45,X/46,X,i(Yp): Importance of Assessment and Support during Puberty and Adolescence

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Abstract

The Y-chromosome genes are primarily involved in sex determination, stature control, spermatogenesis, and fertility. Among structural rearrangements of the Y chromosome, the isochromosome of Yp, i(Yp), appears to be the most uncommon. We describe a detailed evolution of puberty in a boy with 45,X/46,X,i(Yp). Array CGH found 2 cell lines, one with i(Yp) and the other with monosomy X. Genetic analysis of currently known genes involved in Kallmann syndrome/normosomic central hypogonadotropic hypogonadism showed no abnormality. The patient presented with a pubertal course suggestive of a delayed puberty with gynecomastia, reduced growth rate, and infertility that need testosterone treatment to induce the appearance of the secondary sex characteristics. This patient shows the potential effects of i(Yp) and emphasizes the importance of appropriate management of puberty in people with 45,X/46,X,i(Yp). Early hormone treatment, concerns regarding fertility, emotional support, and a successful transition to adult care may help improve the physical and psychosocial well-being of affected patients.

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Gross structural abnormalities of the Y chromosome seem to occur less frequently than microdeletions. Among structural rearrangements of the Y chromosome, the isochromosome of Yp, i(Yp), appears to be the most uncommon; nevertheless, the real incidence of i(Yp) is unknown so far. Patients with gross deletions of Yq are reported as being affected by infertility and short stature [Bühler, 1980], but few persons are reported as patients affected by i(Yp). All these patients were described as males, infertile, or with ambiguous genitalia [Robinson et al., 1998].

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Table 1. Hormone values and sexual characteristics of our patient at different ages

Years	LH, IU/L	FSH, IU/L	Testosterone, ng/mL	Testicular volume, mL	Penis size (length × diameter), cm	Therapy, IM
13	<0.1 (1.5–9.3)	0.3 (0.7–11)	<0.20 (2.62–15.93)	2	3.5 × 1	No
14	0.3 (1.5–9.3)	1.3 (0.7–11)	<0.20 (2.62–15.93)	2.5–3	3.5 × 1	No
15	1.1 (1.5–9.3)	2.0 (0.7–11)	0.40 (2.62–15.93)	4	3.5 × 1	TE 50 mg, once every 28 days
16	7.3 (1.5–9.3)	7.4 (0.7–11)	0.68 (2.62–15.93)	4	7 × 2.5	TE 100 mg, once every 28 days
17	1 (1.5–9.3)	1.7 (0.7–11)	0.63 (2.62–15.93)	4	7.5 × 2.5	TE 100 mg, once every 28 days
18	<0.1 (1.5–9.3)	<0.1 (0.7–11)	1.84 (2.62–15.93)	4	7 × 2.5	TE 100 mg, once every 21 days
18.25	4.18 (0.57–12.07)	2.14 (0.95-11.95)	3.47 (1.66–8.77)	4	7 × 2.5	No
20.5	4.08 (0.57–12.07)	6.6 (0.95-11.95)	2.90 (2.59–8.36)	5	7 × 2.5	No
20.75	2.03 (0.57–12.07)	6.8 (0.95-11.95)	2.49 (2.59–8.36)	7	7 × 2.5	No

TE, testosterone enanthate; IM, intramuscular.

The first person with i(Yp) with a description of testicular histology was reported in 2005. The patient was a 27-year-old man with small testes affected by Sertoli-cell-only syndrome because he had no germ cells in testicular tissue [Lin et al., 2005]. To our knowledge, only 10 patients with 45,X/46,X,i(Yp) mosaicism have been described [Siebers et al., 1973; Moreira-Filho et al., 1979; Rary et al., 1979; Bühler, 1980; Hsu, 1994; Mckinlay Gardner and Sutherland, 2003; Martinerie et al., 2012; Bertelloni et al., 2015], and no data were found regarding the course of puberty in these patients.

Case Report

We report a 21-year-old male with right-sided gynecomastia since the age of 13. The patient's past medical history was negative. His height was 151.4 cm (between the 25th and the 50th percentile on the growth charts of the Center for Disease Control (CDC) and Prevention [www.cdc.gov/growthcharts]) and his weight was 65.8 kg (between the 90th and the 97th percentile, CDC charts). At the first physical examination, he had very sparse pubic hair, no axillary hair, no facial hair, normal scalp hair, and a preadolescent voice. Pubertal development was at Tanner stage 1, with corresponding prepubertal penis and scrotum size. The patient's testicles were bilaterally descended, and both had a volume of 1.5 mL and a normal consistency. The testicular descent was spontaneous during development. The patient showed no eunuchoid habitus and no dysmorphism. The patient's target height was 177.5 cm (on the 50th percentile). Due to absent puberty, an accurate physical examination and biochemical/genetic analyses were performed. We also comment our results revising the so far reported literature in the field.

Materials and Methods

Hormone Assays and Clinical Data

Serum FSH, LH, and testosterone were determined by immunometric assay (Immulite 2000; Siemens, Erlangen, Germany) and serum inhibin B by ELISA (Active Inhibin B ELISA, Diagnostic Systems Laboratories, Webster, TX, USA). Sex hormone-binding globulin levels were measured using a solid-phase, chemiluminescent immunometric assay on Immulite 2000 (Medical Systems Corp., Genoa, Italy).

Testicular volume was assessed using a standard Prader orchidometer. Testicular and breast ultrasound scanning was performed by an experienced radiologist. Smell testing was carried out using the Sniffin' Sticks test.

Genetic Analysis by Targeted Next-Generation Sequencing

The patient underwent a genetic investigation, using a targeted NGS technique, to search for rare allelic variants. We extracted the genomic DNA of the patient from peripheral blood lymphocytes using Gene Catcher gDNA 96 × 10 mL Automated Blood kit (Invitrogen, Life TechnologiesTM, Carlsbad, CA, USA). The *IHH* gene panel was designed using Illumina Design Studio (San Diego, CA, USA) and included the following *IHH* candidate genes: *ANOS1* (*KAL1*), *FGFR1*, *PROKR2*, *PROK2*, *GNRHR*, *GNRH1*, *GNRH2*, *FGF8*, *TAC3*, and *TACR3*. Libraries were prepared using Illumina Nextera Rapid Capture Custom Enrichment kits as previously described [Cangiano et al., 2019] and according to the manufacturer's protocols.

FISH Analysis and Array CGH

Chromosomes were analyzed by GTG-banding. FISH analysis, with specific probes for the *SRY* gene (LSI, Vysis), with centromeric probes of the Y chromosome (DYZ1, Vysis), and with probe KAL1 (Vysis), was carried out according to Pinkel et al. [1986], and an array CGH was done to detect genomic copy number variations at a higher resolution level of 40 kb (GenetiSure Pre-Screen Array Kit 4×180, Agilent).
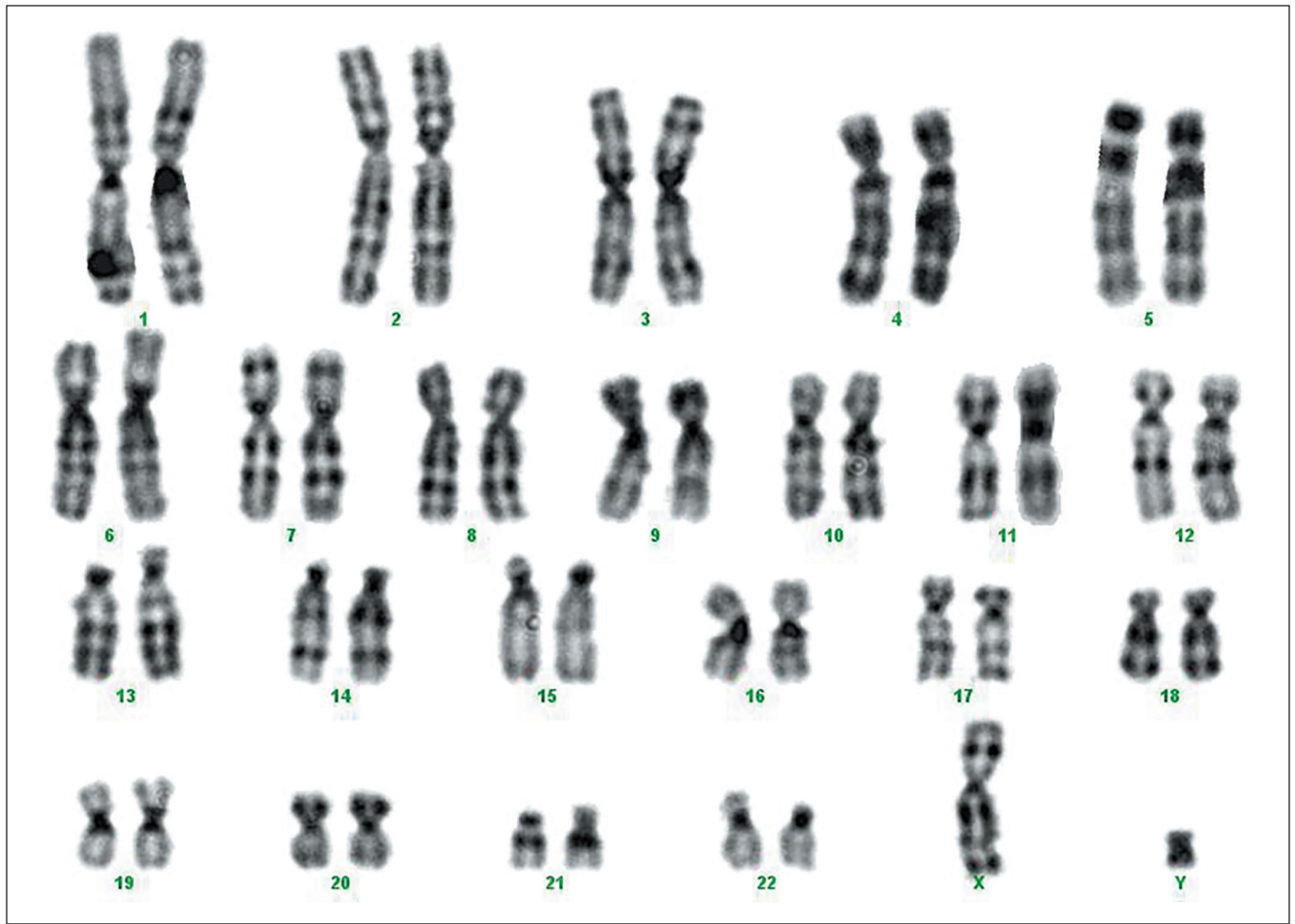
Fig. 1. GTG-banded chromosomes showing an i(Yp).

Detection of Y Chromosome Microdeletions

The detection of Y-chromosome microdeletions was achieved by screening patients according to the European Academy of Andrology guidelines [Krausz et al., 2014].

Results

To investigate the patient's gynecomastia, we initially evaluated the breast and scrotum ultrasonography and basal hormone profile. The scrotal ultrasonography revealed a testicular longitudinal diameter of 18 mm for the right testis, and 17 mm for the left testis, corresponding to a bilateral volume of approximately 2 mL. The breast ultrasonography confirmed a unilateral gynecomastia of the right breast with a diameter of 3 cm. Table 1 shows the hormonal values and sexual characteristics of our patient at different ages. A complete screening of the pituitary functionality excluded other possible pituitary hormone deficits, and inhibin B levels were 44.32 pg/mL (normal range 25–325 pg/mL).

At the age of 14, the patient maintained a prepubertal stage of sexual development and relative short stature. The evaluation of the patient's bone age resulted in a predicted adult height of 162.9 cm according to Bayley-Pinneau (below the 3rd percentile, CDC growth charts). The gonadotropin-releasing hormone stimulation test showed values of LH and FSH in the prepubertal range. The human chorionic gonadotropin stimulation test was normal. The patient reported a reduced sense of smell. We tested his olfactory capacity to evaluate a possible Kallmann syndrome. The test revealed a slight reduction in his ability to recognize nasal stimulants (11/16 tested odorants correctly recognized; reference range ≥12). On

the contrary, the taste examination was normal (total score: 14; reference range 9–16). The patient had a normal brain MRI scan of the pituitary-hypothalamic region and olfactory system, which finally ruled out lesions, masses, or other abnormalities suggestive of Kallmann syndrome. Standard karyotyping was also performed and detected an i(Yp) in the patient (Fig. 1). FISH showed 2 Yp signals, confirming the presence of an i(Yp). The lack of Yq was then confirmed by the inability to amplify any of the AZF loci by PCR with specific primers. FISH analysis using centromeric probes of the Y chromosome showed the signal, in both 100 metaphase cells and 200 nuclei, and evidenced that the Y chromosome was monocentric. FISH specific for Kallmann syndrome did not reveal a microdeletion of the X chromosome in Xp22.3 and our genetic analysis for mutations in *ANOS1* (*KAL1*), *FGFR1*, *PROKR2*, *PROK2*, *GnRH1/2*, *GnRHR*, *FGF8*, *TAC3*, and *TACR3* genes was negative. Therefore, the patient's karyotype was 46,X,i(Yp).ishX(p22.3)(KAL1×1). The karyotype of both parents was normal.

At the age of 15, because of absent puberty progression, the boy received intramuscular injections of testosterone enanthate (TE; Testoviron® 100 mg) to induce sexual development and secondary sex characteristics. This therapy was started with a dose of 50 mg once every 28 days. After 4 months of treatment, baseline serum TE levels were 1.51 ng/mL (reference range: 2.62–15.93 ng/mL), so we increased the dose of TE to 100 mg once every 21 days.

In addition to the chromosomal anomaly, we hypothesized that the patient could also be affected by isolated congenital hypogonadotropic hypogonadism (CHH), since, at the age of 17 and 6 months, he failed to enter puberty in spite of the TE priming, and still presented with a prepubertal bilateral testicular volume <4 mL with low gonadotropins and absence of hypothalamic-pituitary lesions. The array CGH showed an amplification of the chromosomal region Yp.11.32q11.21 of about 14 Mb, containing approximately 40% mosaic cells and a deletion of the region Yq11.21q12 of about 45 Mb, resulting in nullisomy. The result of the analysis, confirmed by molecular cytogenetics, performed on interphase nuclei unstimulated nuc ish (DYZ3 X0) [193/1000] and on interphase nuclei stimulated nuc ish (DYZ3 X0) [96/1000], suggested that our patient had 2 cell lines, one with Yp and the other with monosomy X.

No cardiac or renal abnormalities or stigmata of Turner females have been suspected. The semen analysis performed with valid erections at the age of 18 showed azoospermia and normal viscosity and PH (7.2; normal

range: 7.2–8) as well as a measured volume of 3.5 mL (normal WHO value >1.5 mL). At this stage, since spontaneous increase in gonadotropin levels occurred during androgen therapy, the HPG axis was revaluated at the age of 18 after discontinuing the androgen therapy. At that time, TE (3.47 ng/mL; normal ranges 1.66–8.77), inhibin B (295.16 pg/mL; normal range 25–325), LH (4.18 IU/L; normal range 0.57–12.07), and FSH (2.14 IU/L; normal range 0.95–11.95) levels were within normal range. At the age of 20, he still had normal hormonal levels (see Table 1), although total TE levels remained within low-normal reference range, with a penile length of 7 cm, small testes (5 mL), and mild gynecomastia. His final height was 161 cm, which was 16.5 cm below the correct midparental height. Pubertal growth spurt was 9.6 cm. At the age of 21, total TE was below the reference range, although calculated free TE levels were normal (6.6 ng/mL, normal range >6.5), and the patient did not have specific symptoms of hypogonadism. He reported a normal libido with conserved spontaneous erection and no erectile dysfunction as well as normal concentration ability. Gonadotropin levels were within the normal range.

Discussion

We describe a 21-year-old man who came to our pediatric clinic with persistent gynecomastia and pubertal delay. He had a complex rearrangement involving the X and Y chromosomes, initially interpreted as an i(Yp) and subsequently characterized as 45,X/46,X,i(Yp) mosaicism. To our knowledge, only 10 persons with 45,X/46,X,i(Yp) mosaicism have been described in the literature (Table 2), and this is the first comprehensive evaluation of puberty in such a patient.

Our patient should have 2 doses of Yp, and he did not show a 47,XYY phenotype or a Klinefelter syndrome phenotype [Kanakis and Nieschlag, 2018], only gynecomastia. Karyotyping is not a routine investigation in patients with gynecomastia with the exception of those who present with clinical features suggestive of Klinefelter syndrome [Bonomi et al., 2017].

On the contrary, the presence of persistent gynecomastia associated with central hypogonadism in our patient prompted us to investigate his karyotype leading to a better characterization of the cytogenetic origin of his clinical symptoms and biochemical defect. Moreover, the discovery of this cytogenetic anomaly suggested us to rule out other underlying diseases and testicular tumors. The prevalence of gonadal tumors in persons with a cell line

Table 2. Eleven patients with 45,X/46,X,i(Yp) mosaicism

Reference	45,X cells	Age, years	Genitalia	Hypospadias	Gonads	Spontaneous puberty	LH/FSH	Testosterone therapy	Final stature
Martinerie et al., 2012	25/30, mitoses	24	20 mm, <–2.5 SD at birth; 30 mm, <–3 SD at 24 years	Perineal	Abdominal/inguinal at birth; streak gonad/seminoma at 23 years	Yes (years NA)	NA	IM, 24 years	152 cm, –3.8 SD
Hsu, 1994	25/30, mitoses	17	NA	Scrotal	Scrotal dysgenetic testis/abdominal dysgenetic testis	Yes (14 years)	9.8/26 IU/L	No	155.3 cm, 3.2 SD
Bühler, 1980	1/3 of lymphocytes; 90% of left gonad cells	0	Phallus	Scrotal	Cryptorchidism (left)	A feminizing operation was performed after complete gonadectomy	NA	No	NA
Moreira-Filho, 1979	19/30 mitoses	Adult	Male external genitalia	3rd degree of hypospadias	Asymmetrical gonad; mixed gonadal dysgenesis	NA	Normal testicular androgenic function	No	NA
Rary et al., 1979	40%	5	Ambiguous genitalia	hypospadias and presence of vagina	Normal testis (right); inguinal small testis (left)	NA	NA	No	NA
Siebers et al., 1973	12/50 mitoses	20	Female, external genitalia	No	Bilateral streak gonads	No, Turner stigmata	30/23.2 IU/L	No	138 cm
Mckinlay Gardner and Sutherland, 2003	NA	NA	NA	No	NA	NA	NA	NA	NA
	NA	NA	NA	Yes	Absence of germinal cells	NA	NA	NA	NA
Berteloni et al., 2015	15%	11	Male, ambiguous genitalia	Severe hypospadias	Streak gonad (left)	NA, GH therapy	NA	NA	NA
	30%	11.3	Male, ambiguous genitalia	Severe hypospadias	Streak gonad (right)	NA	NA	NA	NA
Our patient	4/50 mitoses	21	Male, external genitalia	No	NA	No, gynecomastia	4.08/6.6 IU/L	No	161 cm

FSH, follicle stimulating hormone; GH, growth hormone; IM, intramuscular; LH, luteinizing hormone; NA, not available.

including a dicentric Y chromosome has been estimated in about 26% [Verp and Simpson, 1987], and the development of gynecomastia in these patients suggests possible malignant changes. Issa et al. [1998] reported a 33-year-old male with i(Yp) in whom gynecomastia was the sole features of a testicular seminoma. Nevertheless, most cases of gynecomastia are caused by a relative prevalence of estrogen action [Karmisholt et al., 2011] in the breast. The possible presence of testicular mass in the patient was ruled out, thus allowing us to conclude that the gynecomastia was due to the peripheral aromatization of adrenal androgens. This was subsequently confirmed by gynecomastia improvement following TE replacement therapy.

Initially, the differential diagnosis was between constitutional delay in growth and puberty and CHH [Harrington and Palmert, 2012; Palmert and Dunkel, 2012; Boehm et al., 2015; Bonomi et al, 2018]. The patient's inhibin B levels were suggestive of CHH [Adan et al., 2010; Coutant et al., 2010]. As provided for by the international guidelines for CHH [Dunkel and Quinton, 2014; Boehm et al., 2015; Howard and Dunkel, 2018], our patient was initially treated with a long-acting testosterone

ester (TE) with a good advance of secondary sexual development, but there was no testicular growth in terms of volume, and basal/post-stimuli LH and FSH values were still in the prepubertal range. This lack of spontaneous testicular enlargement during the TE replacement therapy in our patient seems to confirm the presence of a failure in the hypothalamic-pituitary-gonadal (HPG) axis activation as in CHH in contrast to constitutional delay in growth and puberty [Boehm et al., 2015]. On the other hand, the lack of the Yq [Lindhardt Johansen et al., 2012] might also have played a major role in this respect. Nevertheless, other aspects of the clinical picture of our patient also seem to suggest at least a partial misfunctioning of the HPG axis. Indeed, the patient showed recovery of the HPG axis functionality after a period of sexual steroid exposure as in the reversal form of CHH [Raivio et al., 2007]. On the contrary, at the age of 21, the FSH levels were inappropriately normal despite a severe defective final testicular volume, and the normal LH with a borderline TE level might suggest a residual frailty of the HPG axis as in the reversal and relapse form of CHH [Sidhoum et al., 2014]. Nonetheless, no genetic allelic variants in the

major CHH candidate genes [Vezzoli et al., 2016] so far analyzed were identified, and no Y chromosomal genes, including those in Yq, are known to be involved in the HPG activation and/or functionality.

The proband showed no physical signs of Ullrich-Turner syndrome, except for a reduced growth rate. This raises the question why did our patient, carrying a duplication of the Yp and thus of the *SHOX* gene, not have a tall stature. His stature and his loss of growth spurt may be the result of 3 opposing effects, i.e., duplication of the *SHOX* gene in i(Yp), haploinsufficiency of the *SHOX* gene related to the 45,X cell, and deletion of the GCY locus in Y [Kirsch et al., 2004; Lin et al., 2005].

Although the question of fertility preservation should arise in the context of adolescent pubertal disorders, this concern has not been frequently addressed in the pediatric and adolescent literature. For the first time, we report the semen analysis in an adolescent with 45,X/46,X,i(Yp) that confirmed azoospermia. Even if we have no data on the gonadal histology of our patient, we have explained the azoospermia in the presence of normal FSH and inhibin B levels, assuming the presence of Sertoli-cell-only syndrome at the end of his puberty. Secondly, 45,X/46,X,i(Yp) formation results in duplication of the Yp pseudoautosomal region and deletion of Yq pseudoautosomal region, outcomes that may disrupt meiotic pairing of chromosomes X and Y and thereby preclude progression through meiosis. Finally, mitotic instability and resultant X0 mosaicism in the germline may also contribute to spermatogenic defects [Lange et al., 2009; Krausz et al., 2011, 2014; Lindhardt Johansen et al., 2012].

Conclusion

In summary, we report the first case of a boy with delayed puberty, gynecomastia, 45,X/46,X,i(Yp), and possible CHH. This report is offering several important take-home messages for both clinicians and patients. First, chromosomal analysis allowed appropriate clinical decision, predicted the patient's response to treatment, and permitted precise genetic counseling. Second, patients with 45,X/46,X,i(Yp) and delayed puberty require constant clinical monitoring in order to verify the normal activation and functionality of the HPG axis. Third, the psychological benefit of achieving normal pubertal milestones for all patients with 45,X/46,X,i(Yp) should not be underestimated. Early hormone therapy, concerns regarding fertility, emotional support, and a successful transition to adult care may help minimize negative impacts on the physical and psychosocial well-being of patients with disrupted puberty.

Statement of Ethics

The study, in accordance with the Declaration of Helsinki, was approved by the Ethic Committee of the coordinating institution (GR-2008-1137632). Patients or their tutors gave a written informed consent for personal and genetic data publication.

Disclosure Statement

All authors declare that there are no conflicts of interest that could be perceived as impairing the impartiality of the research reported.

Author Contributions

The authors' responsibilities were as follows: R. Gaudino designed the study. F. Guizzardi, V. Vezzoli, and P. Cavarzere collected data. R. Gaudino, C. Krausz, and M. Bonomi interpreted the data. R. Gaudino and E. Maines wrote the first draft of the manuscript. R. Gaudino, P. Cavarzere, G. Piacentini, F. Antoniazzi, and M. Bonomi critically reviewed the manuscript for intellectual contents.

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