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Diagnosis of Genome Pathology in Children with Mental Retardation and Autism by SNP-Oligonucleotide Molecular Karyotyping

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ABSTRACT

Since mental retardation and autism are the commonest brain disorders in children, uncovering their genetic basis is an actual direction in current biomedicine. Application of whole genome scan for studying unbalanced DNA copy number variations allows not only the detection of chromosomal and genomic rearrangements leading to these diseases, but also offer an opportunity to describe pathogenic processes resulting in abnormal functioning of the central nervous system. To assess SNP-oligonucleotide molecular karyotyping (molecular cytogenetic method having the highest resolution for detection of such genomic variations) in diagnostic context, we have analyzed the genome of 100 children suffering from mental retardation and/or autism. Eight numerical and structural chromosome abnormalities (size: >5 Mb) and 20 submicroscopic genomic rearrangements (size: 0.5-3 Mb) were detected. Nine cases exhibited gene mutations manifesting as exonic deletions and duplications associated with the phenotype. As a result, it was concluded that this molecular cytogenetic technique has diagnostic yield no less than 37%. Additionally, further analysis by an original bioinformatics technologies allowed uncovering pathogenic processes associated with the aforementioned mental disturbances in another 55 cases. Thus, combination of SNP-oligonucleotide molecular karyotyping and bioinformatics analysis has high efficiency for detection of genomic pathology and identification of molecular mechanisms for mental retardation and autism.

Keywords: molecular cytogenetics, whole genome scan, SNP-oligonucleotide molecular karyotyping, mental retardation, autism

INTRODUCTION

Chromosomal abnormalities and genomic rearrangements are the commonest genetic defects associated with mental retardation and autism. During the last decade, an increase of communications dedicated to contribution of submicroscopic chromosomal abnormalities and copy number variations (CNV) to brain diseases has been noted. This is likely to be linked to active introduction of whole genome scan techniques by molecular karyotyping with an unprecedentedly high resolution (1 kbp and higher) [1-4]. Summarizing the data on genomic variations was used for recommendations concerning detection of unbalanced genomic rearrangements, which suggest using whole genome scan by SNP-oligonucleotide molecular karyotyping as the first tier diagnostic technique [8]. In children with mental retardation and/or autism, such types of genomic rearrangements can be detected in 10-50% cases depending on cohort peculiarities and application of additional bioinformatics techniques for assessment of the pathogenic value. The latter becomes even more actual inasmuch as CNV can be either pathogenic or benign [5, 10]. Here, diagnostic potential of SNP-oligonucleotide molecular karyotyping in combination with original bioinformatics technology [2, 6, 7] for identification of genome pathology in children with mental retardation and autism was addressed.

MATERIALS AND METHODS

SNP-oligonucleotide molecular karyotyping was used to analyze unbalanced genomic variations in 100 children with mental retardation, autism and/or congenital malformations according to previous protocols [2, 6]. Affymetrix platform for SNP-oligonucleotide molecular karyotyping, consisting of about 2.7 million probes and scanning the genome at a resolution of 1 kbp or higher, was used. Moreover, all the genomic variations were addressed by an original bioinformatics technology for assessing the phenotypic outcome as described previously [6, 7].

RESULTS AND DISCUSSION

Each individual demonstrated from 150 to 480 unbalanced genomic changes (CNV manifesting as deletions and duplications; sized from 1 kbp to 1.5 Mb). Bioinformatics analysis has led the way to differ between pathogenic and benign deletions/duplications. Large chromosome abnormalities were detected in eight cases: deletions of 1p32.1p31.1 (12.075 Mb),

6q11.1q14.1 (18.779 Mb), 7q32.3q35 (15.86 Mb), 8p23.3p23.1 (11.152 Mb); duplication of 8p23.1p11.22 (26.642 Mb) concomitant with deletion of 8p23.3p23.1 (6.782 Mb); supernumerary rearranged chromosomes 17 and X, as well as mosaic trisomy of chromosome X. We also detected submicroscopic genomic rearrangements affecting the following chromosomal loci: 1p36.33 (deletion), 1p36.23 (deletion), 2q23.3 (deletion), 2q24.2 (deletion), 5p13.3 (duplication), 5p13.2 (duplication), 5q14.3 (deletion), 5q15 (deletion), 6p11.2 (deletion), 9q21.13 (deletion), 11p14.3 (duplication), 12p13.31 (duplication), 15q11.2 (deletion), 15q13.1 (deletion), 16p11.2 (deletion), 17p13.3 (duplication), Xp22.12 (deletion), Xq21.1 (duplication), Yq11.223 (duplication) и Yq11.23 (deletion/duplication). The size of submicroscopic genomic rearrangements varied from 0.5 to 3 Mb. Interestingly, 4 cases of autism exhibited somatic mosaicism for structural chromosome abnormalities confirming previous studies of somatic genome variations in autism spectrum disorders [11]. Nine cases demonstrated gene mutations: exonic duplications in *KANSL1, EP300, PHEX, AFF2 (FMR2)*, *FMR1, RB1* and exonic deletions in *WT1, ATXN3*, *AKT3*. Summarizing these data, we concluded that diagnostic yield of SNP-oligonucleotide molecular karyotyping in combination with original bioinformatics technology is no less than 37%.

In 55 cases, CNV affecting genes highly expressed in the pre- and postnatal brain as well as involved in pathways of transcriptional regulation, cell cycle regulation, DNA reparation and replication, axonal guidance and neurogenesis. Therefore, combination of SNP-oligonucleotide molecular karyotyping and bioinformatics has provided for uncovering of molecular mechanism for brain malfunction in children with mental retardation and autism, as well.

CONCLUSION

The experience of applying SNP-oligonucleotide molecular karyotyping in combination with bioinformatics analysis, described herein, indicates that this approach towards detection of genetic causes for mental retardation and autism possesses high diagnostic yield. Similar results are able to offer opportunities for further studies of molecular processes leading to such kind of mental impairment in order to develop effective therapeutic interventions. Opening new prospects in personalized (genomic) medicine, the aforementioned technologies can significantly increase life quality in patients with mental retardation and autism due to a wide spectrum of genomic pathology.

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REFERENCES

1. Vorsanova S.G. Jurov I.Ju. Solov'ev I.V. Jurov Ju.B. Geterohromatinovye rajony hromosom cheloveka: mediko-biologicheskie aspekty [Heterochromatic regions of human chromosomes: medical and biological aspects]. Moscow, 2008, 300 p.
2. Jurov I.Ju. Vorsanova S.G. Jurov Ju.B. Genomnye i hromosomnye bolezni central'noj nervnoj sistemy: molekuljarnye i citogeneticheskie aspekty [Genomic and chromosomal disorders of the central nervous system: molecular and cytogenetic aspects]. Moscow, 2014, 384 p.
3. Beaudet, A.L. The utility of chromosomal microarray analysis in developmental and behavioral pediatrics / A.L. Beaudet // Child Dev. — 2013. — Vol.84, №1. — P. 121 - 132.
4. Ellison, J.W. Genetic basis of intellectual disability. / J.W. Ellison, J.A. Rosenfeld, L.G. Shaffer // Annu. Rev. Med. — 2013. — Vol. 64. — P. 441 - 450.
5. Iourov, I.Y. Molecular cytogenetics and cytogenomics of brain diseases / I.Y. Iourov, S.G. Vorsanova, Y.B. Yurov // Curr. Genomics. — 2008. — Vol. 9, №7. — P. 452 - 465.
6. Molecular karyotyping by array CGH in a Russian cohort of children with intellectual disability, autism, epilepsy and congenital anomalies / I.Y. Iourov, S.G. Vorsanova, O.S. Kurinnaia, et al. // Mol. Cytogenet. — 2013. — Vol. 6. — 38.
7. Increased chromosome instability dramatically disrupts neural genome integrity and mediates cerebellar degeneration in the ataxia-telangiectasia brain / I.Y. Iourov, S.G. Vorsanova, T. Liehr, et al. // Hum. Mol. Genet. — 2009. — Vol. 18, №14. — P. 2656 - 2669.
8. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies / D.T. Miller, M.P. Adam, S. Aradhya, et al. // Am. J. Hum. Genet. — 2010. — Vol. 86, №5. — P. 749 - 764.
9. The genetic landscape of autism spectrum disorders / R.O. Rosti, A.A. Sadek, K.K. Vaux, J.G. Gleeson // Dev. Med. Child. Neurol. — 2014. — Vol. 56, №1. — P. 12 - 18.
10. Array CGH in patients with developmental delay or intellectual disability: are there phenotypic clues to pathogenic copy number variants? / M. Shoukier, N. Klein, B. Auber et al. // Clin. Genet. — 2013. — Vol. 83, №1. — P. 53 - 65.

11. Unexplained autism is frequently associated with low-level mosaic aneuploidy / Y.B. Yurov, S.G. Vorsanova, I.Y. Iourov et al. // J. Med. Genet. — 2007. — Vol. 44, №8. — P. 521 - 525.