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Fecundity in an infertile man with r(15) – a challenge to the current paradigm

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KEY MESSAGE

To offer exhaustive genetic counselling to families and pave the way for detection of those genes whose hemizygosity influences the phenotype, determining the haploinsufficiency of genes is of great importance. Regarding three OMIM genes, *SNRPA1*, *PCSK6* and *TM2D3*, our findings do not support the gene-dosage sensitivity.

A B S T R A C T

Ring chromosome 15 [r(15)] is a rare condition with a mild-to-severe growth failure, mental disabilities, café-au-lait spots, specific facial features, fertility difficulties and other minor dysmorphic stigmata. Of almost 50 affected individuals reported in the literature, none were assessed for the precise breakpoint positioning, which creates uncertainty in defining a specific phenotype for the deleted segment. This study reports for the first time the vertical transmission of r(15) in three consecutive generations of a family, including a subfertile man, his mother and his newborn infant. Array comparative genomic hybridization results revealed a 563 kb deletion of 15q26.3, overlapping the OMIM genes *SNRP1*, *PCSK6* and *TM2D3*. The hemizygosity was confirmed with real-time quantitative PCR. Regarding haploinsufficiency in 15q26.3, based on phenotypic characteristics of the carriers, the only rational conclusion is that *SNRPA1, PCSK6 and TM2D3* are not gene-dosage sensitive and are probably inherited in an autosomal-recessive manner. Given growth deficiency in r(15) carriers, this shows that the growth retardation cannot be attributed entirely to *IGF1R*. The predominance of female patients with r(15) is the next as yet unanswered question; incomplete penetrance and/or variable expression of gene(s) in different genders may be involved, but further evidence is needed to support this idea.

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Introduction

Ring chromosome 15 [r(15)] syndrome is an extremely rare finding, with fewer than 50 cases reported in the literature, commonly associated with mild-to-severe failure to thrive, mental disabilities, café-au-lait spots, specific facial features and fertility difficulties, along with other minor dysmorphic stigmata. More than half a century from the first report of r(15) (Jacobsen, 1966) there is still little known about the various aspects of this disorder. The limited number of reported cases of r(15), mostly at pre-pubertal age, has made assessment of the ring chromosome inheritance, as well as the reproductive ability of the affected subjects, very difficult. Another aspect is that there appears to be within-gender phenotypic inconsistency in the fertility of ring chromosome carriers. Whilst females with r(15) have normal gonadal function (Horigome et al., 1992; Moreau and Teyssier, 1982), affected males are unlikely to be fertile (**Table 1**). Hence, the paternal inheritance of ring chromosome is an extremely rare phenomenon (Rajesh et al., 2011a). To date, there have been only three reports (four cases) of paternal ring transmission of which none were bearing r(15) (Rajesh et al., 2011b); and regarding the vertical transmission of r(15), there are also three reports (all maternal) (Fujimaki et al., 1987; Horigome et al., 1992; Nikitina et al., 2003). Here we present a rare hereditary case of the syndrome in a three-generation family, including a mother, her subfertile son, and her newborn grandchild. To the best of our knowledge, this is the first family study of its kind.

Materials and methods

Cases

Three consecutive generations of a family harbouring r(15), including a subfertile man, his mother and his newborn infant (**Figure 1**) were investigated. The index case presented with primary infertility after failing to cause pregnancy after 1 year of unprotected coitus. The patient's initial semen analysis revealed oligoasthenozoospermia (**Table 2**).

Family history and clinical report

I-2 was an asymptomatic 71-year-old female (**Figure 1**). She had no facial or physical dysmorphic features, with unaffected fecundity (having had her last child at 37). Indeed, abnormal findings in the proband led to her evaluation and diagnosis. Owing to the unavailability of her family history, it is unclear whether the ring was inherited or arose *de novo*. Her menstruation started normally at age 13 and stopped

Table 1 – The fecundity status in all reported 'adults' with r(15).

Case		Age[1a]	Sex	Origin[b]	Siblings	Reproductivity	Respective karyotypes
Jacobsen (1966)		41	♂	*de novo*	NR[2]	Infertile, azoospermic, bilateral cryptorchidism	46,XY,r(D)
Emberger et al. (1971)		33	♂	*de novo*	Three healthy sisters	Infertile, right side cryptorchidism	46,XY,r(15)
Meinecke and Koske-Westphal (1980)		37	♂	*de novo*	–	Infertile with small penis, the left testis is not palpable, and the right is small	46,XY,r(15)(p11q26.3)[41]/45,XY,-15[4]
Moreau and Teyssier (1982)		34	♂	*de novo*	NR	Infertile with normal pilosity and external genitalia, severe oligoasthenospermia	46,XY[5]/45,XY,-15[2]/47,XY, + idic r(15)x2[1]/ 46,XY,r(15)[92]
Fryns et al. (1986)		36	♀	*NR*	NR	Normal	46,XX,r(15)
Fujimaki et al. (1987)		33	♀	*NR*	NR	Fertile with three pregnancies: 1st: spontaneous abortion 2nd: child with r(15) 3td: fetus with r(l5)	46,XX,r(15)
Horigome et al. (1992)		43	♀	*de novo*	NR	Subfertility; irregular menarche Three pregnancies: 1st: normal son 2nd: spontaneous abortion 3rd: child with r(15)	46,XX,r(15)(p12q26.3)
Matsuishi et al. (1996)		24	♀	*de novo*	Two healthy siblings	Menstruation commenced at age 17 years	46,XX,r(15)(p11.2q26.3)
Smith et al. (1991)		59	♀	*de novo*	One healthy sister	Menses began at age 16 years and were regular and ceased by age 48	46,XX,15qs+[60]/46,XX,r(15)[38]/ 45,XX,-15[2]
Current report	II-5	32	♂	*Familial*	Three healthy sisters	Severe oligoasthenoteratozoospermia A son with r(15)	46,XY,r(15)(p13q26.3)mat[45]/ 45,XY,-15[3]/ 47,XY, + idic r(15)(p13q26.3)x2[1]/ 46,XY,idic r(15)(p13q26.3)[1]
	I-2	67	♀	*NR*	NR	Six pregnancies; two spontaneously aborted, three normal and one with r(15) children	46,XX,r(15)(p13q26.3)[23]/45,XX,-15[3]/ 48,XXXX,r(15)(p13q26.3)[1]/ 47,XX, + idic r(15)(p13q26.3)x2[1]/ 47,XXX,r(15)(p13q26.3)[1]/ 46,XX,idic r(15)(p13q26.3)[1]

NR= not reported.

[a] Age at diagnosis (years).

[b] Parental origin; *de novo* (spontaneous) or familial.

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