

Clinical Profile of Inversion Y in People of Gujarat, West India

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ABSTRACT The present cytogenetic study was carried out on a total of 1,408 male subjects inhabiting West Indian state of Gujarat diagnosed for various clinical conditions. Inversion Y (inv(Y)) was found in 1.67% of Down syndrome, 55.56% of multiple congenital anomalies, 0.47% of ambiguous genitalia and 2.22% of recurrent pregnancy loss subjects; the overall incidence of the trait was 2.20%. The present results revealed that inv(Y), considered a normal variant, had heterogeneous distribution in different clinical conditions in people of Gujarat. Detailed molecular studies are desirable to validate this observation.

INTRODUCTION

In humans, the male is referred to as the heterogametic sex, due to the presence of 2 different sex chromosomes, X and Y. The Y chromosome causes testis differentiation and therefore determines maleness (Sinclair et al. 1990). This chromosome passes from father to son, and unlike other chromosomes, most of it escapes meiotic recombination (Jobling and Tyler-Smith 2003). The Y chromosome contains a major proportion of segmental duplications (Skaletsky et al. 2003) and shows cytogenetically observable structural polymorphisms such as length variation (Bobrow et al. 1971; Verma et al. 1978) and inversions (Verma et al. 1982b; Bernstein et al. 1986). The former comprises large Y (Yq + greater than size of chromosome 18) and small Y (Yq- less than size of a G-group chromosome) and the latter comprises pericentric inversion (a rearrangement in which a segment, including the centromere, is rotated) and paracentric inversion (a rearrangement in which a segment of chromosome, excluding the centromere, is rotated). The Y chromosome is more polymorphic in the Asians (3.37%) and Hispanics (1.82%) compared to the Whites or Blacks (Hsu et al. 1987).

Cohen et al. (1966) reported that length of human Y chromosome differs in different racial groups. Like normal populations, Y chromo-

some length variation has also been documented in association with different clinical conditions such as mental disorders (Funderburk et al. 1978), abortions (Genest 1979), Down syndrome (Verma et al. 1982a), embryo development (Podugolnikova and Blumina 1983), birth complications (Videbech et al. 1984) and bad obstetric history (Minocherhomji et al. 2009).

Pericentric inversion of Y chromosome (inv(Y)) was first documented by Jacobs et al. (1964) and Solomon et al. (1964) and the condition is familial (Verma et al. 1982b). Using over 12,000 prenatal diagnosis cases the incidence of pericentric inversion Y has been found to be 1.15 per 1,000 and a value of 1-2 per 1,000 was estimated in different human populations by Shapiro et al. (1984). While reviewing human population cytogenetics, Bhasin (2005) has reviewed incidence of inv(Y) in various world populations. A high value of the trait (30.5%) was reported in the immigrant Gujarati Muslim community settled in South Africa by Bernstein et al. (1986). The authors traced the origins of the ancestors of the individuals with inv(Y) to a few small villages near the city of Surat and concluded that the polymorphic frequency of the trait observed has probably been produced through random genetic drift in a reproductively isolated community, maintained by strict endogamy based on religious and linguistic affiliations. There was no indication in the study that the inverted Y was associated with any reproductive disadvantages.

Pericentric inversion in different human chromosomes has been observed to be associated with infertility, repeated foetal loss, congenital

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anomalies and mental retardation, possibly predisposing for inter-chromosomal effect and non-disjunction (Gardner and Sutherland 1996; Krishna et al. 1992). Polymorphic variants of chromosomes were reported in 28.82% males having primary infertility or repeated miscarriages (Madon et al. 2005). According to Motos Guirao (1989) pericentric inversion of human Y chromosome is only a rare chromosomal heteromorphism and there was no clinical significance of the condition because the fathers and male foetuses had the same pericentric inversion. Similarly, Verma et al. (1982b) concluded that inverted Y chromosome does not affect the sperm production and like normal Y chromosome it is inherited without any clinical significance. The present study was planned to investigate the association, if any, of inversion Y with different clinical conditions in people of Gujarat, West India.

MATERIALS AND METHODS

A total of 1,408 male subjects inhabiting Gujarat state in West India were investigated for this cytogenetic work carried out between October 1994 and September 2006. This included 239 children with Down syndrome, 9 children with multiple congenital anomalies, 212 children with ambiguous genitalia and 948 males in couples with recurrent pregnancy loss. Peripheral blood samples were obtained and cultures were established using the original technique of Moorhead et al. (1960) with modifications. The morphology of the Y chromosome was analysed by quinacrine and giemsa banding techniques and inversion Y cases were confirmed using centromere banding.

RESULTS

The incidence of inversion Y (inv(Y)) in different clinical conditions in people of Gujarat is listed in Table 1. Figure 1 shows a karyotype showing inv(Y) in a patient in the present study. Table 1 shows that the percentage of this genetic trait ranged from a low of 0.47 in ambiguous genitalia to a high of 55.56 in multiple congenital anomalies with an average of 2.20% for the entire clinical material tested. It may be noted that the frequency range of inv(Y) found in the present study is comparatively somewhat higher than the range reported in normal world populations (1-2 per 1,000).

Table 1: The incidence of inversion Y (inv(Y)) in different clinical conditions in people of Gujarat, West India

Clinical condition	n	Inversion (Y) cases observed
Down syndrome	239	4 (1.67)
Multiple congenital anomalies	9	5 (55.56)
Ambiguous genitalia	212	1 (0.47)
Recurrent pregnancy loss	948	21 (2.22)
Total	1408	31 (2.20)

Figures in parentheses are percentages

DISCUSSION

The present investigation showed that the incidence of pericentric inversion Y (inv(Y)) in patients of Down syndrome, ambiguous genitalia and recurrent pregnancy loss is low in comparison to rather high percentage of the trait observed in multiple congenital anomalies. This is an interesting observation but it may also be an attribute of small sample size in the latter clinical condition.

In a case study of a Down syndrome reported from California (USA), cytogenetic analysis diagnosed inv(Y) in four male family members studied, including proband (Sparkes et al. 1970). As for Gujarat, there are two case reports of inv(Y) in Down syndrome. In one of the study by Krishna Murthy et al. (1989), a 13 year old boy with Down syndrome was found to have inv(Y). The proband's father and two elder brothers also had inv(Y) with normal phenotype but the mother had two spontaneous abortions. In another case study, a boy with Down syndrome and his normal father showed inv(Y) (García Sagredo et al. 1975) and the authors concluded that the presence of this trait in Down syndrome was by chance and no association can be made. The present study revealed that the incidence of inv(Y) in Down syndrome cases of Gujarat is 1.67%.

Association between multiple congenital anomalies and inversion of different human chromosomes has been reported in literature. In a subject from California (USA) inversion of chromosome 4 was observed with multiple congenital anomalies (Wilson et al. 1970). As for India, Sasikala (1990) showed the presence of pericentric inversion of chromosome 9 in children with this clinical condition. On the other hand, association between inversion Y (inv(Y)) and multiple congenital anomalies is rarely docu-



Fig. 1. A karyotype of recurrent pregnancy loss patient showing pericentric inv(Y)

mented. In a cytogenetic study carried out on 50 patients having multiple congenital anomalies and mental retardation, only one patient showed inversion Y (Magnelli 1976). Like high frequency of inv(Y) reported in normal immigrant Gujarati population settled in South Africa (30.5%), the present multiple congenital anomalies patients studied from Gujarat showed a rather high value of the trait (55.56%). Further studies are desirable to confirm this observation.

A cytogenetic study reported from USA by Liou et al. (1997) showed paracentric inversion in Yq region in a White subject with ambiguous genitalia. The molecular analysis revealed that the short arm of proband's inversion Y was identical to his father. The incidence of the trait in the present Gujarati subjects with this clinical condition was found to be 0.47%. A study in China showed that 22% males in couples with recurrent spontaneous abortion had pericentric inversion Y (Zhou et al. 2006). By contrast, the present figure of 2.22% in cases of this clinical

condition investigated from Gujarat was about one-tenth.

To conclude, although inversion Y (inv(Y)) is generally considered to be of no significance in various clinical conditions, the present study from Gujarat in West India has provided some evidence for its role in multiple congenital anomalies. Studies from other states of India on the patients along with controls are required to confirm this finding.

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