Familial pericentric inversion of chromosome 1 (p34q23) and male infertility with stage specific spermatogenic arrest

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Abstract

We report on two infertile brothers presenting with severe oligozoospermia or azoospermia. Testicular biopsy was performed on one of them and showed spermatogenic arrest at the level of primary spermatocytes. Both brothers were found to be heterozygous for a pericentric inversion of chromosome 1 (46,XY,inv(1)(p34q23)). The inversion chromosome was inherited through the maternal line, with no indication of subfertility in the probands' mother.

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Chromosomal abnormalities have a higher prevalence among infertile males than in the general population. Numerical and structural aberrations of the sex chromosomes prevail, but structural rearrangements of the autosomes are also found with significantly increased frequency.¹ Here we report a family with a rare familial pericentric inversion of chromosome 1 (46,XY,inv(1)(p34q23)) and infertility in two brothers.

Family report

The 30 year old proband (III-2, fig 1) presented with infertility of five years' duration. His wife had undergone a complete gynaecological workup, with no abnormalities detected. Previous examinations of the proband at other hospitals had shown severely impaired sperm counts.

Genital and general physical examination were unremarkable. The results of semen analyses and endocrine studies are summarised in the table. Testosterone and LH were slightly subnormal on one occasion, but all other hormonal values were within the normal range. Semen analysis showed a normal ejaculate volume and normal concentrations of the marker substances for the prostate (zinc), the seminal vesicles (fructose), and the epididymis (α -glucosidase). Sperm concentration was extremely low and on one occasion there was complete azoospermia. Percentages of progressively motile and morphologically normal spermatozoa were reduced. A surgical exploration of the scrotum showed normal epididymides and vas deferentia. A biopsy was taken from both testes. In the majority of tubules spermatogenesis was arrested at the level of primary spermatocytes (fig 2). No tubules with Sertoli cell only histology were seen. Karyotype analysis on peripheral lymphocytes showed heterozygosity for a large pericentric inversion of chromosome 1 (46,XY,inv(1)(pter→p34::q23→p34::q23→qter) (fig 3). A permanent cell line is not available.

The marriage of the proband's younger brother (III-3) had remained barren for several years. Semen analysis at another institution had reportedly shown azoospermia. The brother refused physical examination and diagnostic tests other than chromosome studies and basic hormone measurements. Karyotyping showed heterozygosity for the same large inversion of chromosome 1 (46,XY,inv(1)(p34q23)) as in his brother. The proband's sister had a normal female karyotype (46,XX). His mother was found to be heterozygous for the same pericentric inversion of chromosome 1 (46,XX,inv(1)(p34q23)). She denied pregnancy losses or other reproductive and health problems. Her first child (III-1) had died of a viral infection. Her twin brother's (II-4) marriage had remained barren for unknown reasons. Neither this subject nor any other family members were available for chromosome studies.

Discussion

Heterozygosity for a pericentric inversion of chromosome 1 has been reported in a small number of infertile male patients.²⁻⁸ As is true for other balanced autosomal rearrangements, such inversions appear to compromise the fertility of some male, but not female carriers. The factors determining this selective suscep-

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Figure 1 Pedigree of family with large pericentric inversion of chromosome 1. Proband is indicated by arrow.

Spermatological and endocrine parameters in subject III-2

Parameter	Sample No				Normal range
	1	2	3	4	
Ejaculate volume (ml)	4.5	4.2	3.8	3.9	≥2
Sperm concentration (10 ⁶ /ml)	0.2	0	0.05	0.1	≥20
Sperm with progressive motility (%)	40	—	20	20	≥50
Sperm with normal morphology (%)	30	—	7	8	≥30
α-glucosidase* (mU/ejac)	114	88			≥11
Fructose* (μmol/ejac)	88	69			≥13
Citrate* (μmol/ejac)	64	56			≥32
Luteinising hormone (U/l)	1.9	2.9	4.1		2–10
Follicle stimulating hormone (U/l)	4.3	4.9	3.3		1–7
Testosterone (nmol/l)	10.0	18.2	24.4		≥12

*α-glucosidase, fructose, and citrate are marker substances for the epididymis, the seminal vesicles, and the prostate, respectively.

Figure 2 Photomicrograph of seminiferous tubule from case 1, showing arrest of spermatogenesis at the level of primary spermatocytes (arrowheads). Note one single elongated spermatid (arrow).

tibility of male gametogenesis are obscure. Formal proof for a causal relationship between the karyotypic abnormality and impaired fertility is difficult to obtain in the individual case. The possibility of coincidence must be kept in mind.

The unusual karyotype in our proband was associated with a specific histopathology, that is, stage specific arrest of spermatogenesis. The maturation arrest at the level of primary spermatocytes indicates a disturbance of meiosis I. In non-obstructive azoospermia (and severe oligozoospermia) serum FSH levels are usually raised, a finding notably absent in our patient. There is evidence that increased levels of FSH depend on the presence of seminiferous tubules with Sertoli cell only (SCO) histology.⁹ If no SCO tubules are found, then FSH may be expected to be normal, even if spermatogenesis is compromised. The endocrine data from our patient are in keeping with these observations.

Only one other patient with a pericentric inversion of chromosome 1 with the same breakpoints (p34q23) has been reported so far.⁸ In this and the other published cases of male infertility associated with a pericentric inversion of chromosome 1 (but with different breakpoints involved)^{2–7} the clinical data provided are often scanty and thus difficult to interpret. No clear relationship between the specific chromosomal breakpoints and degree of spermatogenic failure emerges. The fact that several male carriers of pericentric chromosome 1 inversions were ascertained in amniocentesis series¹⁰ indicates that this karyotypic abnormality is not invariably associated with infertility.

To enhance our understanding of the relationship between pericentric autosomal inver-

Figure 3 Karyotype of case 1. Note large pericentric inversion of right chromosome 1.

sions and spermatogenic impairment, a more comprehensive characterisation of inversion carriers at the clinical level is necessary. Only if seminal, endocrine, and histological parameters are meticulously documented might patterns of genotype-phenotype correlation emerge.

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