Small Deletion of 143 Kb Encompassing Exon 2 of the *AUTS2*: Rise of a New Microdeletion Syndrome?

Silvia Serafim; Barbara Marques*; Filomena Brito*; Sonia Pedro*; Cristina Ferreira*; Catarina Ventura*; Isabel Gaspar**; Hildeberto Correia**

*Unidade de Citogenetica, Instituto Nacional de Saude Doutor Ricardo Jorge, I.P., Lisboa, Portugal

**Consulta de Genetica Medica, Hospital Egas Moniz, Centro Hospitalar de Lisboa Ocidental EPE, Lisboa, Portugal

Introduction

Chromosome Microarray Analysis is a powerful diagnostic tool and is being used as a first-line approach to detect chromosome imbalances associated with intellectual disability, dysmorphic features and congenital anomalies. This test enables the identification of new copy number variants (CNVs) and their association with new microdeletion/microduplication syndromes in patients previously studied by conventional cytogenetics analysis.

Here we report the case of a female with severe intellectual disability, absence of speech, microcephaly and congenital abnormalities with a previous normal karyotype performed at a younger age.

Microarray analysis was performed at 17 years of age, in order to assess if a genome unbalance could explain the patient's undiagnosed phenotype. A small deletion was found in *autism susceptibility candidate 2 (AUTS2)* gene .

The *AUTS2* gene has been recently implicated in autosomal dominant mental retardation with variable syndromic phenotype (OMIM *607270, #615834). Common clinical features described in patients with deletions in *AUTS2* gene include autism, intellectual disability, speech delay and microcephaly, among others [1,2,3,4,5,6].

We compare our patient with similar reported cases, adding additional value to the phenotype-genotype correlation of CNVs in this region.

Method

Microarray analysis was carried out in DNA extracted from peripheral blood using Affymetrix CytoScan HD chromosome microarray platform according to the manufacturer's recommendations. CytoScan HD array provide 750,000 polymorphic (SNP, single nucleotide polymorphism) and 1,900,000 non-polymorphic (CNV). The raw data were processed using Affymetrix Chromosome Analysis Suite software (ChAS) and the output data were interpreted with the UCSC Genome Browser (http://genome.ucsc.edu; GRCh37/hg19 assembly), DECIPHER v8.8 (http://decipher.sanger.ac.uk/) and ClinGen (http://clinicalgenome.org/). The function of the gene, which were located within the region of the genomic imbalance, was retrieved from the GeneCards (http://www.genecards.org/) and OMIM (http://www.ncbi.nlm.nih.gov/omim) databases.

Research of other cases involving deletions in *AUTS2* gene has been used for a comparison of phenotype-genotype among this region [1,2,3,4,5,6].

Results and Discussion

A deletion with 143 Kb at the 7q11.22 breakpoint was identified. Parents were not available to assess inheritance for this CNV.

The CNV identified in our patient was classified as of clinical significance, and most likely accounts for the clinical features reported.

At the top of the most frequently reported clinical features, one can easily conclude that in almost all cases ID/DD is present, with the exception of 2/31 cases. Also microcephaly (18/30) and short stature (13/30) are among the clinical features most observed. ASD curiously was only present in 39 % of the total number considered here (12/31), despite the name of the gene (*autism susceptibility candidate 2*).

Considering the exon's phenotype distribution, aparently there are a larger number of clinical features observed at exon 6. Further investigation would be necessary to assess the eventual higher importance for this particular exon.

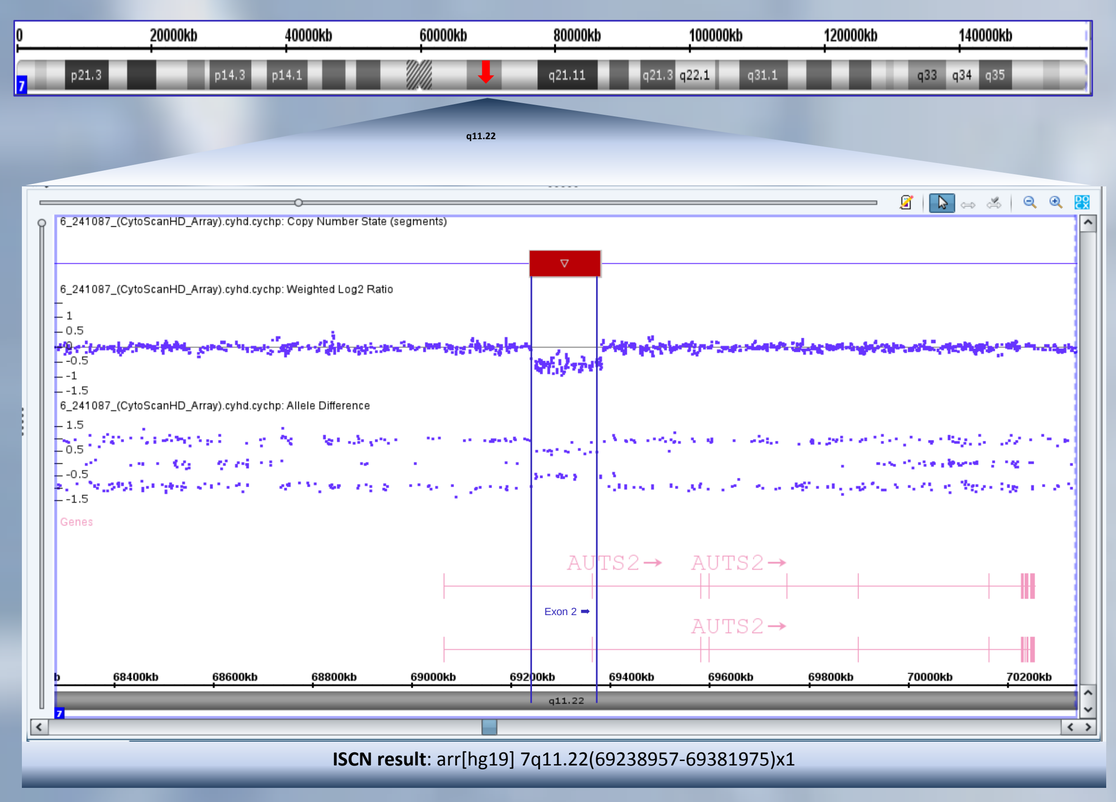

Figure 1 : Deleted region (with allelic concordant distribution) encompassing exon 2 of *AUTS2* gene.

Table 1: Comparison of our case (***INSA***) with other six published case studies (A – F). The total number of patients included in the table is of 31, although case study C, per se, has 21 of the total.

Study	*INSA*	A [5]				B [4]	C [2]	D [1]	E [3]		F [6]
Patient	1	2	3	4	5	6	N=21	8	9	10	11
Sex	F	F	F	F	M	F	13 F + 8 M	M	M	M	M
Exon	2 (del)	6-14 (del)	6-14 (del)	5 (dup)	5 (dup)	6 (del)	-	3-6 (del)	7 (del)	6 (del)	1 (del)
Inheritance	n.a.	dn	n.a.	mat (siblings)		dn	dn= 9/13	dn	dn	dn	dn
Phenotype:											
ID /DD	✓	✓	✓	✓	✓		✓ 20/21	✓	✓	✓	✓
ASD				✓	✓		✓ 7/21		✓	✓	✓
Hiperactivity /ADHA							✓ 3/21		✓		✓
Epilepsy					✓		-				
Dysmorphic features		✓		✓	✓		✓	✓	✓	✓	
Speech delay	✓					✓	-				✓
Microcephaly	✓			✓			✓ 14/20		✓	✓	
Short Stature							✓ 12/20			✓	
Feeding problems							✓ 10/21	✓	✓	✓	
Hipotonia							✓ 8/21				
Strutural brain anomaly							✓ 3/11				
Cerebral palsy /spasticity						✓	✓ 9/21				
Scoliosis	✓	✓					✓ 2/9				
Others		Atrial septal defect		Radioulnar synostosis		Pes planus	✓	Ptosis	✓	✓	Hearing loss

ID = Intelectual Disability; DD = Developmental Delay; ASD = Autism Spectrum Disorder; ADHA = Atention Deficit and Hipercactivity

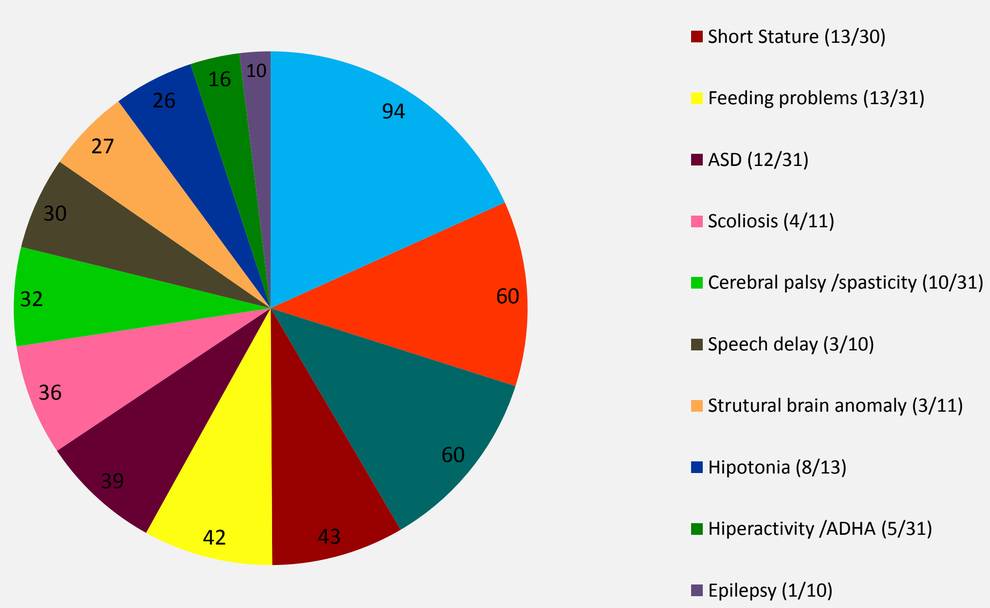

Chart 1: Distribution of the most frequent clinical features, according to the relative percentage of each one (number of affected patients in the total reported for that particular feature).

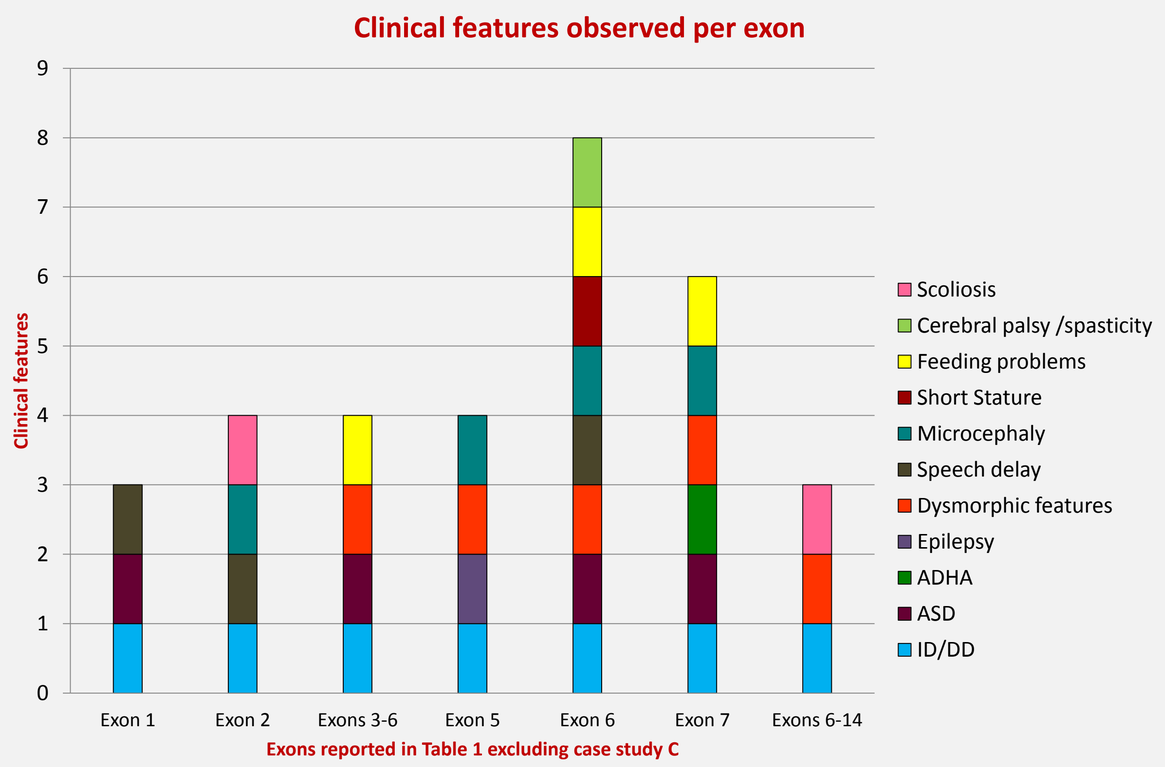

Chart 2: Clinical features observed in the deleted exons for all cases, except for case C for which the reported information includes the 21 patients at once.

Conclusion

In resume, the growing collection of new cases with similar clinical features, and the observation of this deletion occurring frequently *de novo* (in the present cases it occurs with a relative percentage of 71%), indicates the CNV as having a strong likelihood of being associated with a new single gene microdeletion syndrome.

References

1) Alexandra Jolley, et al. De Novo Intragenic Deletion of the Autism Susceptibility Candidate 2 (*AUTS2*) Gene in a Patient With Developmental Delay: A Case Report and Literature Review. Am J Med Genet Part A 161A:1508–1512 (2013)
2) Gea Beunders, et al. Exonic Deletions in *AUTS2* Cause a Syndromic Form of Intellectual Disability and Suggest a Critical Role for the C Terminus. The American Journal of Human Genetics 92, 210–220 (2013)
3) Gea Beunders, et al. Two male adults with pathogenic *AUTS2* variants, including a two-base pair deletion, further delineate the *AUTS2* syndrome. European Journal of Human Genetics 1–5 (2014)
4) Ina E. Amarillo, Wenhui Laura Li, Xinmin Li, Eric Vilain, and Sibel Kantarci. De Novo Single Exon Deletion of *AUTS2* in a Patient with Speech and Language Disorder: A Review of Disrupted *AUTS2* and Further Evidence for Its Role in Neurodevelopmental Disorders. Am J Med Genet Part A 164A:958–965 (2014)
5) Sandesh CS Nagamani, et al. Detection of copy-number variation in *AUTS2* gene by targeted exonic array CGH in patients with developmental delay and autistic spectrum disorders. European Journal of Human Genetics 21,343-346 (2013)
6) Yi Liu, et al. De novo Exon 1 Deletion of *AUTS2* Gene in a Patient With Autism Spectrum Disorder and Developmental Delay: A Case Report and a Brief Literature Review. Am J Med Genet Part A 9999A:1–5 (2015)