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LETTER TO THE EDITOR

Acute lymphoblastic leukemia in a nine-year-old girl with isodicentric chromosome 15 syndrome

Roberto Antonucci[a,*], Nadia Vacca[a], Elisa Ghisu[a], Gloria Acquaviva[b], Carlo Cosmi[a], Anna Maria Marinaro[a], Cristian Locci[a], Claudio Fozza[b]

[a] *Pediatric Clinic, Department of Clinical and Experimental Medicine, University of Sassari, Sassari, Italy;* [b] *Hematology, Department of Clinical and Experimental Medicine, University of Sassari, Sassari, Italy*

Abstract

Isodicentric chromosome 15, also called idic(15), is a rare chromosomal abnormality resulting from inverted duplication of proximal 15q. It is associated with specific clinical findings such as early central hypotonia, developmental delay, cognitive dysfunction, autism spectrum disorders, and seizure. Herein we describe a case of a girl with idic(15) syndrome who developed acute lymphoblastic leukemia (ALL) at the age of 9 years. Our case suggests a possible correlation between idic(15) and ALL, and possible functional links between these two conditions.

Keywords Acute lymphoblastic leukemia, Isodicentric chromosome 15 syndrome, idic(15), Autism spectrum disorders, Children.

To the Editor,

Chromosome 15q11-q13 is a region extraordinarily subject to genomic rearrangements as well generation of supernumerary pseudodicentric chromosomes also known as isodicentric 15 or idic(15) [1]. Deletions usually take place within three commonly known breakpoints (BP1-BP3) [2,3], while duplications and triplications have been described in two additional breakpoints (BP4 and BP5) positioned telomeric to BP3. Since genes in chromosome 15q11.2 are subject to genomic imprinting, deletions involving this region lead to Prader-Willi (PWS) or Angelman syndrome (AS) [4]. The critical ~6 Mb region responsible for both PWS/AS and the duplication chromosome 15 syndromes lies between BP2 and BP3 [5]. Noteworthy, duplications of chromosome 15q11–q13 account for ~1–3% of autism, being the second most prevalent genomic aberration associated with autism, after fragile X syndrome [6]. In further analysis, whole-genome expression profiling revealed that 112 transcripts were dysregulated in samples harboring duplications. Paramount among dysregulated genes was ubiquitin protein ligase E3A (UBE3A; 15q11–q13), which was found to be nearly 1.5–2.0-fold up-regulated in duplicated samples at both the RNA and protein levels [6]. As TP53 is a prominent UBE3A substrate, idic(15) cells, when exposed to genotossic damage, display an increase in ubiquitinated TP53. Based on this interaction, cells harboring duplications of UBE3A might show decreased apoptotic potential or an increased tendency to accumulate DNA damage [6]. Other key findings from gene expression analysis included the downregulation of the genes APP and SUMO1 with well-characterized roles in mechanisms of apoptosis [6]. The incidence of inv dup15 or idic(15) syndrome is estimated in one case every 30,000, with a sex ratio of 1:1 [7]. The disease is generally not inherited but occurs de novo. Multiple genetic mechanisms have been suggested to explain the clinical heterogeneity of the disease. This condition displays distinctive clinical features including early central hypotonia, epilepsy, developmental delay, intellectual disability, and autistic behavior albeit with a wide range of severity [1,8]. Autism or autistic-like behaviors of varying degrees are frequently found in patients with idic(15). Due to this association, some authors recommend that cytogenetic analysis for idic(15) should be performed in all patients affected by autism spectrum disorder [1]. Herein we report, for the first time, the case of a girl with idic(15) syndrome who developed acute lymphoblastic leukemia (ALL) at the age of 9 years. From the first months of life, the patient presented with a delay in emotional and visual development as well as in language and motor skills; furthermore,

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* Corresponding author.
E-mail address: rantonucci@uniss.it

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generalized hypotonia, easy irritability, excessive and frequent crying and difficulties in visual contact were observed. From 12 months of age, both a slowing of head circumference growth and psychomotor delay were observed. Slight facial dysmorphisms with epicanthus, pseudostrabismus and flat nasal bridge were also reported. Karyotype analysis revealed a supernumerary chromosome. The inverted duplication of chromosome 15 was demonstrated by FISH analysis with probes for loci D15S11 and GABRB3 included in the PWS region. In more details, a supernumerary chromosome deriving from the inverted duplication of chromosome 15 was demonstrated with DA-DAPI staining (47,XX,+idic(15)(q13?2).ish idic(15)(D15Z1,D15S11,GABRB3,RP11-268O3,RP11-25D17)x2). Therefore, the diagnosis of idic(15) syndrome with a karyotype 47,XX,+idic(15)(pter->q13::q13->pter) was made. At the age of 9, she was admitted to our clinic for pallor, asthenia, drowsiness, skin ecchymosis, petechiae and hepato-splenomegaly. Complete blood count analysis demonstrated anemia, hyperleukocytosis and thrombocytopenia. A cytomorphological examination of peripheral blood and bone marrow revealed a large number of lymphoid blasts, while cytochemical and immunophenotypic tests allowed the diagnosis of pre-B ALL. All molecular analyses including *t*(4;11), *t*(9;22), *t*(12;21) and *t*(1;19) were negative and no CNS involvement was documented [9]. Treatment according to the AIEOP-BFM ALL 2000 international protocol for children and adolescents was immediately started. Two years after diagnosis and just one month after starting follow-up, a bone marrow relapse was documented. To our knowledge, no association between idic(15) and ALL has been previously reported. In the present case, we may hypothesize that the inverted duplication of chromosome 15 alters the copy number of genes which are subject to an epigenetic mechanism, thus favoring deregulation of normal cell growth and differentiation pathways. Although these findings need to be further confirmed, our case suggests a possible correlation between idic(15) and ALL and possible functional links between these two conditions.

Conflicts of interest

Nothing to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cancergen.2019.05.001.

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