

# Endocrine abnormalities in ring chromosome 11: a case report and review of the literature

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## Summary

Ring chromosomes (RCs) are uncommon cytogenetic findings, and RC11 has only been described in 19 cases in the literature. Endocrine abnormalities associated with RC11 were reported for two of these cases. The clinical features of RC11 can result from an alteration in the structure of the genetic material, ring instability, mosaicism, and various extents of genetic material loss. We herein describe a case of RC11 with clinical features of 11q-syndrome and endocrine abnormalities that have not yet been reported. A 20-year-old female patient had facial dysmorphism, short stature, psychomotor developmental delays, a ventricular septal defect, and thrombocytopenia. Karyotyping demonstrated RC11 (46,XX,r(11)(p15q25)). This patient presented with clinical features that may be related to Jacobsen syndrome, which is caused by partial deletion of the long arm of chromosome 11. Regarding endocrine abnormalities, our patient presented with precocious puberty followed by severe hirsutism, androgenic alopecia, clitoromegaly, and amenorrhea, which were associated with overweight, type 2 diabetes mellitus (T2DM), and hyperinsulinemia; therefore, this case meets the diagnostic criteria for polycystic ovary syndrome. Endocrine abnormalities are rare in patients with RC11, and the association of RC11 with precocious puberty, severe clinical hyperandrogenism, insulin resistance, and T2DM has not been reported previously. We speculate that gene(s) located on chromosome 11 might be involved in the pathogenesis of these conditions. Despite the rarity of RCs, studies to correlate the genes located on the chromosomes with the phenotypes observed could lead to major advances in the understanding and treatment of more prevalent diseases.

## Learning points:

- We hypothesize that the endocrine features of precocious puberty, severe clinical hyperandrogenism, insulin resistance, and T2DM might be associated with 11q-syndrome.
- A karyotype study should be performed in patients with short stature and facial dysmorphism.
- Early diagnosis and adequate management of these endocrine abnormalities are essential to improve the quality of life of the patient and to prevent other chronic diseases, such as diabetes and its complications.

## Background

Reports of ring chromosome 11 (RC11) are rare. To the best of our knowledge, only 19 cases have been described in the literature (Table 1). The clinical characteristics of

these patients are highly variable due to RC instability, mosaicism, and variable extents of genetic material loss, followed by terminal deletion in one or both chromosome arms (1) (2) (3) (4) (5) (6) (7) (8) (9) (10) (11) (12).



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**Table 1** Clinical manifestations and genetic features of the patients with RC11.

| References       | Age <sup>a</sup> /gender                               | Endocrine features            | Dermatological features                   | Physical growth abnormalities                        | Dysmorphic features             | Neurological and psychomotor developmental abnormalities                                    | Other outcomes  | Karyotype and other genetic features   |
|------------------|--|-------------------------------|---|--|---------------------------------|---|---|--|
| (1)              | 4 years/F  | Hypothyroidism                | <i>Cafe au lait</i> spot                  | Microcephaly, short stature, and growth delay        | Minimally dysplastic features   | Behavioral disorders, mild retardation, PMDD hyperreflexia, ankle clonus, and Babinski sign | -   | 46,XX,r(1)(p15q25); no variations in chromosome size; no apparent loss of chromosome material; minimal instability of chromosome constitution; and parents with normal karyotype |
| (2)              | 2 months/F   | Mild hirsutism, clitoromegaly | <i>Cafe au lait</i> spot                  | Microcephaly, weight and height below 3rd percentile | Many dysplastic features, FD    | PMDD, hypotonic, atrophy of the brain, seizures   | Cardiac malformation, pancytopenia, recurrent pneumonia, and death at 2.5 years old due to pulmonary bleeding | 46,XX,r(1)(p15q25)/45,XX; ring instability; clinical features of JS; and karyotype of parents unavailable  |
| (3)              | Neonatal/F   | -                             | <i>Cafe au lait</i> spot, digital anomaly | Microcephaly, short stature                          | FD                              | Mental retardation, hypotrophy, hypotonic PMDD  | Systolic murmur   | 46,XX,r(1); no apparent loss of chromosome material; no instability of chromosome constitution; and parents with normal karyotype  |
| (4)              | 6 months/F   | -                             | -   | Length and weight below 10th percentile              | Several dysplastic features, FD | PMDD  | Cardiac malformation, death at 18 months due to congestive HF   | 46,XX,r(1)(p15q24); clinical features of JS; and parents with normal karyotype   |
| (5)              | 9 months/F   | -                             | <i>Cafe au lait</i> spot                  | Growth delay, height and weight below 3rd percentile | Antimongoloid slant of the eyes | PMDD, speech/behavioral problems  | -   | 46,XX,r(1)(p15.5q25); RC instability; and parents with normal karyotype  |
| (6)              | 8 months/M   | -                             | -   | Syndactyly   | -                               | PMDD  | Wilms tumor, death at 18 months   | 46,XY,r(1)(p15q25); RC instability; and maternal chromosome analysis was normal  |
| (6) <sup>a</sup> | 11 years/M   | Obesity                       | -   | Microcephaly   | -                               | Mild mental retardation, PMDD   | Cryptorchidism, ocular abnormalities, scoliosis, skeletal, muscular, and articular defects                    | 46,XX,r(1)(p15.5q25) and karyotype of parents unavailable <sup>a</sup>   |
| (7) <sup>a</sup> | F  | -                             | -   | Growth delay, low weight                             | -                               | PMDD  | -   | RC11 associated with trisomy X in 15% of metaphases and karyotype of parents unavailable <sup>a</sup>  |
| (8)              | Patient 1: 4 years/F                                   | -                             | <i>Cafe au lait</i> spot                  | Microcephaly, short stature, low weight              | Clinodactyly                    | PMDD  | -   | 46,XX,r(1)(p15q25); chromosome instability; and father with normal karyotype   |
|                  | Patient 2: 33 years/F (mother of patients nos 1 and 3) | -                             | <i>Cafe au lait</i> spot                  | Microcephaly, short stature                          | -                               | Low IQ  | -   | 46,XX,r(1)(p15q25); chromosome instability; and father with normal karyotype   |
|                  | Patient 3: 15 years/F (half-sister of patient no. 1)   | -                             | <i>Cafe au lait</i> spot                  | Microcephaly   | -                               | Mild retardation  | -   | 46,XX,r(1)(p15q25); chromosome instability; and father with normal karyotype   |



Table 1 Continued

| References | Age <sup>a</sup> /gender   | Endocrine features | Dermatological features | Physical growth abnormalities                              | Dysmorphic features                                    | Neurological and psychomotor developmental abnormalities | Other outcomes                                   | Karyotype and other genetic features   |
|------------|----------------------------|--------------------|-------------------------|--|--|--|--|--|
| (9)        | Prenatal diagnosis/F       | –                  | –                       | –  | Immature fetus with abnormal craniofacial features, FD | –  | Bicornuate uterus, kidney calcifications         | 46,XX,r(11)(p15q25) in 14 colonies; the remainder 45,XX,-11. No loss of chromosomal material in the ring; FISH revealed that both the short-arm and long-arm specific sub-telomeric regions for 11p and 11q were preserved in the RC and parents with normal karyotype   |
| (10)       | Neonatal/M                 | –                  | –                       | –  | FD, dysplastic features                                | Generalized hypotonia, PMDD                              | Bilateral Wilms tumor                            | The patient was a mosaic of three cell clones: 46,XY,r(11)(p15.5q25)/45,XY-11/47,XY,r(11)(p15.5q25)x2; the investigation of the neoplasias showed that the right tumor most likely originated from the 46,XY,r(11)(p15.5q25) clone, and the left tumor from the 47,XY,r(11)(p15.5q25)x2 clone. Parents with normal karyotype   |
| (11)       | Patient 1: 1 year/M        | –                  | Cafe au lait spots      | Microcephaly, low weight, short stature                    | –  | Dyspraxia of speech                                      | Hypospadia                                       | 46,XX,r(11)(p15.5q25); complete loss of RC11 was observed in one out of 12 cells; FISH analysis: terminal deletion of the short arm of chromosome 11; SNP array analysis: deletion contained 16 protein-coding genes; SNP array analysis also detected a terminal deletion of the long arm of chromosome 11 (no coding genes are known to be located in this deleted region of 11q); and parents with normal karyotype |
|            | Patient 2: intra-uterine/F | –                  | Cafe au lait spot       | Short stature, intrauterine growth retardation, low weight | Several dysmorphic features, FD                        | Severe mental retardation, PMDD                          | Cardiac malformation and conductive hearing loss | 46,XX,r(11)(p15.5q23.3); complete loss of RC11 in two out of 36 cells; FISH analysis: a terminal deletion of the long arm of chromosome 11; SNP array analysis: minimal deletion of 14 Mb, containing 92 protein-coding genes; clinical features of JS; and parents with normal karyotype  |



Table 1 Continued

| References          | Age <sup>a</sup> /gender                      | Endocrine features   | Dermatological features                 | Physical growth abnormalities | Dysmorphic features | Neurological and psychomotor developmental abnormalities | Other outcomes  | Karyotype and other genetic features   |
|---------------------|---|--|---|-------------------------------|---------------------|--|---|--|
|                     | Patient 3: 6 years/F                          | –  | Café au lait spots                      | Microcephaly, low weight      | Clinodactyly        | Speech delay and mild mental retardation                 | –   | 46,XX,r(11)(p15.5q25); the RC was identical in patient nos 3, 4, and 5. In patient no. 3, all analyzed cells contained RC11; FISH analysis: terminal deletion of the short arm of chromosome 11 in patient nos 3, 4, and 5; SNP array analysis: the deleted region contained 20 protein-coding genes; and father's karyotype unavailable |
|                     | Patient 4: 19 years/F (sister of no. 3)       | –  | Café au lait and hypopigmentation spots | Microcephaly, short stature   | –                   | –  | –   | 46,XX,r(11)(p15.5q25); all analyzed cells contained the ring 11; and father's karyotype unavailable  |
|                     | Patient 5: 37 years/F (mother of nos 3 and 4) | –  | Café au lait and hypopigmentation spots | Microcephaly, short stature   | Clinodactyly        | –  | –   | 46,XX,r(11)(p15.5q25); complete loss of RC11 in seven out of 27 cells, and in two out of 27 cells the RC appeared to be doubled; and parents' karyotypes unavailable   |
| (12)                | 5 years/F                                     | –  | –                                       | Growth delay                  | –                   | PMDD   | Wilms tumor   | 46,XX,r(11)(p15.5q25)  |
| Present case report | 5 years/F                                     | Precocious puberty, severe hirsutism, amenorrhea, androgenic alopecia, clitoromegaly, diabetes, and insulin resistance | –                                       | Short stature                 | FD                  | PMDD   | Ventricular septal defect, severe scoliosis, anemia, and thrombocytopenia | 46,XX,r(11)(p15q25); RC11 in all segments, with loss of p15 and q25 in two out of 25 cells; clinical features of JS; and parents' karyotypes unavailable   |

F, female; M, male; PMDD, psychomotor developmental delay; FD, facial dysmorphism; IQ, intelligence quotient; JS, Jacobsen syndrome; FISH, fluorescence *in situ* hybridization; SNP, single-nucleotide polymorphism; RC, ring chromosome.

<sup>a</sup>The data presented in the table regarding the articles by Daniele *et al.* and Palka *et al.* were based on their abstracts and on other articles that cited them because we did not have access to the full text.

In some cases, patients with RC presented features of Jacobsen syndrome (JS), also known as 11q-syndrome. These cases were caused by a partial deletion of the long arm of chromosome 11 (13). The most common clinical features of 11q-syndrome are a growth delay, psychomotor developmental delay (PMDD), and dysmorphic facial features (13). The hormonal changes previously described in patients with JS include hypothyroidism and growth hormone (GH) deficiency (13) (14) (15).

We herein describe a case of RC11 with clinical features of 11q-syndrome and endocrine abnormalities that have not previously been reported for this condition.

## Case presentation

A 20-year-old female patient was referred to our Endocrinology Service for an evaluation of hirsutism, which started at age 5, and a 5-month history of amenorrhea. She was not using any medications. A physical examination revealed hirsutism (26 points in the Ferriman and Gallwey scale), androgenic alopecia, and clitoromegaly. Her height was below the third percentile, her BMI was 26.7 kg/m<sup>2</sup>, and she had normal blood pressure. There were no signs of increased muscle mass or hoarseness. She presented with a pan-systolic murmur on auscultation.

The patient was the firstborn child to her 25-year-old mother and 32-year-old father, who were non-consanguineous. She was born by a normal vaginal delivery at term following a normal pregnancy. Her birth weight was 1700 g and she was 38 cm long. Interventricular communication of the membranous septum was diagnosed at birth, but surgery was not indicated. The patient presented with a delay in speech and walking, as well as poor school performance. She required a blood transfusion at age 4 because of severe anemia and thrombocytopenia, and she had undergone four orthopedic surgeries since the age of 14 to correct severe scoliosis.

## Investigation

At age 5, the patient underwent a genetic evaluation due to short stature and facial dysmorphism (a high prominent forehead, facial asymmetry, trigonocephaly, asymmetrically set ears, and retrognathia), which demonstrated RC11. Twenty-five metaphases were analyzed by GTG banding, which revealed the presence of RC11 in all segments and a loss of p15 and q25 in two segments (46,XX,r(11)(p15q25)). At that time, the results of a hormonal evaluation (somatotrophic and thyroid axes) were normal. At age 7, she presented with precocious

puberty. At this time, hormonal blocking with a gonadotropin-releasing hormone analogue was initiated and continued from 8 to 11 years of age. She experienced menarche at age 12. These evaluations and treatments were performed at another institution.

At age 13, the patient underwent an investigation for hirsutism, which revealed normal levels of DHEA-S, androstenedione, testosterone, estradiol (E<sub>2</sub>), and thyroid-stimulating hormone (TSH). She had high levels of fasting plasma glucose ((FPG): 138 mg/dl; normal range (NR): 70–99)) and insulin (24.8 U/ml). A pelvic ultrasound examination was unremarkable, except for a borderline ovarian volume of 10 ml. The patient experienced significant weight gain after the age of 15.

At age 20, a laboratory evaluation in our unit showed normal levels of androstenedione (1.11 mmol/l; NR: 0.3–3.3), total testosterone (41 ng/dl; NR: 10–75), and DHEA-S (237.5 ng/ml; NR: 148–407) but dihydrotestosterone levels were elevated (437.5 pg/ml; NR: 23–368). TSH (1.34 μUI/ml; NR: 0.3–5.0) and prolactin (21.1 ng/ml; NR: <23) levels were normal. Cushing's syndrome and congenital adrenal hyperplasia were excluded by a normal overnight suppression 1 mg dexamethasone test (cortisol: 0.4 μg/dl; normal suppression <1.8) and normal levels of 17-hydroxyprogesterone (94 ng/dl; NR: <200) respectively. No signs or symptoms of acromegaly were present. She presented with high levels of FPG (138 mg/dl), HbA1c (7.3%; NR: <5.8%), insulin (26 U/ml), and she had insulin resistance, as assessed by the homeostatic assay (HOMA-IR; 9.82). There was mild thrombocytopenia with normal remaining hematological series. The lipid profile was normal.

## Outcome and follow-up

Treatment was started with 1500 mg/day of metformin, 0.035 mg of ethinyl estradiol combined with cyproterone acetate (1 mg), 5 mg/day finasteride, and a hair lotion containing 17α-E<sub>2</sub>. Spironolactone was administered at an initial dose of 25 mg in the first month and was progressively increased up to 100 mg/day according to the tolerance of the patient.

After 6 months, the patient presented with adequate glycemic control (HbA1c: 5.3%), a weight reduction of 4.3 kg in 4 months, substantial improvement of alopecia, and a slow hair growth rate.

## Discussion

We herein presented the case of a patient with RC11 with clinical features of 11q-syndrome such as facial

dysmorphism, growth delay, PMDD, congenital heart malformation, and thrombocytopenia. She also presented with precocious puberty, severe clinical hyperandrogenism, insulin resistance, and type 2 diabetes mellitus (T2DM). Such conditions have not yet been reported in RC11.

To the best of our knowledge, there have only been 19 cases of constitutional RC11 described in the literature. In our review of these cases, we observed a large variety of phenotypes among the patients. This variety might be explained by the size of the terminal deletion (at the short or long arm), mitotic instability, and the potential mosaic distribution of the RC (16). Only two studies in patients with RC11 (10) (11) used high-resolution genome-wide array techniques; therefore, it is difficult to establish a genotype–phenotype relationship. Table 1 shows the clinical manifestations of the cases reported so far.

JS is caused by a partial deletion of 11q, which is compatible with the present patient's karyotype. JS has already been reported in five patients with RC11 (2) (3) (4) (7) (11) (Table 1) with different degrees of severity. Our patient presented with the main manifestations of JS including facial dysmorphism, growth delay, PMDD, congenital heart malformation, and thrombocytopenia. The latter is a component of the Paris-Trousseau syndrome, a hematological disorder that has been reported in at least 88.5% of cases with JS and suggests the diagnosis of JS in patients with few clinical features of the syndrome (13). Only two cases of RC11 (2), including our present case, manifested these hematological alterations. There is no clear correlation between the size of the deletion and the phenotype (13). In fact, the correlation of the size of the deletion with the phenotype appears to be variable and depends on the location of the breakpoint. Although most of the cases shown in Table 1 fell within the same chromosomal band level, the breakpoint might have varied at the base pair level.

Regarding endocrine disorders in patients with RC11, Valente *et al.* (1) described hypothyroidism diagnosed in a 3-month-year-old girl that was confirmed at age 1 (based on low thyroxine and elevated TSH levels), and Niikawa *et al.* (2) reported on a 2-year-old patient with mild hirsutism and clitoromegaly who died at the age of 2 years and 6 months with no reported hormonal profile. Hypothyroidism and GH deficiency were both reported in the two patients with JS (13) (15).

Our patient met the diagnostic criteria for polycystic ovarian syndrome (PCOS) (17) because she presented with clinical hyperandrogenism (hirsutism, androgenic alopecia) and chronic anovulation (amenorrhea), although

ovulatory dysfunction is difficult to assess accurately. Because PCOS is a diagnosis of exclusion, several conditions that mimic PCOS were excluded, such as thyroid disease, Cushing's syndrome, hyperprolactinemia, congenital adrenal hyperplasia, androgen-secreting tumors, acromegaly, and hirsutism due to medications or illicit drugs. Except for clitoromegaly, no other feature of an androgen-secreting tumor was found (i.e. rapid onset of a change in voice and gain in muscle mass). In fact, the serum testosterone and DHEAS levels were normal. The clitoromegaly could be explained by elevated dihydrotestosterone levels in sensitive peripheral target tissues (18). Niikawa *et al.* (2) also found clitoromegaly in their case report. Elevated dihydrotestosterone levels may have reflected a higher activity of 5 $\alpha$ -reductase in our patient. In the review of the literature, we found no association between chromosome 11 deletions and changes in 5 $\alpha$ -reductase activity. Other common features of PCOS, such as T2DM, overweight, and hyperinsulinemia, were also present.

Multiple biochemical pathways and several genes are related to the pathogenesis of PCOS; however, the etiology of PCOS is multifactorial, and finding a single gene responsible for the syndrome is unlikely. We hypothesized that genes located on chromosome 11 might be involved in the pathogenesis of the syndrome. It is known that hyperinsulinemia plays a central role in the pathogenesis of PCOS (17). Polymorphisms of the *KCNJ11* (Kir6.2) and *ABCC8* (SUR 1) genes located at 11p15.1 may confer greater susceptibility to T2DM and have been reported to be associated with disorders of insulin secretion (19). Additionally, the variable number of tandem repeats (VNTR) locus (on chromosome 11p15.5) upstream of the insulin gene (*INS*) regulates insulin expression. Waterworth *et al.* (20) demonstrated a link between PCOS and the *INS* VNTR locus. The deletion of these genes, or even the involvement of chromosome 11 in our patient, could explain the metabolic disturbances.

In most of the reported cases, the parental chromosomes were normal. Two series reported the presence of RC11 in first-degree relatives (8)(11), but most cases of RC are sporadic (16). In our case, the patient's parents were phenotypically normal, but a karyotype examination was not performed. However, given the absence of any clinical and/or laboratory characteristics of the syndrome, it is unlikely that the patient's parents have any chromosomal abnormalities. Most authors (1) (3) (4) (5) (8) (9) (10) (11) (Table 1) have described patients with RC11 whose parents presented with normal karyotypes.



## Conclusions

RC11 is an extremely rare genetic disorder with very few cases described in the literature and a highly variable clinical presentation. We have herein described a case of RC11 that presented with precocious puberty, severe clinical hyperandrogenism, insulin resistance, and T2DM, which is an association that has not yet been reported. Despite the rarity of RCs, studies to correlate the genes located on the chromosomes with the phenotypes observed could lead to major advances in the understanding and treatment of more prevalent diseases.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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### Patient consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

### Author contribution statement

Study design: L Vieira Neto; Study conduct: L Vieira Neto and R Lange; Literature review: R Lange, C Von Linsingen, F Mata, A B Moraes, M Arruda, and L Vieira Neto; Data collection: R Lange, C Von Linsingen, and F Mata; Data analysis: L Vieira Neto; Data interpretation: L Vieira Neto, M Arruda, A B Moraes, R Lange, C Von Linsingen, and F Mata; Drafting manuscript: R Lange, C Von Linsingen, F Mata, A B Moraes, M Arruda, and L Vieira Neto; Revising manuscript contents: L Vieira Neto, M Arruda, A B Moraes, R Lange, C Von Linsingen, and F Mata; Approving final version of manuscript: L Vieira Neto, M Arruda, A B Moraes, R Lange, C Von Linsingen, F Mata; Integrity of the data analysis: L Vieira Neto, and M Arruda.

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