, epilepsy and congenital anomalies. Mol Cytogenet. 2012;5(1):46.

31. Depienne C, Nava C, Keren B, Heide S, Rastetter A, Passemard S, *et al.* Genetic and Phenotype dissection of 1q43q44 microdeletion syndrome and neurodevelopmental phenotypes associate with mutation in ZBTB18 and HNRNPU. Human Genet. 2017;136(4):463-79.

32. Shaffer LG, Theisen A, Bejjani BA, Ballif BC, Aylsworth AS, Lim C, *et al.* The discovery of microdeletion syndromes in the post-genomic era: review of the methodology and characterization of a new 1q41q42 microdeletion syndrome. Genet Med. 2007;9(9):607-16.

33. Lefroy H, Fox O, Javaid MK, Makaya T, Shears DJ. 1q24 deletion syndrome. Two cases and new insights into genotype-phenotype correlations. Am J Med Genet A. 2018;176 (9):2004-8.

34. Rosenfeld JA, Patel A. Chromosomal microarrays: understanding genetics of neurodevelopmental disorders and congenital anomalies. J Pediat Genetics. 2017;6(01):42-50.

35. Kirov G, Rees E, Walters JT. The penetrance of copy number variations for schizophrenia and developmental delay. Biol Psychiatry. 2014;75(5):378-85.

36. Catusi I, Recalcati MP, Bestetti I, Garzo M, Valtorta C, Alfonsi M, *et al.* Testing single-combined clinical categories on 5110 italian patients with developmental phenotypes to improve array-based detection rate. Mol Genet Genom Med. 2020;8:1056.

37. Polyak A, Rosenfeld JA, Girirajan S. An assessment of sex bias in neurodevelopmental disorders. Genome Med. 2015;7(1):94.

38. Luo T, Chen HY, Zou X, Wang T, Cheng YM, Wang HF, *et al.* A novel copy number variation in CATSPER2 causes idiopathic male infertility with normal semen parameters. Hum Rep. 2019;34(3):414-23.

38. Takumi T, Tamada K. CNV biology in neurodevelopmental disordes. Curr Opin Neurobiol. 2018;48:183-192.

39. Männik K, Mägi R, Macé A, Cole B, Guyatt AL, Shihab HA, *et al.* Copy number variations and cognitive phenotypes in unselected populations. JAMA. 2015;313(20):2044-54.

40. Iourov IY, Vorsanova SG, Yurov YB. In silico molecular cytogenetics: a bioinformatic approach to prioritization of candidate genes and copy number variations for basic and clinical genome research. Mol Cytogenet. 2014;7(1):98.

41. Iourov IY, Vorsanova SG, Voinova VY, Kurinnaia OS, Zelenova MA, Demidova IA, *et al.* Xq28 (MECP2) microdeletions are common in mutation-negative females with Rett syndrome and cause mild subtypes of the disease. Mol Cytogenet. 2013;27;6(1):53.

42. Vorsanova SG, Iurov IY, Voinova VY, Kurinnaia OS, Zelenova MA, Demidova IA, *et al.* Subchromosomal microdeletion identified by molecular karyotyping using DNA microarrays (array CGH) in Rett syndrome girls negative for MECP2 gene mutations. Zh Nevrol Psikhiatr Im SS Korsakova. 2013;113(10):63-8.

43. Pizzo l, Jensen M, Poliak A, Rosenfeld JA, Mannik K, Krishnan A, *et al.* Rare variant in the genetic background modulate cognitive and developmental phenotypes in individuals carring disease- associated variants. Gene Med. 2019;21:816-25.

44. Moreno-De-Luca A, Evans DW, Boomer KB, Hanson E, Vernier R, Goin-Kochel RP, *et al.* The role of parental cognitive, behavioral, and motor profiles in clinical variability in individuals with chromosome 16p11.2 deletions. JAMA Psychiatry. 2015;72(2):119-26.

45. Ho KS, Twede H, Vanzo R, Harward E, Hensel CH, Martin MM, *et al.* Clinical Performance of an Ultrahigh Resolution Chromosomal Microarray Optimized for Neurodevelopmental Disorders. Biomed Res Int. 2016;2016:3284534.

Conflict of interest

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Author contributions

Luis Alberto Méndez Rosado: Conceived the manuscript, bibliographical revision, wrote the first draw of the paper.

Ivan Iourov: bibliographical revision, wrote the final version of paper.

Aracelis Lantigua Cruz, Maria Zelenova, SvetlanaVorsanova. bibliographical revision, participation in the design of the article.

All authors participated in the final review of the manuscript and agree with the scientific content and objetives of the paper.

Abbreviations

NDD - Neurodevelopmental disorders

CA - Chromosomal aberrations

CNVs - copy number variations

CGSs - Contiguous gene syndromes

MMSs - Microdeletion or microduplication syndromes