

A report on chromosomal translocation types in relation to male infertility

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ABSTRACT

Introduction: Male infertility (MI) in about 50% of couples is constituted due to genetic, hormonal, and epigenetic factors. Almost 10% of it is contributed to genetic anomalies. **Objectives:** This study was undertaken in 787 males with infertility and the impacts of the type of translocations in these cases were studied in relation to MI. **Materials and Methods:** Five milliliters (ml) of blood were drawn from referred cases suspected with MI and were used for cytogenetic analysis with Giemsa stain following International System for Human Cytogenetic Nomenclature. **Results:** Of 6142 referral cases, 787 were detected with MI (787/6142; 12.8%). Forty-four translocations (44/787; 5.6%) were detected in 787 infertile men. Other chromosomal abnormalities were 21% (167/787) in them. Among all translocations, an autosome-autosomal translocations were higher in frequency (24/787; 3.1%) than Robertsonian (15/787; 1.9%) and autogonosomal translocations (5/787; 0.6%). Few translocations seemed to be rare as our knowledge is concerned. Maharashtra had high frequency of translocations followed by Delhi union territory (UT) and Gujarat (07 each) and other states. Most of the translocations were related to infertility. Seven males had primary infertility (7/44) and six with secondary type (6/44) in this study. **Conclusions:** These reciprocal translocations are important in causation of infertility affecting testicular spermatogenesis. Few are rare in our study. Such cases are clinically suggested for counseling before adopting assisted reproductive technologies.

Key words: Reciprocal translocations, Types, Karyotype, Male infertility, Patients

Infertility is one of the health-related concerns. In the male, it is caused by factors such as hormonal, physiological, psychological, neuronal, environmental, and genetic factors. Male infertility (MI) contributes about 50% of couples [1]. Genetic causes include chromosomal and Y chromosome microdeletion including gene mutations [2]. Keymolen *et al.* [3] Xie *et al.* [4], and Ching *et al.* [5] documented that chromosomal translocations play a major role in causation of MI. Cytogenetic analysis of patients is a basis for the evaluation of these genetic diseases [6-8]. Vozdova *et al.* [9] mentioned that Robertsonian (Rob) and other reciprocal translocations are associated with infertility and low sperm counts. Yq microdeletions are also second factor for infertility in the male. Deletions in azoospermia factor cause abnormal semen types such as azoospermia, oligozoospermia, and others [1,10-13], leading to fertility anomalies. It has been reported that the chromosomal translocations which are structural anomalies reduce fertility in both men and women. These are higher (6–10%) among infertile men compared to the general population [14,15]. Hence, this study was undertaken from March 2019 to March 2021 (2 years) to evaluate chromosomal translocations in referral cases with infertility on advice of clinicians for in our Neuberger Supratech Referral Laboratories (NSRLs), Ahmedabad, Gujarat, India.

MATERIALS AND METHODS

Patient Selection

Patients suspected infertility as suggested by clinician ranging in age from 21 to 43 years was referred to our NSRLs, Ahmedabad, for blood collection with duly filled consent forms. Blood samples from other centers were carefully transported at 4°C and were also pooled in our main centers, Ahmedabad, during this period of 2 years (March 2019–March 2021) for analysis.

Karyotyping from Blood

The blood samples were collected in sodium heparin vials as per the instructions and then utilized for karyotyping analysis. A volume of 0.5 milliliter (ml) of blood sample was used for chromosome preparation with phytohemagglutinin as mitogen using the method of Moorhead *et al.* [16]. These samples are incubated at 37°C (post-colchicine addition, 30 µl at 69th h) for 72 h. Then, they were harvested after treating with hypotonic potassium chloride solution. The metaphase slides were prepared with fixative and stained with G bands after trypsin and Giemsa or G-banding. These slides were subjected to Carl Zeiss Automated

Meta-systems for karyotyping. Twenty metaphase plates were prepared for each sample to identify chromosomal anomalies using International System for Cytogenetic Nomenclature [17].

Statistics

Descriptive statistics were prepared using Excel sheet data of patients. The categorical variables were mentioned as counts and frequencies.

RESULTS

Karyotyping was done in 6142 referral cases. Only 787 cases were detected with infertility in males (787/6142; 12.8%). Among 787 patients; 167 were with chromosomal abnormalities (167/787; 21%) and 44 had chromosomal translocations (44/787; 5.6%) in these males. From 44 translocations, Rob translocations constituted 1.9% (15/787) and auto-autosomal translocations were 3.1% (24/787) followed by gono-autosomal reciprocal translocations (5/787; 0.6%) (Tables 1-3). Reciprocal autosomal translocations contributed high frequency followed by Rob translocations and gonosomal types. Few were seemed to be rare (Tables 1-3). Among 44 translocations in our study, 20 cases were from Maharashtra, whereas Gujarat and Delhi (UT) contributed each of seven cases (7/44) followed by other states (Fig. 1). Most of the males were infertile (31/44) and few were with primary (7) and secondary (6) types of infertility (Tables 1-3). Examples of each translocation type were presented (Figs. 2-4).

DISCUSSION

Chromosomal translocations are the most structural chromosomal anomalies. These are known to reduce fertility in men and women. A study conducted by Dong *et al.* [1] who showed that 16.1% had chromosomal abnormalities in infertile men with

2.1% translocations. Other study also stated that infertile males have high frequency of the reorganization of chromosome architecture including Rob translocations compared to general population [18]. In our study of 6142 referral cases, the infertile male cases contributed to 12.8% (787/6142). Among 787 infertile men, 167 had chromosomal anomalies (21%), whereas 44 had total reciprocal translocations (5.6%) aging from 21 to 43 years. Fifteen cases suffered with Rob type (15/787; 1.9%) and 24 infertile men exhibited an autosome-autosomal translocations (24/787, 3.1%) and others had gonosome-autosomal reciprocal types (05/787; 0.6%). The frequencies of these types are well comparable with the study of Dong *et al.* [1] and are related to MI. Further, they documented that these translocations reduce spermatogenesis and are correlated to reduced sperm quality. No changes were noticed in hormone level except testosterone levels where markedly affected in Rob and gonosome-autosomal reciprocal cases. These translocation groups might have not overcome meiosis I and become blocked differentiation of primary spermatocyte stage forcing them to oligozoospermia. Infertile men with 44 translocations, higher frequency of autosome-autosomal translocations were seen in this study, as reported by earlier workers [1,4,5]. Parent carriers with reciprocal translocations are at a risk of infertility and recurrent pregnancy loss (RPL). The incidence of balanced autosomal translocations in infertile men has been reported between 1.6 and 6.65% to support our data [5-7,19,20]. Two rare cases of double autosome-autosome translocations t(5;21)/t(11;21) and t(1;8)/t(7;15) and another case of translocation t(19;20) with heteromorphism (21ps+;22ps+) were noticed. Similarly, cases with reciprocal translocations between Y chromosome and an autosome are rare and highly associated with male sterility [21]. Such patients of five were obtained in our study.

Rob translocations are also common balanced type, occur between acrocentric chromosomes of 13, 14, 15, 21, and 22. Their incidence in general population is 0.1% with 1.1% in

Table 1: Robertsonian translocations in our study

Case no.	Age (Year)	State	Karyotype	History
1	26	Gujarat	45, XY, inv (9),(p11;q13), rob (13;14)(q10;q10),21ps+*	Infertility
2	43	Rajasthan	45, XY, rob (13;14)(q10;q10)	Infertility
3	33	Tamil Nadu	45, XY, rob (13;14)(q10;q10)	Infertility
4	42	Maharashtra	45, XY, rob (13;14)(q10;q10)	Infertility
5	39	Tamil Nadu	45, XY, rob (13;14)(q10;q10)	Infertility
6	39	Maharashtra	45, XY, rob (13;14)(q10;q10)	Infertility
7	39	Maharashtra	45, XY, rob (13;14)(q10;q10)	Secondary infertility
8	38	Delhi (UT)	45, XY, rob (13;14)(q10;q10)	Infertility
9	38	Maharashtra	45, XY, rob (13;14)(q10;q10)	Primary infertility
10	33	Maharashtra	45, XY, rob (13;15)(q10;q10)	Infertility
11	28	Tamil Nadu	45, XY, rob (13;22)(q10;q10)	Infertility
12	43	West Bengal	45, XY, rob (14;21)(q10;q10)	Infertility
13	32	Maharashtra	45, XY, rob (15;21)(q10;q10)	Primary infertility
14	26	UT	45, XY, rob (22;22)(q10;q10)	Infertility
15	33	Maharashtra	45, XY, rob (3;14)(q10;q10)	Primary infertility

*Rob with inversion q and 21ps+(Rare); UT=Union territory

Table 2: Autosome-autosomal translocations in our study

Case no.	Age (Year)	State	Karyotype	History
1	31	Tamil Nadu	45, XY, t (5;21)(p15;q10)[15]/45, XY, t (11;21)(q25;q10)[5]**	Infertility
2	31	Maharashtra	46, XY, t (5;17)(q10;p10)	Secondary infertility
3	31	Maharashtra	46, XY, t (1;12)(q31;q14)	Primary infertility
4	33	Maharashtra	46, XY, t (1;17)(q10;p10)	Secondary infertility
5	21	Gujarat	46, XY, t (1;2)(p36.2;p13)	Infertility
6	38	Maharashtra	46, XY, t (1;3)(p22;q21)	Infertility
7	37	Maharashtra	46, XY, t (1;3)(q10;p10)	Primary infertility
8	30	Madhya Pradesh	46, XY, t (1;6)(p32;q27)	Infertility
9	43	Delhi (UT)	46, XY, t (1;8)(q31;q11.2)/46, XY, t (7;15)(q32;q26)**	Infertility
10	26	Gujarat	46, XY, t (13;19)(22q; 12p)	Infertility
11	29	Gujarat	46, XY, t (17;19)(p12;p13)	Infertility
12	39	Maharashtra	46, XY, t (19;20)(q13.1;q13.3),21ps+,22ps+ ***	Primary infertility
13	48	Gujarat	46, XY, t (2;17)(p16;p11.2)	Infertility
14	29	West Bengal	46, XY, t (2;7)(q32;p21)	Infertility
15	28	West Bengal	46, XY, t (4;6)(q35;q24)	Infertility
16	35	Maharashtra	46, XY, t (5;6)(p15;q21)	Secondary infertility
17	32	Maharashtra	46, XY, t (6;10)(p23;q22)	Secondary infertility
18	37	UT	46, XY, t (6;16)(p21;p13.1)	Infertility
19	40	West Bengal	46, XY, t (6;9)(q22;p21)	Infertility
20	41	Maharashtra	46, XY, t (7;8)(q21;q24)	Secondary infertility
21	24	UT	46, XY, t (8;10)(p23;q22)	Infertility
22	33	Maharashtra	46, XY, t (8;10)(q24.2;p11.2)	Infertility
23	38	Gujarat	46, XY, t (9;12)(p24;q24.1)	Infertility
24	41	Gujarat	46, XY, t (9;22)(q13;q11.2)	Infertility

Double translocations, *translocation with polymorphism; UT=Union territory

Table 3: Gonosome-autosomal translocations in our study

Case no.	Age (Year)	State	Karyotype	History
1	36	Delhi (UT)	46, X, t (Y; 13),(q11.21;q22)	Infertility
2	28	Maharashtra	46, X, t (Y; 13),(q12;q32)	Infertility
3	25	Assam	46, X, t (Y; 22),(p11.3;q11.2)	Infertility
4	28	Maharashtra	46, X, t (Y; 3),(p11.2;q21)	Primary infertility
5	30	Delhi (UT)	46, X, t (Y; 3),(q12;p22)	Infertility

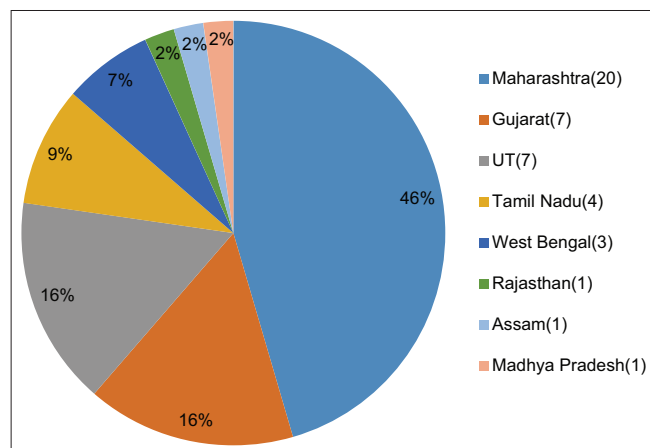


Figure 1: State-wise distribution percent of translocation in our study number in parentheses indicate cases. UT: Union territory

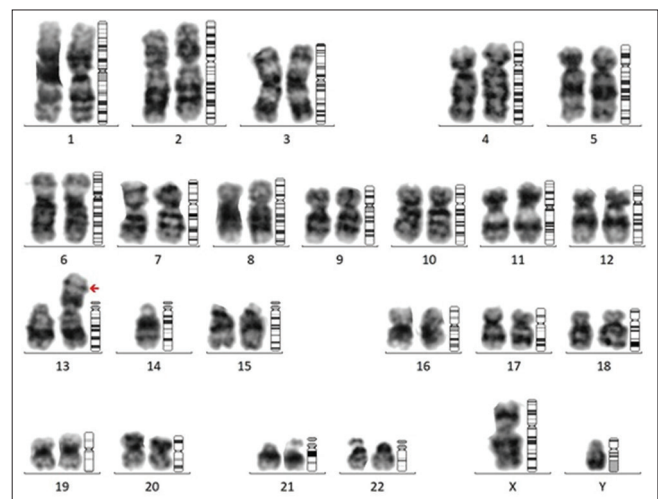


Figure 2: Typical Robertsonian translocation, t(13;14)

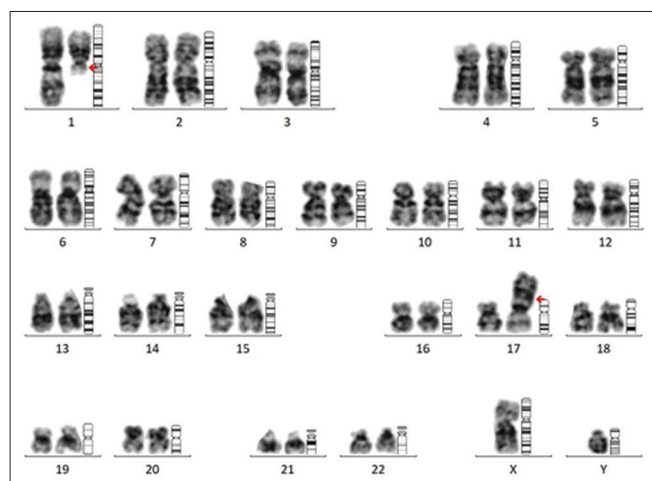


Figure 3: Autosome-autosomal translocation, t(1;17)

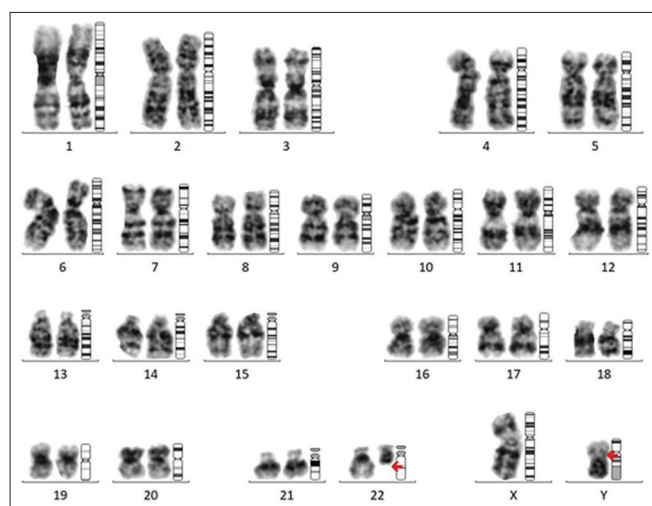


Figure 4: Gonosome-autosomal translocation, t(y;22)

patients with RPL and men of 3% infertile [22]. In our study, 1.9% Rob translocations were detected. One patient with inversion 9 and heteromorphism (21ps+) was observed which seemed to be rare in our study (Table 1). The carriers of these translocations were infertile. Most of the Rob translocations are inherited from paternal, nearly 40% can be *de novo* translocations due to rearrangements in meiosis [23]. Mostly chromosomal translocations may affect fertility due to disruption of meiosis leading to reduced spermatogenesis as stated above. Some studies indicate that aberrant chromosomal pairing during meiosis in balanced translocation carriers may interfere with certain genetic processes and cause germ cell arrest [5]. Certain cases with MI having Rob translocations cause primary infertility and their semen show oligozoospermia and azoospermia [18].

In addition, geographically, Maharashtra had high incidence of these cases followed by Gujarat and Delhi, indicating environment, hormonal, genetic, and other epigenetic factors which are to be taken into consideration in this report. In-depth epidemiological survey is called for with more sample analysis in future. Few of these infertile cases were with primary and secondary infertility, probably contributed to altered testicular spermatogenesis causing azoospermia, oligospermia, and other

semen types to support the reports of earlier workers [1,19,23]. These cases may thus serve as clinical reference for genetic counseling and assessment.

CONCLUSIONS

Auto-autosomal reciprocal translocations are higher in frequency followed by Rob and gonosomal translocations causing MI due to low semen quality and hormone alterations. Few of the cases reported with primary and secondary infertility. Maharashtra exhibited more patients with this genetic cause of MI in our report. Genetic counseling and genetic testing are offered to such families.

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AUTHORS' CONTRIBUTIONS

Ms. Somali and Ms. Krishna along with Dr. Mudra assisted in collection, analysis of karyotyping samples, and writing the paper. Dr. Nidhi and Dr. Parth reviewed the manuscript. Dr. Mudra and Ms. Nirali helped in technical work and preparation of figures. Dr. Sandip and Dr. Rao had edited it critically for publication along with others.

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