ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 08, Issue, 07, pp.21783-21785, July, 2018

CASE REPORT OPEN ACCESS

GENOMIC INVESTIGATION OF AUTISM SPECTRUM DISORDER IN A PUBLIC HEALTH SERVICE: A CASE REPORT

***[1,2,3]Thaís C. Vieira, [4]Fabíola F. de Medeiros, [4]João V. de P. Mendanha, [2]Irene P. Pinto, [1,2]Aparecido D. da Cruz and [1,2,3,4] Marc A. D.Gigonzac**

[1]LaGene, Laboratório de Citogenética Humana e Genética Molecular, Secretaria de Saúde do Estado de Goiás (LACEN/SES-GO)
[2]MGene, Mestrado em Genética, Pontifícia Universidade Católica de Goiás – PUC-GO
[3]Universidade Estadual de Goiás – UEG
[4]Faculdade de Medicina, Pontifícia Universidade Católica de Goiás – PUC-GO

ARTICLE INFO

Article History:
Received 28th April, 2018
Received in revised form
07th May, 2018
Accepted 09th June, 2018
Published online 30th July, 2018

Key Words:
Autism Spectrum Disorder,
Chromosomal Deletions,
Chromosome Analysis by Microarray.

ABSTRACT

Autism Spectrum Disorder (ASD) is a complex and heterogeneous clinical condition, which involves an inability to establish affective and interpersonal contact. The etiology of this disorder may be associated with hundreds of different genes, and the use of large-scale genome screening techniques such as Chromosome Analysis by Microarray (CMA) is usually required for its determination. In this report, a child with clinical indication of ASD was evaluated by CMA on the CytoScan HD platform (Affymetrix®), revealing a de novo microdeletion of 248.87Kb at the 21q11.2 locus involving the POTED and C21orf15 genes. CMA has been shown to be an effective method for the identification of genes with potential relation with ASD, and new research that allows recognition of the affected neurobiological pathways is still necessary for a correct understanding of the molecular mechanisms involved.

Citation: Thaís C. Vieira, Fabíola F. de Medeiros, João V. de P. Mendanha, Irene P. Pinto, Aparecido D. da Cruz and Marc A. D.Gigonzac. 2018. "Genomic investigation of autism spectrum disorder in a public health service: A case report", *International Journal of Development Research*, 8, (07), 21783-21785.

INTRODUCTION

The term "autism" was first used to denote an innate inability to establish affective and interpersonal contact, resulting in great difficulty or impossibility of communication, as well as different repetitive patterns and stereotypies (Kanner, 1943; Brentani, 2013). Currently, the group of neuro developmental disorders that share these characteristics is known as Autism Spectrum Disorder (ASD) and includes Classical Autism, Asperger's Syndrome, Childhood Disintegrative Disorders and Invasive Developmental Disorders Without Other Specification (Mazefsky *et al*., 2013). The diagnosis of ASD is essentially clinical, with the most commonly used criteria being those described in the American Psychiatric Association's Diagnostic and Statistical Manual, DSM-V (2013), which evaluates the social interaction, communication, restricted and stereotyped activities and interests and delays or abnormal functions in behavior (Araújo and LotufoNeto, 2014). In this sense, the screening can be done through different tests, such as the Autism - Modified Screening Scale (M - CHAT), the Autism Assessment Scale in Childhood (CARS) and the Diagnostic Interview for Autism - Revised (ADIR -R) (Kulage *et al*., 2014). This disorder is quite complex and heterogeneous, with varying degrees of severity, presenting an estimated prevalence of 1 in every 68 children (Grafodatskaya *et al*., 2010, Butler *et al*., 2015). There are reports of TEA associations with changes in the intestinal microbiota (Mulle *et al*., 2013), use of Thimerosol (Fombonne *et al*., 2008), infectious diseases such as rubella (Gadia *et al*., 2004) and foods with glyphosate *et al*., 2014). However, the presence of a major genetic component acting in the determination of the disorder is evident (Brasa *et al*., 2016; Hens *et al*., 2016). According to Pinto (2014), there are

Corresponding author **[1,2,3]Thaís C. Vieira**
[1]LaGene, Laboratório de Citogenética Humana e Genética Molecular, Secretaria de Saúde do Estado de Goiás (LACEN/SES-GO)
[2]MGene, Mestrado em Genética, Pontifícia Universidade Católica de Goiás – PUC-GO
[3]Universidade Estadual de Goiás – UEG

convergent pathways between a hundred genes that could lead to the autistic phenotype, such as neuronal development, axoniogenesis and synaptic functioning. In recent years, the development of molecular techniques has identified more than 600 genes associated with ASD (Hernandez *et al*., 2015). In this context, Brasa *et al*. (2016) points out that the determination of the etiology of these disorders, which may involve structural chromosomal abnormalities or genetic alterations, is only possible with large-scale genome screening techniques, such as Microarray Chromosome Analysis (CMA). CMA has been shown to be a precise and high-throughput method, with a significant improvement in the sensitivity of the analysis of the large number of DNA sequences, allowing a wide coverage of the genome. Knowing the exact location of the genomic changes found in the patient, it is possible to identify the genes involved and try to establish clinical correlations, especially in patients who do not have an easily identifiable syndrome (Lay-Son, 2015).

CASE REPORT

Patient

CCM, 9 years old, eldest, male, black, native of Sinope - MT and resident of Goiânia, Goiás, attended the Association of Parents and Friends of Exceptional Goiânia (APAE) and referred to the Laboratory of Human Cytogenetics and Molecular Genetics LaGene) of the State Health Department (SES-GO), which was awarded a grant from the Replicon Research Center (NPR) and located at the Pontifical Catholic University of Goiás (PUC-GO) in August / 2014 for genomic research, Neuropsychomotor (DNPM), mental retardation with no known aetiology and characteristics of Autism Spectrum Disorder. The mother, ESC, 36 years old, had no relationship to the child's father and had a nonintercurrent pregnancy, reporting only 1 episode of Urinary Tract Infection in the 4th month of pregnancy (sic), treated with antibiotics, and use of anticonvulsant in early pregnancy. C.C.M. was born in 2007 with 41 weeks in a hospital setting, cesarean section due to the absence of uterine dynamics; weighing 2800g, measuring 45cm, cephalic perimeter of 33cm, APGAR 9/10, without cyanosis and other morbidities. He presented normal reflexes, did not develop jaundice and remained in Joint Housing until discharge. At the fifth month of life, the mother noticed that the patient presented a certain delay for the age, because she did not firm the trunk and did not look at her parents. He sat with support only at 1 year and 4 months; crawled with 2 years after several sessions of physiotherapy and at the moment, still does not walk and only stands with support. The parents did not report any similar signs or symptoms in the family and refer to normal development of the patient's younger sister.

Clinical and Cytogenetic Analysis

A fluorescence in situ hybridization (FISH) for the 15q11-13 region (SNPRN / ICI gene) was performed in October 2009, which ruled out the initial clinical suspicion of Angelman Syndrome. In May 2014, the patient was then referred to LaGene / Replicon for a screening for TEA, where the CARS application was performed, confirming the Disorder. Subsequently, a K-Band Karyotype of the child was elaborated, with 20 cells analyzed, with a normal cytogenetic register for the male (46, XY).

Chromosome Analysis by Microarray – CMA

As no alterations were found by conventional diagnostic methods, the patient was referred to a Chromosomal Microarray Analysis (CMA) in September 2014 through a pioneering project in the State of Goiás to use these techniques in a partnership of PUC-GO with LaGene / LACEN / SES-GO, which makes it possible to perform genetic tests free of charge through the Unified Health System (SUS). The CMA was conducted on a CytoScan HD (Affymetrix®), which is a comprehensive genotyping matrix for the human genome, providing a high power of investigation of structural genetic variations, with more than 2.6 million copies of polymorphic markers 750,000 Simple Nucleotide Polymorphisms (SNPs). The methodology consists of an assay composed of multiple allele-specific hybridization probes that are complementary to the SNP regions present in the reduced fraction of the amplified genome in the assay. After hybridization, the DNA Chips used are digitized in GeneChip® Scanner 3,000-7G (Affymetrix®) and analyzed in ChAS (Chromosome Analysis Suite®, V.3.1) software.

RESULTS

Through the CMA technique, a de novo microdeletion of 248, 87Kb at the 21q11.2 locus was detected in the linear position 15.006.457-15.255.326, not being reported as a common variation in the general population (figure 1). In the analysis by OMIM (Online Mendelian Inheritance in Man) / NCBI (National Center for Biotechnology Information), the range of microdeletion recorded involves two genes, called POTED and C21orf15.

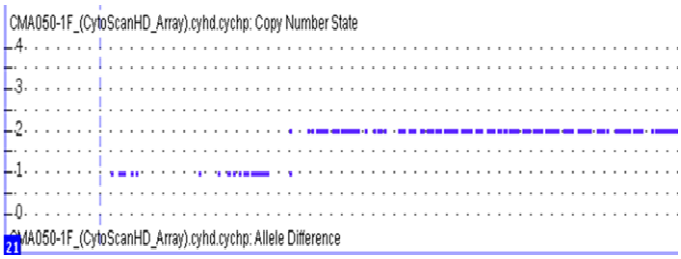

Figure 1. ChAS software panel indicating a microdeletion of 248.87Kb at the 21q11.2 locus

DISCUSSION

The POTED gene (or POTE) was first described by Bera *et al* in 2002 and is characterized by having 11 exons and encoding a protein of approximately 66 kDa expressed in different tissues such as prostate, testis, ovary and placenta. An important aspect is that the expression of this gene in the brain has never been evaluated. More recently, Bera *et al*. (2012) reported that it is not yet possible to attribute to POTED a structural or operational function and highlighted an apoptotic activity associated with certain caspases that are involved in several synaptic and glutamatergic dysfunctions, strongly associated with the autistic phenotype (Martins, 2014). C21orf15 has never been correlated to any phenotypic alterations, nor is its function known. According to OMIM, it is probably a conserved pseudogene in humans, presenting homology with family 4 of Cytochrome P450 (CYP4F29P). On the other hand, C21orf15 is juxtaposed to the AUTS12 gene, which is a gene reported for susceptibility to autism

(Ahmed *et al*., 2015). With resolution of the technique, however, it is still not possible to state whether C21orf15 could participate in the regulation of AUTS12 or whether it could also have been affected by microdeletion. The TEA presents an important clinical diversity, being much under-diagnosed and still lacking specific exams in the routine. The American College of Medical Genetics (ACMG) recommends AMC as the first-line test in the population of individuals with developmental delays, intellectual disabilities, autism spectrum, and multiple congenital anomalies. The method leads to a diagnosis in at least 10-15% of cases, which is better than the 3% of traditional chromosome analysis, in addition to detecting severe anomalies that are identified in the karyotype (Schaefer, 2013). CMA is a highly accurate and high-throughput method and has shown significant improvement and sensitivity in the analysis of the large number of DNA sequences, allowing a wide coverage of the genome, with hundreds of genes already described with a strong association with TEA (Lay-Son, 2015).

Conclusion

X1: Despite the development of new techniques and the evident importance of AMC in the diagnosis of ASD, the etiological heterogeneity of the disease and the innumerable genetic factors reveal that there may be a link between the deletions in the cited region and the involvement of the POTED and C21Orf15 genes. These data demonstrate that further research and in-depth studies on Autistic Spectrum Disorder, which allow the identification of the affected neurobiological pathways, along with complementary techniques, such as next generation genomic sequencing (NGS), are necessary. Likewise, the increased use of large-scale genome screening techniques to investigate these complex genetic alterations becomes crucial. Although the recognition is clinical, the identification of the genes and their functions is fundamental to allow an early diagnosis and to evaluate potential future therapies.

REFERENCES

Ahmed, I., Rafiq, M. A., Vincent, J. B., Bhatti, A., Ayub, M., and John, P. 2015. Homozygosity mapping of autosomal recessive intellectual disability loci in 11 consanguineous Pakistani families. *Actaneuropsychiatrica,* 27(01), 38-47.

American Psychiatric Association. 2013. Diagnostic and statistical manual of mental disorders (DSM-5®).American Psychiatric Pub.

Araújo, Á. C., and Lotufo Neto, F. 2014. A nova classificação americana para os transtornos mentais: o DSM-5. Revista brasileira de terapia comportamental e cognitiva, 16(1), 67-82.

Bera, T. K.,Zimonjic, D. B., Popescu, N. C., Sathyanarayana, B. K., Kumar, V., Lee, B., andPastan, I. 2002. POTE, a highly homologous gene family located on numerous chromosomes and expressed in prostate, ovary, testis, placenta, and prostate cancer. *Proceedings of the National Academy of Sciences,* 99(26), 16975-16980.

Brasa, S., Mueller, A., Jacquemont, S., Hahne, F., Rozenberg, I., Peters, T. andGrenet, O. 2016. Reciprocal changes in DNA methylation and hydroxymethylation and a broad repressive epigenetic switch characterize FMR1 transcriptional silencing in fragile X syndrome. Clinicalepigenetics, 8(1), 1.

Brentani, H., Paula, C. S. D., Bordini, D., Rolim, D., Sato, F., Portolese, J. and McCracken, J. T. 2013. Autismspectrumdisorders: an overview ondiagnosis and treatment. *Revista brasileira de psiquiatria*, 35, S62-S72.

Butler, M G. *et al*. 2015. Whole exome sequencing in females with autism implicates novel and candidate genes. *International Journal of Molecular Sciences*, v. 16, n. 1, p. 1312-1335.

D'Amelio, M., Cavallucci, V., Middei, S., Marchetti, C., Pacioni, S., Ferri, A. and Moreno, S. 2011. Caspase-3 triggers early synaptic dysfunction in a mouse model of Alzheimer's disease. *Nature neuroscience*, 14(1), 69-76.

Fombonne, E. 2008. Thimerosal disappears but autism remains. Archives of General Psychiatry, 65(1), 15-16.

Gadia, C. A., Tuchman, R., andRotta, N. T. 2004.Autismo e doenças invasivas de desenvolvimento. *Jornal de pediatria,* 80(2), 83-94.

Grafodatskaya, D., Chung, B., Szatmari, P., andWeksberg, R. 2010.Autism spectrum disorders and epigenetics. Journal of the American Academy of Child and Adolescent Psychiatry, 49(8), 794-809.

Hernandez, L. M., Rudie, J. D., Green, S. A., Bookheimer, S., andDapretto, M. 2015. Neural signatures of autism spectrum disorders: insights into brain network dynamics. *Neuropsychopharmacology,* 40(1), 171-189.

Kanner, L. 1960. Child Psychiatry, Springfield, Illinois, Charles C.

Kulage, K. M., Smaldone, A. M., and Cohn, E. G. 2014. How will DSM-5 affect autism diagnosis? A systematic literature review and meta-analysis. *Journal of autism and developmental disorders,* 44(8), 1918-1932.

Lay-Son, G., Espinoza, K., Vial, C., Rivera, J. C., Guzmán, M. L., and Repetto, G. M. 2015. Chromosomal microarrays testing in children with developmental disabilities and congenital anomalies. *Jornal de pediatria*,91(2), 189-195.

Martins, A. L. B. 2014. Análise de genes envolvidos na neurotransmissão, formação e manutenção sináptica em indivíduos com transtornos do espectro do Autismo.

Mazefsky, C. A., McPartland, J. C., Gastgeb, H. Z., andMinshew, N. J. 2013. Brief report: Comparability of DSM-IV and DSM-5 ASD research samples. Journal of autism and developmental disorders, 43(5), 1236-1242.

Mulle, J.G, Sharp, W.G., Cubells, J.F. The Gut Microbiome: A New Frontier in Autism Research. *CurrPsychiatry Rep*. Fevereiro, 2013.

Nunes, G. D. F. 2015. Modelo animal de autismo por exposição pré-natal ao ácido valpróico: análise de sinapses excitatórias e inibitórias.

Pinto, D., Delaby, E., Merico, D., Barbosa, M., Merikangas, A., Klei, L., ... andVorstman, J. A. 2014. Convergence of genes and cellular pathways dysregulated in autism spectrum disorders. The American Journal of Human Genetics, 94(5), 677-694.

Schaefer, G. B., Mendelsohn, N. J., and Professional Practice and Guidelines Committee. 2013. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genetics in Medicine, 15(5), 399-407.

****