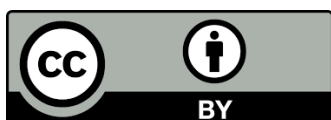


Original Research

Reciprocal Translocations in Prenatal Diagnosis: Latin America Data

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Abstract

Generally, in reciprocal translocations there are no gains or losses of genetic material. From the clinical point of view, its primary importance lies in the fact that it can generate errors due to incorrect chromosome segregation during meiosis in carriers. On the other hand, other mutations are less frequent in the genome, specifically in the DNA breakpoints implied in these translocations. In Latin America there are no large-scale reports about this topic. To contribute to the study of reciprocal translocations detected during prenatal diagnosis in Latin American countries through different aspects: frequency of occurrence, possible association with phenotypic alterations, most frequently involved chromosomal breakpoints, and other issues. Methods: This was a retrospective observational study based on the analysis of 143,093 prenatal test data conducted from 1984 to 2021 in Cuba, Uruguay, Costa Rica, Mexico, Panama, and Colombia (19 laboratories) and two publications. Cytogenetic laboratories and publications provided information that included: total number of cases analyzed, number of reciprocal translocations detected, detailed descriptions of the karyotypes, reasons for referral to the laboratory, sonographic findings, and follow-up studies in translocation carriers. One hundred forty-three thousand ninety-three data points from prenatal diagnosis were collected. 243 translocations were reported, 210 balanced and 33 unbalanced. The most frequently referred reasons were advanced maternal age with 56%, a parent carrying a balanced translocation 23%, and sonographic findings 10%. 76 reciprocal translocations were

inherited, 46 were *de novo* cases, and 121 were undetermined. 10% of the translocations had some type of fetal ultrasound abnormality and/or subsequent abnormality during the follow-up of the patients over time. Seven recurrent breakpoints were found. The breakpoints with significant difference from international studies were 1p13 and 9p24. The frequency of reciprocal translocations is consistent with international studies. Follow-up studies and prenatal ultrasound showed 10% of phenotypic alterations. Recurring breakpoints specific to the Latin American region were detected.

Keywords

Reciprocal translocations; prenatal diagnosis; *de novo* rearrangements; chromosomal breakpoints

1. Introduction

Reciprocal translocations imply the exchange of chromosomal segments, typically between two chromosomes, although they can also involve three or more chromosomes. This group constitutes the most frequent chromosomal abnormality in humans, with a frequency between 1:300 and 1:600 people [1, 2].

Generally, in reciprocal translocations there are no gains or losses of genetic material. From a clinical perspective, its primary significance lies in the potential for erroneous outcomes during meiosis in carriers due to improper chromosome segregation. This may increase the risk of having offspring with trisomies and partial monosomies of the chromosomes involved, leading to the possibility of recurrent miscarriages [3].

However, microarray-based comparative genomic hybridization in prenatal diagnosis has demonstrated that reciprocal translocations can result in submicroscopic chromosomal imbalances, including deletions, duplications, and copy number variations, that have the potential to alter gene dosage, inactivate genes susceptible to uniparental disomy, inactivate dominant genes, and so forth [4, 5].

One of the indications for prenatal cytogenetic diagnosis is the presence of progenitors carrying balanced rearrangements, with translocations being the most frequent. Furthermore, the possibility of an apparently *de novo* event introduces additional uncertainty.

In 1991, Warburton conducted a study involving 377,000 prenatal diagnoses in the USA and Canada. Among these cases, where a balanced structural rearrangement *de novo* was detected, she estimated an empirical risk of approximately 6.1% (10/163) for severe congenital anomalies [6]. More recently, Halgren et al. (2018) identified a 26.8% (11/41) risk of morbidity associated with genomic abnormalities in a reanalysis of carriers of *de novo* translocations and inversions using advanced molecular methods [7]. Similarly, Méndez et al. (2018) reported a 15.3% (6/39) risk of phenotypic alterations detected using conventional cytogenetics in *de novo* balanced rearrangements (translocations and inversions) identified during prenatal diagnosis in Latin American countries [8].

The identification of a translocation during prenatal diagnosis can occasionally facilitate the detection of this rearrangement within the family and its potential future implications. Several

international studies have been conducted on this type of rearrangement and its consequences in the prenatal and postnatal period [9, 10]. Nevertheless, in Latin America there are no large-scale reports about this topic.

This region, with its own social and demographic characteristics, has a unique genome product of a *melting pot* of Amerindians, Africans, Caucasians, and, to a lesser extent, Asians [11-14].

The objective of this work is to contribute to the study of reciprocal translocations identified during prenatal diagnosis in several Latin American countries from a variety of perspectives, including their frequency of occurrence, potential correlation with phenotypic alterations, the most commonly involved chromosomal breakpoints, and other characteristics.

2. Materials and Methods

This retrospective observational study analyzed data from 143,093 prenatal tests conducted between 1984 and 2021 across six countries: Cuba, Uruguay, Costa Rica, Mexico, Panama, and Colombia, involving 19 laboratories and two published studies [15, 16]. Breakpoints in translocations were determined using chromosome ideograms with a resolution of 450–550 G-bands.

Cytogenetic laboratories and publications provided information that included: the total number of cases analyzed using various cytogenetic prenatal diagnostic modalities (amniotic fluid culture, chorionic villus culture, and fetal blood lymphocyte culture), the number of reciprocal translocations detected, detailed descriptions of karyotypes by the International System for Human Cytogenetic Nomenclature [17], reasons for laboratory referral, sonographic findings, and follow-up studies of translocation(s) carriers.

Additionally, all participating laboratories were requested to specify the origin of each translocation as inherited, *de novo*, or undetermined.

The results were compared with other studies worldwide:

- Daniel et al. (1989), which contains data from 1157 independent translocations [9].
- Youings et al. (2004) in England found 448 translocations [10].
- The database of Dr. Liehr from the University of Jena in Germany, which collects the positive cases, specifying the breakpoints. This database provides the evidence of 779 constitutional reciprocal translocations [18].

In the sample under study, a recurrent breakpoint was defined as one that was present six or more times and was always involved in a reciprocal translocation. This definition was employed to minimize the potential for bias resulting from purely random occurrences (i.e., by chance) about the occurrence of a given breakpoint. Furthermore, the breakpoints were determined in different laboratories by different individuals using conventional cytogenetic methods, which could introduce some bias in their determination.

The follow-up studies were conducted on the following issues:

1. Abortive material analyzed through pathological anatomy reports from interrupted pregnancies.
2. Newborns, using data provided by neonatologists or geneticists.
3. Children carrying a translocation, with information obtained through data provided by medical geneticists. This follow-up was typically carried out over a period exceeding two years of life.

Many of this data regarding follow-up were obtained from the research previously carried out by Méndez-Rosado et al. [19]. Although they were updated and, in some cases, corrected to take into account the present work.

2.1 Statistical Analysis

The data was presented in absolute frequency values and percentages. The test for comparison of proportions of two tails was used to compare the recurrent breakpoints (observed at least six times) in our work on international data. A value of $p < 0.05$ was established as statistically significant. We used the EPIDAT V.3 software.

2.2 Ethics Statement

Genetic counseling was provided to all participating couples, and written consent was obtained before the collection of samples. Following the conclusion of the prenatal diagnosis, all samples that were not utilized were discarded. The couples were provided with the results of the cytogenetic prenatal diagnosis. In all laboratories, a unique identifier was assigned to each patient in the database to ensure patient anonymity during data management. The study was approved by the respective institutional review boards of each participating institution.

3. Results

A total of 143,093 cases were collected from prenatal diagnosis invasive procedures in Brazil, Colombia, Costa Rica, Cuba, México, Panamá, and Uruguay. The majority of prenatal cases were analyzed by amniotic fluid culture (91%). However, other methods, including chorionic villus culture (8%) and culture of fetal blood lymphocytes obtained by cordocentesis (1%), were also employed (Table 1).

Table 1 Cases of prenatal diagnosis collected from different laboratories in Latin America and two publications from Latin American authors.

Laboratory	Period	Amniotic fluid cases	Chorionic villus sampling cases	Cordocentesis Cases	Total
CNGM ^a	1984-2021	29031	1776	1123	31930
Villa Clara	1988-2019	14529	2805		17334
Holguin	1989-2019	9250			9250
Cienfuegos	2007-2019	3441			3441
Pinar del Rio	2007-2019	4067			4067
Camagüey	1986-2012	4073			4073
Gonzalez Coro	2009-2019	10391			10391
Matanzas	2007-2019	2784			2784
Sancti Spiritus	2007-2020	5270			5270
Santiago de Cuba [†]	1986-2020	14751	1721		16472
Grether México [15]	Publication	1500			1500
México ^{b, c}	1983-2016	4945			4945

Kesler, Brasil [16]	Publication	879			879
Panamá ^d	2000-2020	1000			1000
Colombia ^e	2018-2021	1996		7	2003
Costa Rica ^f	2013-2021	1402			1402
Colombia ^g	2010-2016	1662	16	36	1714
Toluca, México ^h	2008-2021	769	66		835
Montevideo. Uruguay ⁱ	2004-2020	18262	5541		23803
Total (%)		130002 (91%)	11925 (8%)	1166 (1%)	143093 (100%)

[†] Samples from 2002 and 2013 are not available at the Santiago de Cuba laboratory.

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A total of 243 reciprocal translocations were observed (210 balanced and 33 unbalanced) (see supplementary material, balanced translocation (Table S1) and unbalanced translocations (Table S2)) for a frequency of one translocation per 588 cases of prenatal diagnosis. Table 2. Out of these 243 translocations, 237 cases had a well-defined reason for referral. The most common reason for referral was advanced maternal age, accounting for 56% (134/237) of cases. This was followed by the translocation carrier parent (23%, 55/237), ultrasonographic findings (10%, 24/237) (with ultrasound information available in only 19 cases), maternal anxiety (6%, 14/237), and other reasons (7%, 16/237). The latter includes adolescent pregnancy, biochemical markers in maternal blood, the study of monogenic diseases, and fetal sex determination for suspected X-linked disease.

Table 2 Classification of reciprocal translocations according to their origin and the form of aberrant segregation found in this study.

Origin	Balanced	Unbalanced	Familial studies	Unbalanced Segregation		
				Adjacent 1	Adjacent 2	3:1
<i>de novo</i>	42	4	-	2	0	1
Inherited	65	11	26	9	0	1
Unknown	103	18		11	0	3
Total	210	33 [†]	26	22	0	5

[†] Two cases of free trisomy 21, one case of deletion, three cases of complex rearrangements (one of them diagnosed by FISH) were excluded from further analysis to determine the mode of segregation. See annex Unbalanced Karyotype.

A total of 46 *de novo* balanced rearrangements were identified (Table 2) in 76 cases (65 balanced and 11 unbalanced, Table 2). It was possible to ascertain that the rearrangements were inherited from a single parent. In 26 cases, it was determined that multiple family members carried analogous rearrangements (Table 2). Among the translocations inherited in the 26 families, 43 individuals with a balanced form and 18 individuals with an unbalanced form of the rearrangement were detected. Among the translocations with a greater prevalence of carriers within the family were identified the following ones: t(3;8)(p21;p23.3), which affected 17 individuals, the translocation t(9;10)(p24;q22), which was present in six carrier relatives, t(11;18)(q14;q23), and t(5;9)(p15.3;p13), which affected five carrier relatives. Four individuals were identified as carriers for each of the following translocations in independent families: t(4;12)(q12;p13.3), t(9;21)(p24;q11.1), t(1;7)(p34.1;q11.2), t(1;14)(p13.1;q11) and t(5;18). In some of these families, the index case was a prenatal diagnosis due to advanced maternal age in which a reciprocal translocation was detected in three generations without causing alterations in the offspring [20].

Nevertheless, in many cases, it was not possible to study both parents; in most instances, only one parent, typically the mother, was analyzed. Consequently, it was not feasible to determine whether the rearrangement was inherited or *de novo* in 121 cases (103 balanced and 18 unbalanced; see Table 2).

3.1 The Occurrence of Abnormal Ultrasound Findings and/or the Presence of an Abnormal Phenotype in the Case of Translocations

In 10% (25/243) of the reciprocal translocations (balanced or not, Table 3), alterations were observed in the fetal ultrasound and/or abnormalities were noted in the translocation carrier. This was determined through follow-up of the aborted material or a live-born child. Cases in which the phenotypic abnormality is due to aneuploidy unrelated to a reciprocal translocation were excluded.

Table 3 Reciprocal translocations associated with ultrasonographic findings (soft markers and/or fetal malformations) and/or phenotypic abnormalities detected in follow-up study.

Case	Karyotype	Indication of study	Center	Findings and/or Phenotypical abnormalities
1	46,XX,der(2)t(1;2)(q32; q37)	sonographic findings	Panamá	Bilateral ventriculomegaly
2	45,XX,der(18)t(18;22)(q10;q10),-22	sonographic findings	Colombia	Intrauterine Growth Restriction
3	47,XY,t(8;13)(q10;q10),+13	sonographic findings	Colombia	Severe Intrauterine Growth Restriction, multicystic renal dysplasia
4	46,XX,t(1;14)(q32;q13)	sonographic findings	Colombia	High obstetric risk, nasal bone agenesis
5	46,XY,t(2;17)(p12;p12)dn	sonographic findings	Costa Rica	Megabladder, anhydramnios
6	46,XY,der(8) t(8;13)(p23;q21)	sonographic findings	Costa Rica	Omphalocele, single umbilical artery
7	46,XY,t(10;18)(q22.1;q21.1)	sonographic findings	Costa Rica	Polyhydramnios. Hydranencephaly
8	46,XY,t(5;8)(q31.1;p21.3)pat	sonographic findings	Costa Rica	Cervical shortening, claw hand
9	46,XX,t(7;14)(q11.2;q22)dn	advanced maternal age	Havana	Normal ultrasound. Psychomotor retardation (6 years old)
10	46,XY,t(3;7)(p25;p14) mat	advanced maternal age	Havana	Greig cephalopolysyndactyly (11 years old boy)
11	46,XY,t(3;7)(q13.2;q22)dn	advanced maternal age	Villa Clara	Dysmorphic features, asymmetry of cerebral ventricles, coloboma of iris, no intellectual disability (12 years old)
12	46,XY,t(2,20)(q32;p13)dn	unknown	Uruguay	Cardiopathy, seizures, unable to hold head (4 years old)
13	45,XX,t(18;21)(p11.2;q11)dn	sonographic findings	Gramma	Hydrocephalus, cleft lip
14	46,XX,der(13)t(13;18)(q33;q21.1)	family history	Panama	malformations of the hands and feet, microcephaly
15	46,XY,der(13)t(13,21)(q22;q11.2)mat	Translocation carrier parent	Sancti Spiritus	Down's syndrome phenotype (5 years old)
16	47,XX,+22,t(1;22)(q21;q11.2)dn	sonographic findings	Panama	Severe hydrops fetalis
17	46,XX,der(22),t(9;22)(p12;p11.2)	Sonographic findings	Sancti Spiritus	Ventriculomegaly, persistent left cava vein, and coronary sinus dilatation
18	46,XY,der(9),t(9;18)(q13;q11.2) mat	sonographic findings	Stgo Cuba	Congenital heart disease, aortic stenosis

19	46,XY,t(1;4)(q13;q32)	sonographic findings	Havana	intestinal echogenicity, bilateral choroid plexus cysts
20	46,XX,t(7;19)(q22;p13.1)	sonographic findings	Havana	Increased nuchal translucency
21	45,XX,t(5;17)(q31.3;q25)dn, der(15;22)(q10;q10)mat	Translocation carrier parent	Havana	Moderate intellectual disability (9 years old)
22	46, XX,der(10)t(2;10)(p23;q26)	unknown	Havana	Dysmorphic features, intellectual disability
23	46,XY,der(9)t(9;21)(p24;q11.1)mat	Translocation carrier parent	Havana	Increased nuchal translucency, Shortening of the femur
24	46, XX,t(4;5)(p16;q22) pat	sonographic findings	Pinar del Rio	Polyhydramnios, severe hypotonia at birth, seizures, and dysmorphological features. Death at the age of 6 months
25	46,XX,t(1;7)(p36.2;p11.2) dn	advanced maternal age, sonographic findings	Havana	intestinal echogenicity, choroid plexus cysts Normal 2 years-old girl

There were 19 cases in which some type of anomaly was detected in the fetal ultrasound that could well be related to soft markers or fetal malformations. Soft marker detection predominated. In 63% (12/19) of the cases, two or more soft markers or a soft marker associated with a malformation were found in Table 3.

Follow-up studies, especially of *de novo* balanced reciprocal translocations, were performed for a period exceeding two years of age (Table 3). Follow-up was achieved for 38 patients. In the long-term follow-up of the children, a range of distinctive characteristics were observed, including cases of moderate to profound psychomotor retardation accompanied by dysmorphic features (cases 9, 12, and 15; cases 21 and 22), cases of normal neurodevelopment with some anomalous features (case 11), and cases of prenatal ultrasound alterations (case 25).

In Case 10, the clinical analysis revealed a phenotype highly suggestive of Greig Cephalopolysyndactyly. Notably, one of the breakpoints of the translocation was located on 7p14, where the *GLI3* gene is mapped. The translocation, as mentioned earlier, was inherited from the mother, who also exhibited clinical manifestations of the syndrome, albeit to a lesser degree. Due to the methods used in this study, it is impossible to determine exactly what may have happened in the *GLI3* gene (single point mutation or disruption). Still, the appearance of this phenotype and its association with the breakpoint in the translocation are suggestive.

3.2 Recurrent Translocations in Our Study

In this study, recurrent translocations were defined as those involving identical chromosomes and identical or highly similar breakpoints within the chromosome, as analyzed at the specified resolution level. The recurrent translocation, t(11;22) (q23;q11.2), has been observed in three families. In one family from Cuba, the translocation appears to be inherited. In another family, it seems to be *de novo*. Additionally, a third family from Uruguay has been reported to have inherited the translocation. In none of the three were there apparent consanguinity links. The other “recurrent translocation”, detected on two occasions in separate families, is as follows: t(5;7) (p15.3;q34). This aberration was observed in one family as a *de novo* event and in another as an inherited one (with two distinct surnames hailing from disparate regions of Cuba).

3.3 Recurrent Breakpoints

In reciprocal translocations, not all breakpoints are equally involved. In this study, seven breakpoints were classified as recurrent. The breakpoints that were identified with a higher frequency were as follows: 5p15 y 9p24 (10 times), 7q11.2, 11q23 and 22q11.2 (7 times), 1q32 y 14q24 (6 times).

Table 4 compares the frequency of recurrent breakpoint occurrences in this study with those in extensive international studies. Notably, recurrent breakpoints in Latin America are underrepresented in these international studies. For instance, the 7q11 breakpoint exhibited notable differences for the Daniels and Youings studies, yet demonstrated consistency with the Liehr database. The 1p13 and 9p24 breakpoints showed even more significant frequency differences compared to international reports.

Table 4 Compares the frequency of recurrent breakpoint occurrences in this study with those in extensive international studies.

Breakpoint	Latin America (243 tr) n (%)	Daniels (1157 tr) n (%)	P value	Youings (448 tr) n (%)	P value	Liehr (779 tr) n (%)	P value
1p13	5(2.0)	5 (0.4)*	0.02	1 (0.2)*	0.04	3(0.3)*	0.03
1q32	6 (2.5)	28 (2.4)	0.85	9 (2)	0.90	8 (1)	0.16
5p15	10 (4.1)	34 (2.9)	0.45	14 (3.1)	0.64	13 (1.67)*	0.04
7q11	7 (2.9)	14 (1.2)	0.09	4 (0.9)	0.09	15 (1.9)	0.52
9p24	10 (4.1)	5 (0.4)**	p < 0.0001	6 (1.3)*	0.04	6 (0.77)**	0.0007
11q23	7 (2.9)	52 (4.5)	0.33	28 (6.25)	0.08	14 (1.79)	0.43
14q24	6 (2.5)	15 (1.3)	0.28	7 (1.6)	0.58	3 (0.38)*	0.008
22q11.2	7 (2.9)	48 (4.1)	0.45	24 (5.3)	0.19	22 (2.8)	0.86

n: number of times repeated; %: percentage; tr: translocations; p: Probability.

* p < 0.05, Differences between proportions obtained from our data and each of the international studies.

**p < 0.001 differences between proportions obtained from our data and each of the international studies.

In the case of 1p13, an exception is made, as it is below the cut-off point defining a recurrent breakpoint in this work, having only been observed in five patients. Nevertheless, due to its notable divergence from the findings of international studies, it was included in the analysis.

4. Discussion

Analysis of the extended prenatal diagnosis period (1984–2021) revealed that advanced maternal age was the primary reason for referral in this study. Advanced maternal age remains a significant factor in prenatal diagnosis today, along with biochemical markers in maternal blood and, particularly, fetal ultrasonographic findings [15, 16, 21–23]. Five percent (12 of 243) of the identified translocations were unexpected findings, allowing the investigation of multiple families and the identification of additional translocation carriers. Boué and Gallano's study determined that 8% of observed structural rearrangements occurred randomly, with advanced maternal age being the predominant contributing factor [24].

The frequency of reciprocal translocations reported in this study was one in 588 prenatal diagnoses (0.17%). These findings are consistent with reports from other researchers. Forabosco et al. documented a reciprocal translocation frequency of one in 560 prenatal diagnoses (0.17%) in Italy, while Van Dyke reported a frequency of one in 582 cases (0.17%) in U.S. laboratories [1, 25].

The international studies cited above primarily utilized amniocentesis as their diagnostic method. In the current study, 91% of cases were diagnosed by amniocentesis. Therefore, the observed consistency in the frequency of reciprocal translocations was to be expected.

Balanced rearrangements (210 cases) were observed more frequently than unbalanced ones (33 cases). This is possible, given that the most common invasive method was amniocentesis, typically performed between 16 and 20 weeks of gestation. Translocations resulting in severe chromosomal imbalances are generally known to result in early miscarriages during the first trimester [26].

As shown in Table 2, the predominant forms of segregation observed with chromosomal imbalances were adjacent segregation I and various types of 3:1 segregation. Gametes resulting from adjacent 2 segregation typically lead to trisomies or partial monosomies severe enough to result in early miscarriages.

4.1 Alterations and Findings in Fetal Ultrasound and Follow-Up Studies

Fetal malformations and soft markers are commonly associated with significant chromosomal abnormalities such as trisomies 21, 18, and 13, Turner syndrome, and triploidy [27-29]. However, the application of advanced diagnostic methods has also linked these findings to structural rearrangements, such as translocations. These rearrangements can result in segmental aneuploidies (deletions and duplications) near breakpoints or disrupt genes [30, 31].

Conventional karyotyping has limitations in detecting minor aberrations (<5 Mb) in the context of prenatal ultrasound anomalies. It often identifies only half the alterations detectable by microarray. For instance, Meiyang Cai et al. reported nearly double the rate of genomic abnormalities—12.4% (26/210)—in fetuses with growth retardation when using single nucleotide polymorphism arrays, compared to the 6.7% (14/210) detected by conventional karyotyping [32]. Similarly, Hui et al. observed comparable findings in fetuses with normal karyotypes but prenatal ultrasound anomalies [33].

In the present study, a few cases exhibited malformations, and these were generally associated with unbalanced translocations. Such translocations lead to more severe genomic alterations that significantly impact embryogenesis [34]. Most fetal ultrasounds revealed the presence of soft markers. Wang et al. indicate that the risk of segmental aneuploidy increases with the observation of two or more soft markers [30]. In this cohort, 63% of cases presented with either two associated soft markers or one soft marker combined with a malformation. While this suggests the potential for genomic alterations in carriers, even with balanced translocations, definitive conclusions are limited by the lack of supporting molecular studies.

Of the seven cases with long-term follow-up, five exhibited anomalies. Only one inherited case, involving an unusual reciprocal translocation between chromosomes 13 and 21, presented with an apparent Down syndrome phenotype. The remaining four children, despite carrying balanced reciprocal translocations, all shared neurodevelopmental disorders with intellectual disability as a standard feature. The scientific literature extensively documents similar findings in apparently balanced chromosomal rearrangements [34-39]. These observations have prompted a reevaluation of the risk estimates associated with detecting a *de novo* balanced rearrangement during prenatal cytogenetic diagnosis [7, 8].

The majority of laboratories in our region lack the capacity for advanced techniques such as next-generation sequencing or SNP microarrays. Furthermore, the relatively high cost of these techniques often makes them inaccessible to patients, preventing the corroboration of findings from conventional cytogenetic studies. Given these limitations, prenatal ultrasound findings and follow-up studies of pregnancies and/or live-born children are crucial for empirically establishing risk estimates for the prenatal diagnosis of specific balanced reciprocal translocations, particularly in *de novo* cases.

A careful analysis of the relationship between balanced rearrangements and potential prenatal ultrasound findings is essential. In this study, fewer than 10% of cases were found to have associated

phenotypic effects detectable by prenatal ultrasound. Structural rearrangements often lack discernible phenotypic implications through prenatal ultrasound. Couples or those at risk of pregnancy complications must undergo evaluation by geneticists. Utilizing conventional methodologies, including interviews, pedigree analysis, and assessment of other family members, geneticists can evaluate risks with greater precision. Additionally, cytogenetic techniques such as high-resolution chromosome analysis and fluorescence in situ hybridization (FISH) should be fully utilized. These relatively low-cost procedures can significantly enhance prenatal diagnoses when performed by appropriately trained professionals.

4.2 Recurrent Breakpoints

The breakpoints involved in recurrent translocations are typically located near regions of low-copy repeats (LCRs). The most likely mechanism driving reciprocal translocations is non-allelic homologous recombination (NAHR), which requires microhomology-containing regions as substrates [40]. In the current study, we identified breakpoints at 1p13 and 7q11.2, both of which have been previously shown to have adjacent LCRs [41]. Additionally, breakpoints at 11q23 and 22q11.2 are well-established regions enriched with palindromic AT repeats, which promote interactions and contribute to the occurrence of recurrent reciprocal translocations [41-44] (Table 4).

For an analysis of other breakpoints, we refer readers to Ou et al. [45]. These authors used bioinformatics methods to construct a map of potential constitutional recurrent translocations within the human genome, demonstrating the influence of low-copy repeat (LCR) regions. Their study found that 33.64% of the mapped LCR regions were located in subtelomeric areas. Breakpoints 5p15 and 9p24 from the current investigation are represented within LCR regions in their study. Notably, these two regions are recognized as unstable in the human genome and are involved in various deletion and duplication events, processes in which LCRs likely play a critical role [46-49].

LCR regions have been mapped to the 1q32 breakpoint, specifically 1q32.1, as reported in the study mentioned earlier [45]. In contrast, no LCR regions were mapped at the 14q24 breakpoint in the same study [45]. Neither of these breakpoints appears to be frequently involved in constitutional chromosomal aberrations; instead, they are more commonly associated with somatic rearrangements in malignant diseases [50-52].

When comparing our findings to international studies [9, 10, 18], breakpoints at 1p13 and 9p24 appear to be underrepresented in the studies above (Table 4). The breakpoint at 1p13 is associated with several dominant genes linked to neurodevelopmental disorders, as well as genes encoding proteins like sortilin, which are involved in lipid metabolism [53, 54]. Subtelomeric LCRs, such as those on 9p24, exhibit high polymorphism, with structural variation observed across individuals and populations [55, 56].

The notable recurrence of breakpoints 1p13 and 9p24 in Latin America underscores the importance of investigating the genomic architecture surrounding these regions in our populations. These regions are rich in genes associated with various diseases and disorders. Numerous studies have documented unique genomic findings specific to the Latin American region [12, 14, 57].

4.3 High Number of Translocations of Undetermined Origin

When a balanced rearrangement, such as a translocation, is identified during prenatal diagnosis, it is essential to study both parents. The necessity of genetic counseling is primarily dictated by whether the rearrangement is *de novo* or inherited. This crucial investigation is complicated in Latin America by several distinct factors.

Latin America stands out globally in terms of wealth distribution, exhibiting the highest income inequality, according to the 2019 Human Development Report [58]. This disparity significantly affects the population's access to medical services, particularly in the field of medical genetics. In the current study, we found that the origin (inherited or *de novo*) of the translocation detected during prenatal diagnosis could not be determined in 49.8% of cases. This was primarily due to a lack of paternal karyotype information. Similar challenges in determining parental origin have been reported elsewhere; for example, Youings et al. reported a 36% failure rate in determining the parental origin of balanced rearrangements in a study conducted in England [10].

However, the inability to determine the origin of nearly half of the translocations in this study is strongly influenced by patient-specific socioeconomic factors. These include financial constraints that prevent testing in private laboratories, the inability to take leave from work for karyotyping appointments, and patient relocation, often due to migration. These practical challenges introduce considerable uncertainty for genetic counselors and geneticists providing care to these couples.

Despite these circumstances, some countries, or specific population segments within countries, offer greater patient access to genetic studies. This accessibility facilitates follow-up investigations of other family members once a balanced chromosomal rearrangement is identified during prenatal diagnosis. Such investigations enable the proactive identification of healthy carriers within a family, allowing for the provision of appropriate genetic counseling and the option of prenatal diagnosis when they reach reproductive age.

4.4 Limitations

This study acknowledges the inherent limitations of using conventional cytogenetic methods for breakpoint definition compared to molecular approaches. The location of a breakpoint involved in a rearrangement in this research may have an imprecision of several megabases. To address this limitation, we analyzed a large cohort of cases from the region and compared them with extensive international studies. This approach allowed us to identify genomic regions with sequences that appear to predispose to balanced rearrangements, such as reciprocal translocations.

5. Conclusions

This study found that the frequency of reciprocal translocations in our region is similar to that reported in international investigations. A low frequency of fetal ultrasound findings was observed in association with reciprocal translocations. The study identified two recurrent translocations and seven recurrent breakpoints, two of which occurred at an unusually high frequency. Furthermore, we documented that the origin of 50% of prenatal reciprocal translocations could not be determined.

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Author Contributions

Correct interpretation of the diagnosis of Reciprocal Translocation and determination of breakpoints, Obtaining and analyzing data (Period covered by the research, type of inheritance, follow-up study of the aborted fetus or newborn), Correct drafting of the draft with the required information from the laboratory to which they belong. Revision of the draft of the paper. The following authors from each laboratory performed the functions described above: Cytogenetics Laboratory. National Center of Medical Genetics. Havana. Cuba: **ABM, MST, MS, AC, EM, DG, NG, OQ**; Pinar del Rio Cytogenetics Laboratory. Pinar del Rio. Cuba: **SM, IB, DL**; Matanzas Cytogenetics Laboratory. Matanzas. Cuba: **MC, OR**; Santiago de Cuba Cytogenetics Laboratory. Santiago de Cuba: **DE, MM**; Institute of Medical Genetics and Genomics. Ciudad de la Salud. Panamá. **LSB, JSL**; Holguín Cytogenetics Laboratory. Cuba. Holguin. Cuba: **JHG**; Camagüey Cytogenetics Laboratory. Cuba. Camagüey. Cuba: **HPB**; Villa Clara Cytogenetics Laboratory. Villa Clara.Cuba: **MET**; Granma Cytogenetics Laboratory. Granma. Cuba: **HM**; Cienfuegos Cytogenetics Laboratory. Cienfuegos. Cuba: **PDV**; Cytogenetics Laboratory. Montevideo Italian Hospital. Uruguay: **AV, RQ**; Biogenetic Diagnosis SAS, Bogotá. Colombia: **DSP**; Reproduction and Genetics, National Archives of Mexico and 12- 20 de Noviembre. National Medical Center, Institute for Social Security and Services for State Workers, Mexico City: **MCH**; Sancti Spiritus Cytogenetics Laboratory. Sancti Spiritus. Cuba: **PCT**; Cytogenetics Laboratory. National Children's Hospital, San José. Costa Rica: **RSH, CO**; Cytogenomics Laboratory - Genomics Sciences Unit, COLCAN. Colombia: **LP**; Hospital Glez Coro Cytogenetics Laboratory. Habana. Cuba: **LT, MM**; Clinical and Perinatal Cytogenetics Laboratory of Toluca, Mexico: **CUG, MAO**; **JPB y RLF**: Statistical analysis, research design, review of draft publication; **LAMR**: conceptualized and designed the research study. Acquisition of data from all laboratories, analysis of the information. Correct interpretation of the diagnosis of Reciprocal translocation and determination of breakpoints. Writing of manuscript, Reviewed and edited the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Table S1: Data balancead.

2. Table S2: Data unbalanced.

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