Frequency of balanced reciprocal translocations from couples with recurrent miscarriages correlates with the density of Alu and L1 repeat elements: literature finding-based study

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Background
Balanced reciprocal translocations constitute the most frequently encountered structural chromosome abnormality in couples experiencing recurrent miscarriages. The present work was undertaken to assess the relation between reported reciprocal translocations and the density of Alu and L1 repetitive elements in the human chromosomes.

Patients and methods
Data analyzed were obtained from 55 relevant articles that investigated 98 054 individuals. The overall prevalence of reciprocal translocations reached 2.31% and was 1.65 times more frequent in the female patients. The 2262 (1402 in females and 860 in males) counted translocations were tested for association with Alu and L1 densities using Pearson's correlation test.

Results
A strong positive correlation ($r = 0.87–0.89$, $P \leq 0.0001$) was observed between the frequency of translocations and the densities of L1 and Alu in the human genome.

Conclusion
The results thus obtained reinforce the involvement of Alu and L1 DNA repeat elements in the generation of reciprocal translocations.

Keywords:
Alu, DNA repeat elements, L1, reciprocal translocations, recurrent miscarriage

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Introduction

Balanced reciprocal translocations between nonhomologous chromosomes constitute the most frequently detected chromosomal structural abnormality in couples with recurrent miscarriages. They are responsible for 2–5% of the recurrent miscarriages and more predominantly seen in female partners (Ozawa *et al.*, 2008; Pal *et al.*, 2018).

Apart from reproduction problems, such as pregnancy loss and infertility, carriers of balanced reciprocal translocations are oftentimes phenotypically normal. This reflects the balanced nature and the mitotic stability of the derivative chromosomes. Derivative chromosomes may, however, undergo abnormal segregation during meiosis (gamete formation) that can affect the survival of gametes, cause recurrent miscarriages, or even lead to the birth of malformed children (Fantes *et al.*, 2008; Suzumori and Sugiura-Ogasawara, 2010).

Occasionally, breakpoints of translocation may alter gene-expression regulatory elements or disrupt gene structure and may thus be associated with various human diseases, including many cancers (Vandeweyer and Kooy, 2009; Sandberg and Meloni-Ehrig, 2010).

The human genome is swarmed with various families of interspersed retrotransposons, notably the long interspersed elements (LINEs) and the short interspersed elements, which constitute around 45% of the genome. LINE-1 (L1) family makes up about 21% of the genome and consists of about 6500-bp long repetitive sequences. The human genome contains around 500 000 copies of the L1 family. The 200–300-bp long Alu repeat elements are the most abundant short interspersed elements in the genome. More than one million Alu sequences exist in the human genome, making up about 10% of its length (Jelinek *et al.*, 1980; Korenberg and Rykowski, 1988; Hancks and Kazazian, 2012).

DNA double-strand breaks (DSBs) furnish the substrate for the nonhomologous end joining repair system that inaccurately join the breakpoints in nonhomologous chromosomes resulting in reciprocal translocations and formation of derivative chromosomes (Godwin *et al.*, 1994; Fantes *et al.*, 2008; Suzumori and Sugiura-Ogasawara, 2010; Cornforth

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et al., 2018). Current evidence suggests that DSBs take place stochastically and that the breakpoints consistently occur in, or near repetitive elements, such as Alu and L1 (Suzumori and Sugiura-Ogasawara, 2010; Cretu Stancu *et al.*, 2017; Huddleston *et al.*, 2017; Cornforth *et al.*, 2018; Hu *et al.*, 2018; De Coster *et al.*, 2019; Eisfeldt *et al.*, 2019). Importantly, it seems that, somehow, repeat elements participate in creating the DSBs during their (retro) transposition. Gasior *et al.* (2006) have demonstrated that L1 expression leads to a high level of DNA DSB formation (Gasior *et al.*, 2006). Therefore, Alu and L1 may be implicated in the generation of balanced chromosomal translocations.

The current work was carried out to assess the possible correlation between the frequency of reciprocal translocations, reported in couples with recurrent miscarriages from different populations, and the densities of Alu and L1 repeat elements in the human genome.

Patients and methods

Approval for conducting the study was granted by the Ethical Review Committee of the Islamic University of Gaza. Data analyzed in this work were obtained from studies of chromosomal abnormalities observed in couples with recurrent miscarriages. Relevant literature was searched from PubMed database, or by citation search and reference lists of relevant articles. All reported karyotypes were established by conventional cytogenetic techniques. The 55 manuscripts considered in this work included 98 054 individuals (Turleau *et al.*, 1979; Sant-Cassia and Cooke, 1981; Davis *et al.*, 1982; Husslein *et al.*, 1982; Lippman and Veremans, 1983; Sachs *et al.*, 1985; Bourrouillou *et al.*, 1986; Castle and Bernstein, 1988; Fortuny *et al.*, 1988; Gadow *et al.*, 1991; Fryns and Van Buggenhout, 1998; Al-Hussain *et al.*, 2000; Sugiura-Ogasawara *et al.*, 2004; Dubey *et al.*, 2005; Celep *et al.*, 2006; Stephenson and Sierra, 2006; Clementini *et al.*, 2007; Farcas *et al.*, 2007; Iyer *et al.*, 2007; Tavokina *et al.*, 2007; Meza-Espinoza *et al.*, 2008; Nazmy, 2008; Sugiura-Ogasawara *et al.*, 2008; Goud *et al.*, 2009; Kiss *et al.*, 2009; Pal *et al.*, 2009; Chen *et al.*, 2010; Cirakoglu *et al.*, 2010; Cutiongco-de la Paz *et al.*, 2011; Dutta *et al.*, 2011; Niroumanesh *et al.*, 2011; Vansenne, 2011; Karakus *et al.*, 2012; Saxena *et al.*, 2012; Sharif, 2012; Karman, 2013; Kochhar and Ghosh, 2013; Rajasekhar *et al.*, 2013; Sheth *et al.*, 2013; Gonçalves *et al.*, 2014; Gaboon *et al.*, 2015; Ghazaey *et al.*, 2015; An *et al.*, 2016; Atli *et al.*, 2016; Demirhan *et al.*, 2016; Fan *et al.*, 2016; Sudhir *et al.*, 2016; Tunç *et al.*, 2016; Ayed *et al.*, 2017; Kalotra *et al.*, 2017; Веропотвелян *et al.*, 2017; Behbahani *et al.*, 2018; Cavalcante *et al.*, 2018; Elkarhat *et al.*, 2018; Houmaid *et al.*, 2018). The number of reciprocal translocations between nonhomologous autosomes reached 2262 (1402 females and 860 males). Owing to the rarity of translocations between sex chromosomes and autosomes, only autosomal translocations were taken into consideration. The frequency of translocation per autosome, regardless of the breakpoints location, was calculated by counting the number of times each autosome participated in the translocations (Tables 1 and 2).

The density of human-specific L1 and Alu per autosome was obtained from the articles published by Carter *et al.* (2003), Otieno *et al.* 2004, and Tang *et al.* (2018).

The strength of association between frequency of translocations and the density of human-specific mobile elements, L1, Alu, AluYa, and AluYb repeat elements was measured by Pearson's correlation test using a freely available statistics software (Wessa, 2017).

Results

The prevalence of reciprocal translocations among couples having recurrent miscarriages is 2.31% (2262/98 054). This is more than 10-fold higher than the translocation frequency encountered in the general population. The frequency of translocation per autosome is presented in Table 3. The table also includes the densities of human-specific L1, Alu, AluYa, and AluYb repeat elements. Females constituted about 62% (1402/2262) of the translocation carriers. The higher translocation frequencies in the female patients was evident for all the autosomes (Fig. 1).

Strong and significant (all $P < 0.0001$) associations were observed between the autosomal densities of human-specific retrotransposons (mobile elements, L1, Alu, AluYa, and AluYb) and reciprocal translocations, as indicated in Table 3. The association however, was the strongest between the translocations and AluYb elements (Table 4 and Fig. 2).

Discussion

The objective of this work was to examine the association between L1/Alu repeat elements densities and reciprocal translocations reported in couples experiencing more than or equal to 2 recurrent miscarriages from various populations (Turleau *et al.*, 1979; Sant-Cassia and Cooke, 1981; Davis *et al.*, 1982;

Table 1 Distribution of the different autosomal translocations ascertained in males

Chr.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Total
1	–																						
2	5	–																					5
3	4	1	–																				5
4	5	2	6	–																			13
5	3	5	2	6	–																		16
6	5	4	5	5	5	–																	24
7	1	5	5	4	5	4	–																24
8	4	4	5	2	1	6	7	–															29
9	4	2	2	7	5	1	1	1	–														23
10	3	2	2	5	4	3	2	5	3	–													30
11	3	3	2	1	2	3	0	6	2	4	–												26
12	4	2	4	2	4	1	0	3	1	0	0	–											21
13	1	1	1	2	3	2	9	4	2	3	3	2	–										33
14	0	0	2	3	2	1	3	3	1	5	1	0	0	–									21
15	0	1	2	6	1	2	0	2	2	3	2	3	3	0	–								27
16	1	0	1	1	3	3	1	1	0	1	2	0	1	1	0	–							16
17	1	1	1	0	2	3	4	3	2	1	1	4	0	3	1	3	–						33
18	3	0	3	2	0	2	1	2	1	2	2	3	0	2	0	2	0	–					25
19	3	0	0	1	0	0	0	0	0	1	0	0	2	1	0	0	0	0	–				8
20	1	1	1	1	1	2	0	0	0	1	0	1	1	0	0	2	0	2	1	–			15
21	1	2	0	2	0	0	3	1	1	1	2	1	0	0	0	2	0	2	0	0	–		18
22	0	0	0	1	0	0	2	0	0	3	8	1	0	0	0	1	1	2	1	0	0	–	20
Total	52	36	44	51	38	33	33	31	15	25	21	15	7	7	1	10	1	6	2	0	0		

Table 2 Distribution of the different autosomal translocations ascertained in females

Chr.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Total
1	–																						
2	8	–																					8
3	6	2	–																				8
4	8	6	8	–																			22
5	2	3	4	6	–																		15
6	6	10	12	15	6	–																	49
7	8	7	7	8	3	7	–																40
8	2	4	9	5	4	9	4	–															37
9	6	7	5	3	4	2	3	4	–														34
10	7	2	3	7	5	7	8	3	2	–													44
11	5	6	4	4	3	7	4	6	2	8	–												49
12	0	4	3	5	4	8	5	2	2	2	7	–											41
13	4	4	3	4	3	4	5	6	7	4	3	3	–										50
14	3	1	4	6	1	3	6	2	4	3	1	2	1	–									37
15	2	9	4	5	1	4	1	1	2	2	2	1	2	3	–								39
16	8	3	2	1	0	3	2	0	2	3	1	4	0	1	1	–							31
17	1	1	3	3	0	0	2	3	2	2	3	3	2	2	0	2	–						29
18	2	6	1	1	2	1	8	1	2	1	7	0	3	3	2	3	4	–					47
19	3	0	3	1	0	1	0	4	0	1	2	0	0	0	1	1	0	0	–				17
20	0	1	0	3	0	3	4	1	0	0	1	0	3	1	1	5	2	0	0	–			25
21	3	1	0	3	0	1	2	4	0	3	1	0	0	0	2	3	0	1	1	2	–		27
22	1	0	0	1	0	0	2	1	2	1	22	1	1	0	1	3	0	0	2	0	0	–	38
Total	85	77	75	81	63	60	56	38	27	30	50	14	12	10	8	17	6	1	3	2	0		

Husslein *et al.*, 1982; Lippman and Veremans, 1983; Sachs *et al.*, 1985; Bourrouillou *et al.*, 1986; Castle and Bernstein, 1988; Fortuny *et al.*, 1988; Gadow *et al.*, 1991; Fryns and Van Buggenhout, 1998; Al-Hussain *et al.*, 2000; Sugiura-Ogasawara *et al.*, 2004; Dubey *et al.*, 2005; Celep *et al.*, 2006; Stephenson and Sierra, 2006; Clementini *et al.*, 2007; Farcas *et al.*, 2007; Iyer *et al.*, 2007; Tavokina *et al.*, 2007; Meza-Espinoza *et al.*, 2008; Nazmy, 2008; Sugiura-Ogasawara *et al.*, 2008; Goud *et al.*, 2009; Kiss *et al.*, 2009; Pal *et al.*, 2009; Chen *et al.*, 2010; Cirakoglu *et al.*, 2010; Cutiongco-de la Paz *et al.*, 2011; Dutta *et al.*, 2011; Niroumanesh *et al.*, 2011; Vansenne, 2011; Karakus *et al.*, 2012; Saxena *et al.*, 2012; Sharif, 2012; Karman, 2013; Kochhar and Ghosh, 2013; Rajasekhar *et al.*, 2013; Sheth *et al.*, 2013; Gonçalves *et al.*, 2014; Gaboon *et al.*, 2015;

Table 3 Frequencies of translocations counted for each autosome along with the densities of retrotransposons across the 22 autosomes

Chr.	Males	Females	Both	MEs[a]	L1[a]	Alu[a]	AluYb[b]	AluYa[c]
1	52	85	137	1147	297	667	123	213
2	41	85	126	1190	310	735	121	206
3	49	83	132	1036	268	633	119	166
4	64	103	167	1025	321	619	123	151
5	54	78	132	970	256	597	141	146
6	57	109	166	902	257	531	125	152
7	57	96	153	794	188	505	128	154
8	60	75	135	692	196	417	93	99
9	38	61	99	635	144	405	75	95
10	55	74	129	564	137	350	66	91
11	47	99	146	667	184	382	82	118
12	36	55	91	625	155	382	78	125
13	40	62	102	507	113	340	76	114
14	28	47	75	423	120	243	61	104
15	28	47	75	370	92	225	51	48
16	26	48	74	344	78	210	44	62
17	34	35	69	350	49	212	51	62
18	31	48	79	376	110	238	47	43
19	10	20	30	280	45	141	27	60
20	15	27	42	282	72	152	41	52
21	18	27	45	162	35	101	35	20
22	20	38	58	128	29	68	26	18
Total	860	1402	2262	13 469	3456	8153	1733	2135

ME, mobile element. [a]From Tang *et al.* (2018) (MEs include human specific: Alu, L1, and SVA retrotransposons). [b]From Carter *et al.* (2003). [c]From Otieno *et al.* (2004).

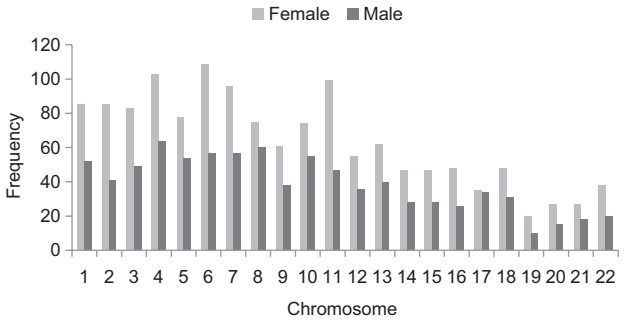
Table 4 Association between repeat elements and translocation frequency in the study sample

Repeat element	Pearson's correlation coefficient (*r*)		
	Males	Females	Both (males and females)
Human MEs[a]	0.80	0.85	0.85
Human L1	0.81	0.87	0.87
Human Alu	0.81	0.85	0.85
Human AluYb	0.86	0.88	0.89
Human AluYa	0.72	0.80	0.79

ME, mobile element. [a]MEs include: Alu, L1, and SVA retrotransposons.

Ghazaey *et al.*, 2015; An *et al.*, 2016; Atli *et al.*, 2016; Demirhan *et al.*, 2016; Fan *et al.*, 2016; Sudhir *et al.*, 2016; Tunç *et al.*, 2016; Ayed *et al.*, 2017; Kalotra *et al.*, 2017; Веропотвелян *et al.*, 2017; Behbahani *et al.*, 2018; Cavalcante *et al.*, 2018; Elkarhat *et al.*, 2018; Houmaid *et al.*, 2018). The strong correlation observed denotes an important role of those elements in the generation of translocations. Supporting evidence for this conclusion can be derived from prior research that focused on the characterization of breakpoint junctions involved in the formation of chromosomal structural variants, for example, translocations (Suzumori and Sugiura-Ogasawara, 2010; Liu *et al.*, 2012; Xu *et al.*, 2014; Cornforth *et al.*, 2018; De Coster *et al.*, 2019). For instance, Eisfeldt *et al.* (2019) showed that all breakpoint junctions contained repeat regions, mostly Alu and LINE elements (Eisfeldt *et al.*, 2019). Additionally, the translocation breakpoints characterization study of

Figure 1



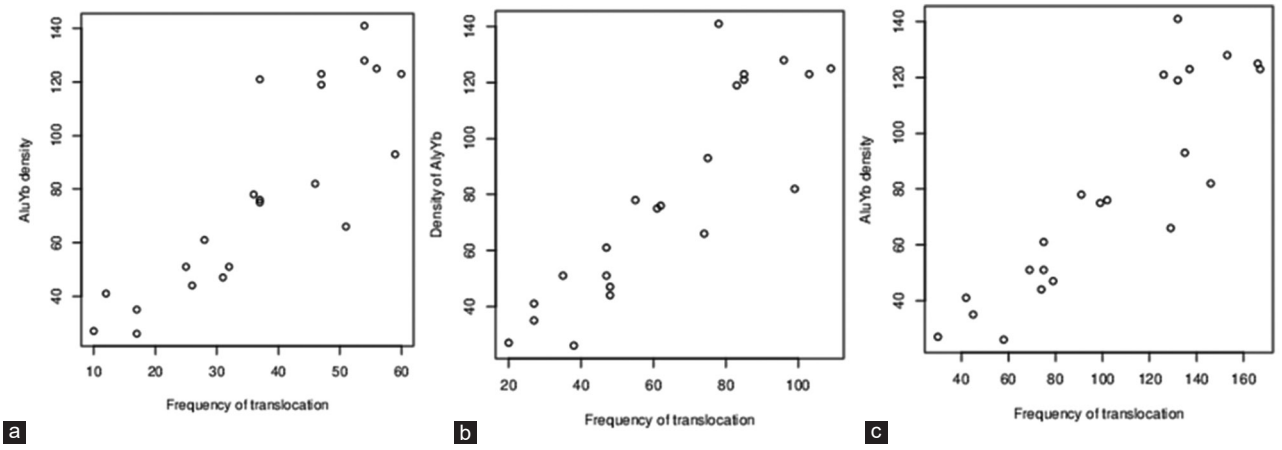
Frequency with which individual autosomes participated in reciprocal translocations in female and male patients.

Cornforth *et al.* (2018) indicated that the breakpoints frequently occurred within interspersed Alu and LINE repeats (Cornforth *et al.*, 2018). Importantly, it seems that Alu/LINE repeat elements participate in creating the DSBs needed for the translocation, as illustrated by Gasior *et al.* (2006) who demonstrated that L1 expression leads to a high level of DSB formation (Gasior *et al.*, 2006). Moreover, studies on human cancers have also shown that repeat elements are mediators of chromosomal aberrations (Kolomietz *et al.*, 2002; Tubio *et al.*, 2014). The ubiquitous nature of Alu and L1 elements in the human genome and their vast residence in the noncoding (intergenic and intronic) regions of the genome make them plausible players in the formation of translocations.

In the current analysis, the strongest association was evident between translocations and AluYb elements. Interestingly, AluYb is one of the largest and most biologically active Alu lineage in the human genome (Carter *et al.*, 2003). AluYb lineage composes ~40% of the human-specific Alu elements (Hedges *et al.*, 2004). Meanwhile, no association was found between the dormant AluJ and AluS families and the analyzed translocations (results not shown). This further points to a link between retrotransposition and translocations.

On analysis of reciprocal translocations in couples having recurrent miscarriages, and as is evident in the current work and that of other researchers in the field, translocations are consistently more predominant in female patients (Tharapel *et al.*, 1985; Tunç *et al.*, 2016). This observation raises the question as whether the number of actively transposing Alu/L1 elements are different between males and females. Although there is no mention of this in the literature, this seems possible given that, DNA repeat elements methylation (and overall genome methylation) levels tend to be higher in males (El-Maarri *et al.*, 2007; Hall *et al.*, 2014). The methylation of repeat elements is an important mechanism in suppressing

Figure 2



Diagrams illustrating the correlations between translocation frequencies and AluYb density in the human autosomes. (a) Males; (b) females; (c) both males and females.

retrotransposition (Slotkin and Martienssen, 2007; Luo *et al.*, 2014; Zheng *et al.*, 2017). In the same context, epigenetic changes and deregulation of methylation can affect transposition and translocation frequency. Moreover, many environmental factors, for example, radiation and various pollutants had been shown to affect *Alu* methylation (Luo *et al.*, 2014).

The same reasoning can be used to partly explain why certain autosomes, for example, t(11;22) are involved more than others [e.g. t(5;19)] in translocations. Another part of the explanation lies in the effect of certain translocations (i.e. genomic stability) on the survival of the cells.

An additional question that needs to be answered is why balanced translocations are seen in certain individuals. It has been estimated that balanced translocation carriers account for around 0.2 of the general population (Karakus *et al.*, 2012). As with the rest of many genetic disorders, the genetic/epigenetic makeup of the individual along with the environmental exposures may explain why this genetic error is restricted to particular people.

Conclusion

The current literature finding-based synthesis denotes the high prevalence of balanced chromosomal translocations in couples experiencing recurrent miscarriages and emphasizes the predominance of those chromosomal abnormalities in female patients.

Considerable evidence from published articles and from the correlations observed in this work underscores the important contribution of Alu/L1 repeat elements to the development of reciprocal translocations.

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Conflicts of interest
There are no conflicts of interest.

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