Twenty-year cytogenetic and molecular follow-up of a patient with ring chromosome 15: a case report

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Abstract

Introduction: Ring chromosome 15 is a rare disorder, with only a few over 40 cases reported in the literature. There are only two previous reports of cases where patients with ring chromosome 15 have been followed-up.

Case presentation: We report here on the 20-year clinical and cytogenetic follow-up of a patient with a ring chromosome 15. Our patient, a Caucasoid Asian woman, presented with short stature, microcephaly, minor dysmorphic features, hyperextensible knees, generalized hirsutism, café-au-lait and small hypochromic spots spread over her face and the front of her chest and abdomen, dorsolumbar scoliosis and mild intellectual disability. She was followed-up from the age of eight to 28 years. When she was 27 years old, she was reported by her mother to present with compulsive overeating and an aggressive mood when challenged. Karyotyping revealed that the majority of her cells harbored one normal chromosome and one ring chromosome. Silver staining revealed the presence of the nucleolar organizer region in the ring chromosome. Ring loss and/or secondary aberrations exhibited a slight increase over time, from 4.67% in 1989 to 7.67% in 2009, with the presence of two monocentric rings, cells with interlocked rings, a dicentric ring, and broken or open rings. A genome-wide array technique detected a 5.5Mb deletion in 15q26.2.

Conclusions: We observed that some phenotypic alterations in our patient can be associated with gene loss and haploinsufficiency. Other features may be related to different factors, including ring instability and epigenetic factors.
We report here on the 20-year clinical and cytogenetic follow-up of a patient with r(15).

**Case presentation**

Our patient is the third child of non-consanguineous, healthy parents and has four brothers. Her mother is Caucasian and her father is Asian. At birth her measurements were: weight of 2050g (<fifth centile); length of 48cm (fifth centile); and head circumference (HC) of 30cm (<2 standard deviations SD). The first genetic evaluation at eight years and 10 months of age showed her height to be 106cm (<fifth centile); weight 17kg (<fifth centile); and HC 48cm (<2SD). She presented with microcephaly, brachycephaly, high forehead, exotropia, hypoplastic alae nasi, high palate, retroglossitis, hyperextensible knees, rough and dry skin of her lower limbs, generalized hirsutism, four café-au-lait spots, disseminated small hypochromic spots and dorsolumbar scoliosis. She had mild intellectual disability, a reduced verbal repertoire, and a docile and cooperative personality.

At 27 years and 3 months of age, our patient’s mother reports that her daughter had compulsive overeating, an aggressive mood when challenged, and could not read or write. At this time, her measurements were: weight 58kg; height 146.5cm (<third percentile); HC 51.5cm (<2 SD); and a body mass index of 27.23 (+1 SD), corresponding to overweight. In addition to the previous clinical features described above she presented with centripetal obesity, sparse and thin hair, exotropia of her left eye, a thin upper lip, hypoplastic thumbs with proximal implantation, disseminated hypopigmented leaf-shaped spots, acanthosis nigricans, dry skin, subclinical hypothyroidism and regular menstrual cycles since 14 years of age.

A chromosome analysis was first performed in 1989, when our patient was eight years old, from 72-hour lymphocyte cultures according to standard procedures. Giemsa chromosome banding stain (G-banding) revealed a ring chromosome 15 substituting one normal chromosome 15 (Figure 1a). Centromere banding stain (C-banding) and silver staining showed that the ring was monocentric and euchromatic. Our patient’s parents silver staining showed that the ring was monocentric and euchromatic. Our patient’s parents silver staining showed that the ring was monocentric and euchromatic. Our patient’s parents silver staining showed that the ring was monocentric and euchromatic. Our patient’s parents silver staining showed that the ring was monocentric and euchromatic. Our patient’s parents silver staining showed that the ring was monocentric and euchromatic. Our patient’s parents silver staining showed that the ring was monocentric and euchromatic. Our patient’s parents silver staining showed that the ring was monocentric and euchromatic. Our patient’s parents silver staining showed that the ring was monocentric and euchromatic. Our patient’s parents silver staining showed that the ring was monocentric and euchromatic. Our patient’s parents silver staining showed that the ring was monocentric and euchromatic. Our patient’s parents silver staining showed that the ring was monocentric and euchromatic. Our patient’s parents silver staining showed that the ring was monocentric and euchromatic.

The loss of the IGF1R gene located at 15qter and r(15) may be responsible for her growth delay, commonly observed in patients with a deletion in the 15qterm and r(15), since it is required for normal embryonic and postnatal growth [10-12]. The IGF1R gene also plays an important role in carbohydrate metabolism and central nervous system...
development [13,14]. It is supposed that the loss of one copy of this gene could also explain the growth delay observed in patients with a deletion of 15q26 [15,16]. Discrete growth delay is a common feature associated with any autosomal ring chromosome and has been attributed to the ring instability, which causes a high frequency of ring loss or duplication, resulting in cell death [17]. In the case of r(15), the growth delay is much more evident due to the loss of an IGF1R gene [15-18].

In our study, we observed dynamic mosaicism upon cytogenetic analysis that was not identified by array technique considering its resolution for mosaicism detection [19].

The mosaicism level of the ring chromosome, the variation of tissue-specific mosaicism, the mitotic instability of ring chromosomes and the parental origin of the r(15) have also been proposed as contributing factors for phenotype determination [4,15].

Conclusion
Both the literature and our data suggest that the wide spectrum of clinical signs and symptoms reported in patients with r(15), extending from a near-normal phenotype to multiple malformations, may result from the interaction of several factors. These include the variation in the amount of euchromatin loss from the short and/or long arm, somatic mosaicism due to ring instability, and epigenetic factors. The latter might relate to the phenotype of the patients because the genomic architecture changes due to the circularization of the chromosome may cause a position effect and an altered expression of genes present in the ring chromosome.

Consent
Written informed consent was obtained from the patient for publication of this manuscript and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
RSG performed cytogenetic and fluorescent in situ hybridization studies and wrote the paper. VFAM and DB collected the clinical data of the patient at age 8 and 28 years. RP performed array and analyzed the results. SST performed cytogenetic studies. LDK and MIM coordinated the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgments
This work was supported by FAPESP, Brazil (grant to MIM #07/58735-5).

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Figure 1 Partial Giemsa chromosome banding stain (G-banding) karyotype. Showing one normal chromosome 15 and (a) one ring chromosome 15; (b) two monocentric ring chromosomes 15; (c) one open ring chromosome 15; (d) fluorescent in situ hybridization result with a centromeric probe showing one dicentric ring chromosome 15; and (e) representation from Genotyping Console™ Software 3.0 (Affymetrix Inc., Santa Clara, CA, USA) showing a terminal deletion of chromosome 15. The results are shown for log 2 ratio (a measure of chromosomal copy number; y-axis) versus genomic position on chromosome 15 (HapMap samples).
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