














## ORIGINAL ARTICLE

# Multi-institutional experience of genetic diagnosis in Ecuador: National registry of chromosome alterations and polymorphisms

César Paz-y-Miño<sup>1</sup>  | Verónica Yumiceba<sup>1</sup>  | Germania Moreta<sup>2</sup> | Rosario Paredes<sup>2</sup>  |  
 Mónica Ruiz<sup>3</sup> | Ligia Ocampo<sup>4</sup> | Arianne Llamas Paneque<sup>2</sup>  | Catalina Ochoa Pérez<sup>5</sup> |  
 Juan Carlos Ruiz-Cabezas<sup>6,7</sup> | Jenny Álvarez Vidal<sup>8</sup> | Idarmis Jiménez Torres<sup>9</sup> |  
 Ramón Vargas-Vera<sup>10</sup>  | Fernando Cruz<sup>11</sup> | Víctor Hugo Guapi N<sup>12</sup> |  
 Martha Montalván<sup>13</sup> | Sara Meneses Álvarez<sup>14</sup> | Maribel Garzón Castro<sup>2</sup> |  
 Elizabeth Lamar Segura<sup>2</sup> | María Augusta Recalde Báez<sup>2</sup> | María Elena Naranjo<sup>2</sup> |  
 Nina Tambaco Jijón<sup>2</sup> | María Sinche<sup>6</sup> | Pedro Licuy<sup>6</sup> | Ramiro Burgos<sup>6</sup> |  
 Fabián Porras-Borja<sup>11</sup> | Gabriela Echeverría-Garcés<sup>11</sup> | Andy Pérez-Villa<sup>1</sup>  |  
 Isaac Armendáriz-Castillo<sup>1</sup>  | Jennyfer M. García-Cárdenas<sup>1</sup>  | Santiago Guerrero<sup>1</sup>  |  
 Patricia Guevara-Ramírez<sup>1</sup>  | Andrés López-Cortés<sup>1</sup>  | Ana Karina Zambrano<sup>1</sup>  |  
 Paola E. Leone<sup>1</sup> 

<sup>1</sup>Centro de Investigación Genética y Genómica, Facultad de Ciencias de la Salud Eugenio Espejo, Universidad UTE, Quito, Ecuador

<sup>2</sup>Servicio de Genética Médica, Hospital de Especialidades, Quito, Ecuador

<sup>3</sup>CitoGen, Quito, Ecuador

<sup>4</sup>Laboratorio de Genética, Génica Laboratorios, Quito, Ecuador

<sup>5</sup>Laboratorio de Citogenética, SOLCA Núcleo de Cuenca, Cuenca, Ecuador

<sup>6</sup>Hospital "Dr. Juan Tanca Marengo", SOLCA Matriz, Guayaquil, Ecuador

<sup>7</sup>Facultad de Medicina, Universidad Espíritu Santo, Guayaquil, Ecuador

<sup>8</sup>Centro de Diagnóstico y Estudios Biomédicos, Facultad de Ciencia Médicas, Universidad de Cuenca, Cuenca, Ecuador

<sup>9</sup>Hospital Gineco Obstétrico Isidro Ayora, Ministerio de Salud Pública, Quito, Ecuador

<sup>10</sup>Facultad de Ciencias Médicas, Universidad de Guayaquil, Guayaquil, Ecuador

## Abstract

**Background:** Detection of chromosomal abnormalities is crucial in various medical areas; to diagnose birth defects, genetic disorders, and infertility, among other complex phenotypes, in individuals across a wide range of ages. Hence, the present study wants to contribute to the knowledge of type and frequency of chromosomal alterations and polymorphisms in Ecuador.

**Methods:** Cytogenetic registers from different Ecuadorian provinces have been merged and analyzed to construct an open-access national registry of chromosome alterations and polymorphisms.

**Results:** Of 28,806 karyotypes analyzed, 6,008 (20.9%) exhibited alterations. Down syndrome was the most frequent autosome alteration (88.28%), followed by Turner syndrome (60.50%), a gonosome aneuploidy. A recurrent high percentage of Down syndrome mosaicism (7.45%) reported here, as well as by previous Ecuadorian preliminary registries, could be associated with geographic location and admixed ancestral composition. Translocations (2.46%) and polymorphisms (7.84%) were not as numerous as autosomopathies (64.33%) and gonosomopathies (25.37%). Complementary to conventional cytogenetics tests, molecular tools have allowed

César Paz-y-Miño, Verónica Yumiceba, and Paola E. Leone contributed equally to the study.

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<sup>11</sup>Centro de Genética Médica, CEGEMED, Ministerio de Salud Pública, Quito, Ecuador

<sup>12</sup>Hospital General Provincial “Luis G. Dávila”, Ministerio de Salud Pública, Tulcán, Ecuador

<sup>13</sup>Centro de Investigaciones, Universidad Espíritu Santo, Guayaquil, Ecuador

<sup>14</sup>Hospital General Docente Ambato, Ministerio de Salud Pública, Ambato, Ecuador

#### Correspondence

Cesar Paz-y-Miño, Centro de Investigación Genética y Genómica, Facultad de Ciencias de la Salud Eugenio Espejo. Universidad UTE, Av. Mariscal Sucre y Av. Mariana de Jesús, Sede Occidental, Bloque I, 2nd floor, 170129 Quito-Ecuador.  
Email: cesar.pazymino@ute.edu.ec

identification of submicroscopic alterations regions or candidate genes which can be possibly implicated in patients' symptoms and phenotypes.

**Conclusion:** The Ecuadorian National Registry of Chromosome Alterations and Polymorphisms provides a baseline to better understand chromosomal abnormalities in Ecuador and therefore their clinical management and awareness. This data will guide public policy makers to promote and financially support cytogenetic and genetic testing.

#### KEYWORDS

chromosome alterations, chromosome polymorphisms, cytogenetics, genetic testing

## 1 | INTRODUCTION

Chromosomal disorders are categorized as numerical or structural abnormalities, affecting autosomes and sex chromosomes. Effects of these disorders are diverse depending on the specific chromosome region involved, such as syndromes, miscarriages, disabling diseases, congenital malformations, facial dysmorphism, intellectual disability, abnormal sexual development, malignancy, among others (Moorthie et al., 2017; Vikraman, 2015). Chromosome segregation during gametogenesis or mitosis during early fetal development, maternal age and environmental factors increase the risk of chromosomal abnormalities (Kim, Lee, Kim, Shim, & Cha, 2013; Mohammed, Shawky, Soliman, & Ahmed, 2011; Moorthie et al., 2017). Particularly, Ecuadorian population has adapted to live at high-altitude, besides being exposed to high UV radiation levels and other genotoxic agents (Paz-y-Miño, Cumbal, & Sánchez, 2012b; Paz-y-Miño, Guillen Sacoto, & Leone, 2016).

In Ecuador, the first initiatives to create a registry started in the early 90s with Varas (1990) who showed that 0.25% of 12,112 newborns in Quito had chromosomal alterations. Paz-y-Miño et al. (1990) reported 560 altered karyotypes from the Andean region. Eight years later, Paz-y-Miño et al. expanded his previous register, from a total of 1,453 karyotypes, 72.40% were abnormal. In 2006, a study conducted with shamans (witchdoctor) and suburban groups with low educational attainment and low socioeconomic status revealed that genetic terminology was poorly understood. Thus, some genetic alterations might not be diagnosed unless patients displayed a disabling phenotype that force them to attend to a medical appointment. Otherwise shamanic and natural medicine is preferable, as it is cheaper and accessible (Paz-y-Miño, Sánchez, Sarmiento, & Leone, 2006). The ECLAMC (Latin American

Collaborative Study of Congenital Malformations) reported that between 1995 and 2008 the global rate of congenital malformations was 2.7%, an upright tendency from previous periods (Nazer & Cifuentes, 2011). According to the First Genetic Clinical Biopsychosocial Ecuadorian Study in disabled, named “Manuela Espejo Mission” and led by the Vice Presidency, showed that chromosome and monogenic etiologies represent the 42% and 16% of prenatal causes of intellectual disability, respectively (Misión Solidaria Manuela Espejo, 2012). In 2012, Paz-y-Miño et al published another chromosome registry, where 47.42% karyotypes out of 2,636 examined had chromosomal alterations and polymorphisms. In 2014, the National Institute of Statistics and Census (INEC) reported that congenital malformations and chromosomal abnormalities in Ecuador are the sixteenth cause of mortality with a percentage of 1.35% and a rate of 5.30, affecting regularly infants from birth to one year old (INEC, 2014).

The aim of this work is to unify cytogenetic registers of chromosomal alterations and polymorphisms of patients from different provinces of Ecuador to create an open-access National Chromosome Registry. For medical geneticists and public policy makers, it is essential to know the frequency of chromosomal abnormalities in the country, to promote cytogenetic and genetic testing for prenatal and post-natal diagnosis.

## 2 | MATERIALS AND METHODS

### 2.1 | Sample collection

In this retrospective and descriptive study, thirteen Ecuadorian cytogenetic sub-registers from Paz-y-Miño's Groups (data

collected from 1984 to 2019), Servicio de Genética Médica, Hospital de Especialidades No.1 FFAA (1983–2014) (Leone & Paz-y-Miño, 2016), (2016–2018), CitoGen Laboratorio (1992–2013), Centro de Diagnóstico y Estudios Biomédicos de la Facultad de Ciencias Médicas, Universidad de Cuenca (2001–2010) (Álvarez, Jerves, Encalada, & Pesantez, 2010), Hospital “Dr. Juan Tanca Marengo”, SOLCA Guayaquil (2004–2018), Facultad de Ciencias Médicas, Universidad de Guayaquil (2005–2018), Laboratorio de Citogenética, SOLCA Cuenca (2006–2013) (Leone & Paz-y-Miño, 2016), Génica Laboratorios (2009–2018), Centro de Investigaciones, Universidad Espíritu Santo (2010), Hospital Gineco Obstétrico Isidro Ayora (2014–2018), Hospital General Docente (2016–2017), Hospital General Provincial “Luis G. Dávila” (2016–2018) and Centro Especializado en Genética Médica (2017–2019), were included. Data used contained no identifiable personal information to protect individual privacy.

## 2.2 | Ethical compliance

This study was approved by the Human Research Ethics Committee of Universidad San Francisco de Quito 2018-127E.

## 2.3 | Cytogenetic and clinical analysis

GTG-banding technique was performed in peripheral blood, amniotic fluid, fetal tissues and placenta chorionic samples. Karyotypes were reported according to the International System for Human Cytogenomic Nomenclature (ISCN 2016) (International Standing Committee on Human Cytogenomic Nomenclature, 2016). When clinical indications for cytogenetic analysis were available, they were grouped into different categories: known chromosomal syndromes, rare phenotype (included > than 2 dysmorphic traits), chromosomopathies, disorders of sex development (DSD), intellectual disability/psychomotor delay and/or neurobehavioral alterations, growth delay, genetic diseases, infertility and recurrent miscarriages, family history of congenital diseases or chromosomopathies, prenatal diagnosis, preconceptional genetic counselling and infectious diseases. The cohort was divided in two age groups 0–17 years (infant-children) and  $\geq 18$  years (adults) to detect the most common clinical indications during lifespan.

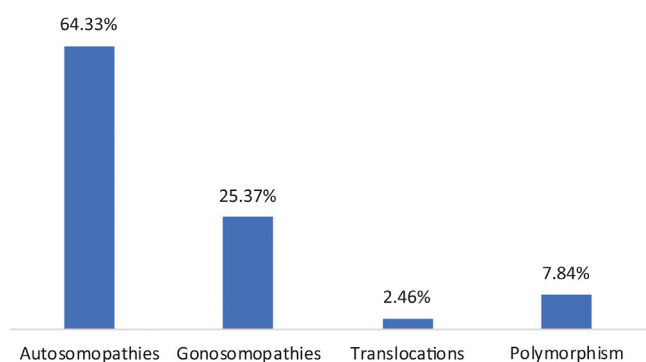
## 2.4 | Molecular genetic analysis

With the advent of molecular technologies, diagnostic and research centers have been able to deepen the analysis to find an accurate cause of the patient's phenotype. While karyotyping reveals large chromosomal changes (typically > 5 Mb), chromosome painting (CP), comparative genomic hybridization

(CGH), fluorescence in situ hybridization (FISH), genetic mapping array (GMA), multiplex ligation-dependent probe amplification (MLPA), and PCR of target regions detect genetic alterations at a higher resolution level. All techniques were performed according to standardized internal laboratory protocols.

## 3 | RESULTS

A total of 28,806 individuals (mean age 12.1 years, median age 7 years, age range of 0 to 80 years at diagnosis) from several provinces around Ecuador have been analyzed, of which 6,008 (20.9%) exhibited altered karyotypes. Those were classified in four tables according to the abnormality they displayed: autosomopathies 64.3% (3,865/6,008), gonosomopathies 25.4% (1,524/6,008), translocations 2.5% (148/6,008) or polymorphisms 7.8% (471/6,008) (Figure 1) (Tables 1–4). The mean parental age at the birth of their offspring is 30.93 years (median 31 years and range 15–50 years). By far, trisomy 21 was the most frequent autosomopathy described with 88.28% (all types added), followed by trisomy 18 and 13. It was noticed an elevated percentage of Down syndrome (DS) mosaicism. When referring to partial trisomies, monosomies (Table 1), and translocations (Table 3), breakpoints were not specified as patients have different affected regions in the same chromosome arm. Among all gonosomopathies, Turner syndrome (TS) was a representative aneuploidy with 60.50% (all types added), followed by all DSD (19.55%) (Table 2). More than one third of the polymorphism correspond to the Yqh+ polymorphism (Table 4). In certain cases, complementary to cytogenetic testing, molecular assays were performed to ascertain genetic alterations that could possibly explain the patient's phenotype (Table 5). The two-main clinical indications for cytogenetic referral in the cohort were DS and infertility (Figure 2). Being DS, the most commonly confirmed by cytogenetic test in the infant-children group and infertility in the adult group (Figure 3a,b).



**FIGURE 1** Abnormal Karyotype Distribution. Distribution of 6,008 positive karyotypes by chromosomal alterations. More than 50% of karyotypes displayed autosomopathies, while translocation grouped the least number of patients with altered karyotypes

TABLE 1 Chromosomal Autosomopathies in the Registry

Abnormal Karyotype	Number	Percentages
Trisomy 2	2	0.05
Trisomy 3	2	0.05
Trisomy 5	7	0.18
Trisomy 6	2	0.05
Trisomy 8 (mosaic)	7	0.18
Trisomy 7	1	0.03
Trisomy 9 (mosaic)	2	0.05
Trisomy 13	72	1.86
Trisomy 13 (mosaic)	7	0.18
Trisomy 14	1	0.03
Trisomy 15	4	0.10
Trisomy 16	3	0.08
Trisomy 18	108	2.79
Trisomy 18 (mosaic)	6	0.16
Trisomy 19	5	0.13
Trisomy 19 (mosaic)	1	0.03
Trisomy 20	3	0.08
Trisomy 21		
Free trisomy	3,017	78.06
Mosaic	288	7.45
Translocation	104	2.69
Translocation (mosaic)	3	0.08
Trisomy 22	15	0.39
Other Mosaicism	5	0.13
Partial trisomy		
add(1)(q) (mosaic)	1	0.03
add(2)(qter)	1	0.03
add(4)(p)	2	0.05
add(5)(q)	1	0.03
add(7)(p)	1	0.03
add(8)(p) (mosaic)	1	0.03
add(8)(q)	1	0.03
add(9)(p)	2	0.05
add(9)(q)	3	0.08
add(11)(p) (mosaic)	1	0.03
add(13)(p)	2	0.05
add(14)(p)	4	0.10
add(14)(p) (mosaic)	1	0.03
add(15)(p)	6	0.16
add(15)(q)	2	0.05
add(18)(p)	1	0.03
add(18)(q)	3	0.08
add(19)(p)	2	0.05
add(19)(q)	2	0.05
add(21)(p)	3	0.08
add(21)(q)	1	0.03
add(22)(p)	17	0.44

(Continues)

TABLE 1 (Continued)

Abnormal Karyotype	Number	Percentages
Other partial trisomies	24	0.62
Monosomy 9	2	0.05
Monosomy 16	1	0.03
Monosomy 17	2	0.05
Monosomy 21	1	0.03
Monosomy 22	2	0.05
Partial monosomy		
del(1pter) (mosaic)	1	0.03
del(1q) (mosaic)	1	0.03
del(2p) (mosaic)	1	0.03
del(2q)	1	0.03
del(2q) (mosaic)	1	0.03
del(4p)	2	0.05
del(4pter)	1	0.03
del(4q) (mosaic)	1	0.03
del(5p)	16	0.41
del(5p) (mosaic)	1	0.03
del(5q)	1	0.03
del(5q) (mosaic)	1	0.03
del(8q) (mosaic)	1	0.03
del(9pter)	1	0.03
del(9q) (mosaic)	4	0.10
del(10q)	1	0.03
del(11q)	1	0.03
del(12p)	1	0.03
del(12p) (mosaic)	1	0.03
del(13q)	3	0.08
del(15q)	2	0.05
del(17q)	1	0.03
del(18p)	1	0.03
del(18qter)	1	0.03
del(21q)	1	0.03
del(22q)	5	0.13
Other monosomies	5	0.13
i(17)	1	0.03
Ring Chromosomes		
r(4) (mosaic)	3	0.08
r(6)	1	0.03
r(9)	1	0.03
r(10)	1	0.03
r(15)	2	0.05
Other rings chromosomes	6	0.16
inv(8)	1	0.03
inv(9)	34	0.88
inv(9) (mosaic)	1	0.03

(Continues)

**TABLE 1** (Continued)

Abnormal Karyotype	Number	Percentages
inv(12)	1	0.03
inv(21)	1	0.03
TOTAL	3,865	100.00

## 4 | DISCUSSION

Chromosomal disorders are generally related to complex phenotypes characterized by intellectual disability, developmental disabilities, and birth defects (Theisen & Shaffer, 2010; Wang et al., 2011). After genetic evaluation, we can establish the etiology of 43%, 7% are due to environmental factors, but about 50% remain unknown (Armas García et al., 2016). Besides, chromosome alterations caused 20% of newborns death (Fernández-Hernández, Domínguez-Castro, Carlos Ibañez-Salvador, Grether-González, & Aguinaga-Ríos, 2013). Hence, efforts have been made to collect data to create an Ecuadorian Chromosome Registry to evaluate for the first time the status of disorders linked to chromosomes abnormalities. The period of karyotype collection does not match in all sub-registries owing to recent creation of cytogenetic laboratories or institutional management flaws to keep registries updated. From late 1980s to present, an increasing number of cytogenetic laboratories in healthcare institutions and geneticists have contributed to an exponential rise of the number of karyotypes processed (Paz-y-Miño, 2012). Most of the institutions that offer genetic services without age discrimination in Ecuador were included. A heterogeneous sample was joined to have a better national approach to chromosome prevalence; however, one should be careful to generalize conclusions. Another pitfall of this study is that the cohort may not be representative as it is made up of cases referred to genetic institutions with suspicion of a genetic condition. In addition, possibly some native closed populations are excluded from the cohort since they do not have access to healthcare.

DS is the most common birth defect and its estimated prevalence in USA is 14 per 10,000 livebirths (Presson et al., 2013) and in Europe 11.2 per 10,000 livebirths (Loane et al., 2012). The ECLAMC determined that DS prevalence corresponded to 18.8 per 10,000 livebirths. Ecuador has a reported prevalence of 14.8 per 10,000 livebirths (Nazer & Cifuentes, 2011). It should be stated that abortion is illegal in Ecuador, except when the pregnant woman's life and health are in danger or when a mentally disabled woman was raped (Center for Reproductive Rights), whereas in other European countries and in the United States DS-related elective pregnancy termination is allowed (De Graaf, Buckley, & Skotko, 2015; Morris & Springett, 2014). Trisomy 21 was the most frequent autosomopathy

in all the sub-registries, comprising all together 3,412 cases (88.28%). Chromosomes 21 and 22 are the smallest chromosomes in the genome with approximately 225 and 545 genes, respectively, thus trisomy 21 can be tolerated more often than trisomy 22, even in the absence of mosaicism. (Littooij, Hochstenbach, Sinke, Tintelen, & Giltay, 2002; Modi, Berde, & Bhartiya, 2003). It is evident in our registry, as more patients displayed free trisomy 21 (78.06%) than mosaicism (7.45%).

Mosaicism can be caused during embryonic growth by non-disjunction, anaphase lagging or endoreplication. The percentage of mosaicism depends on the embryonic development stage when the aforementioned errors occur. Small percentages are generally associated with less severe phenotype, as the normal cell line might moderate the effects (Taylor et al., 2014). Mosaicism is seen in 2%–4% of patients diagnosed with DS (Papavassiliou et al., 2009), while in prenatal diagnosis the rate ranged from 1%–2% (Taylor et al., 2014; Vikraman, 2015). Therefore, 7.45% of trisomy 21 mosaics in the present registry showed a high incidence. Ecuadorians living at high-altitude have elevated ultraviolet radiation exposure, hypobaric hypoxia, hypoxemia; factors that can possibly modulate the genome and epigenome (Colleen, 2017). It has been described that hypoxia can cause chromosomal abnormalities and genomic instability in tumor endothelial cells inducing oxidative stress reactions and impairment of DNA repair (Kondoh et al., 2013; Luoto, Kumareswaran, & Bristow, 2013). Two studies have found that anotia-microtia is highly prevalent in patients living above 2,500 meters above sea level such as Bolivia and Ecuador (González-Andrade, López-Pulles, Espín, & Paz-y-Miño, 2010). Polydactyly, harelip and DS are the top-three congenital malformations in Ecuador among 26 studied in nine South American countries. Prevalence heterogeneity of congenital malformations found in all Latin countries could be explained by different environmental factors or ethnic origin (Nazer & Cifuentes, 2011). A previous genetic study has shown that Ecuador is an admixed population with an ancestral contribution of Native American (59.6%), European (28.8%), and African (11.6%) (Zambrano et al., 2019). Polydactyly and harelip are often reported in African and Amerindian origins respectively, congruent with our ethnicity (Nazer & Cifuentes, 2011).

Knowing DS high frequency, routine prenatal tests such as cell-free fetal DNA, amniocentesis or chorionic villus sampling should be offered as a public health service, with the surveillance of a geneticist and physician, to women at risk (advanced maternal age > 35 years, previous history of congenital malformations, teratogens exposure). Especially, since children with DS have an elevated risk of congenital heart disease, vision disturbances, hearing loss or infection, hypothyroidism, digestive problems, and leukemia. (De Rubens Figueroa, Del Pozzo, Pablos Hach, Calderón Jiménez, & Rocío, 2003; Jørgensen et al., 2019). The fact that



**TABLE 2** Chromosomal gonosomopathies in the registry

Abnormal Karyotype	Number	Percentages	
Turner syndrome	45,X	616	40.42
	mos 45,X/46,XX	227	14.90
	mos 45,X/46,XX/47,XXX	4	0.26
	mos 45,X/47,XXX	2	0.13
	iXp	1	0.07
	iXq	34	2.23
	iXq (mosaic)	16	1.05
	del(Xp)	1	0.07
	del(Xp) (mosaic)	4	0.26
	del(Xq)	5	0.33
	del(Xq) (mosaic)	5	0.33
	Ring (mosaic)	7	0.46
Trisomy X	47,XXX	31	2.03
	mos 46,XX/47,XXX	26	1.71
	Partial trisomy: Xq+	4	0.26
	Partial trisomy: Xq+ (mosaic)	2	0.13
	Partial trisomy: Xp+ (mosaic)	1	0.07
Fra (X)(q27.3)	44	2.89	
Klinefelter syndrome	47,XXY	121	7.94
	mos 46,XY/47,XXY	13	0.85
	mos 47,XXY/48,XXXY	1	0.07
XYY syndrome	47,XYY	34	2.23
	mos 45,X/47,XYY	1	0.07
	mos 46,XY/47,XYY	2	0.13
mos 47,XXX/47,XXY	12	0.79	
48,XXYY	10	0.66	
49,XXXXY	2	0.13	
Disorder of Sexual Development (DSD)	46,XX DSD	88	5.77
	46,XY DSD	118	7.74
	Ovotesticular DSD	39	2.56
	46,XX Testicular DSD	17	1.12
	46,XY Complete Gonadal Dysgenesis	36	2.36
<b>TOTAL</b>	<b>1,524</b>	<b>100</b>	

people with mosaic DS have a better survival rate, besides achieving higher education, jobs and reproduce, makes cytogenetic testing a suggestive predictor of DS social conditions (Zhu et al., 2014). In Ecuador, prenatal tests are performed privately and newborn screening as a public health service is available only for 4 disorders: phenylketonuria, galactosemia, congenital adrenal hyperplasia, and congenital hypothyroidism (Paz-y-Miño et al., 2016).

In this registry, after DS, trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome) are the autosome abnormalities with more karyotypes listed. This could be possibly tolerated owing to the low gene density in those chromosomes

and low genomic imbalance produced in trisomies (Wiseman, Alford, Tybulewicz, & Fisher, 2009). It has been reported that when trisomy 8 and 9 occur, they are mosaic, which correlate with our results (Theisen & Shaffer, 2010).

Among gonosomopathies, TS is one of the most common genetic disorders affecting 1:2,500 liveborns females, perhaps due to X-inactivation. It presents as complete or partial monosomy of the second X chromosome (Armas García et al., 2016). Our results are consistent with previous studies in México, Argentina, Chile and Colombia that reported 45,X monosomy as the most common karyotype associated with TS: 30%, 35%, 60%, and 73%, respectively

**TABLE 3** Translocations in the registry

Translocations	Number	Percentages
t(X;1)	1	0.68
t(X;8)	3	2.03
t(X;9) (mosaic)	1	0.68
t(X;21)	1	0.68
t(Y;14) (mosaic)	1	0.68
t(1;2)	1	0.68
t(1;4) (mosaic)	1	0.68
t(1;19)	1	0.68
t(1;20)	1	0.68
t(2;7)	1	0.68
t(2;8)	3	2.03
t(2;9)	1	0.68
t(2;12)	2	1.35
t(2;13)	4	2.70
t(2;14)	1	0.68
t(2;16)	1	0.68
t(2;18)	3	2.03
t(2;21)	3	2.03
t(3;15)	1	0.68
t(4;6) (mosaic)	1	0.68
t(4;11)	3	2.03
t(4;13)	1	0.68
t(4;15)	3	2.03
t(5;9) (mosaic)	1	0.68
t(5;14)	5	3.38
t(5;19)	1	0.68
t(6;7)	2	1.35
t(6;13)	1	0.68
t(7;10)	1	0.68
t(7;14) (mosaic)	3	2.03
t(7;15)	1	0.68
t(8;15)	1	0.68
t(9;11)	1	0.68
t(9;13) (mosaic)	1	0.68
t(9;14)	1	0.68
t(11;21)	2	1.35
t(11;22)	3	2.03
t(14;17) (mosaic)	1	0.68
t(3;6;11)	1	0.68
URET	24	16.22
t(13;13)	3	2.03
t(13;14)	20	13.51
t(13;14) (mosaic)	1	0.68
t(13;15)	4	2.70

(Continues)

**TABLE 3** (Continued)

Translocations	Number	Percentages
t(14;21)	4	2.70
t(15;15)	1	0.68
t(21;21) (mosaic)	2	1.35
t(21;22)	1	0.68
UROT	23	15.54
TOTAL	148	100.00

Abbreviations: URET, Unidentified Reciprocal Translocations; UROT, Unidentified Robertsonian Translocations

(Cortés-Gutiérrez, Dávila-Rodríguez, Vargas-Villarreal, & Cerda-Flores, 2007; Del Rey et al., 2018; Román et al., 2002; Saldarriaga, Valencia, Fandiño-Losada, Andrés Ruiz, & Isaza, 2014). In contrast, in a Brazilian register somatic mosaicism (53.6%) was more common than the classic karyotype (28.6%) (Duarte et al., 2004). TS diagnosis is usually postponed until adolescence when pubertal delay, infertility and amenorrhea are present. Nevertheless, early TS diagnosis will provide the affected a close medical management of recurrent conditions, as there are associated comorbidities in childhood such as cardiovascular disease, hearing loss or infection, ophthalmologic impairments, gastrointestinal diseases, bone or kidney affections, dental abnormalities among others (Jørgensen et al., 2019; Shankar & Backeljauw, 2018).

DSD are the following sex chromosome alteration. Karyotype is a standard test used to classify them, yet laboratory tests and imaging of the genitourinary tract are key for differential diagnosis. It has been reported that intersexual status is a rare phenomenon, with an incidence of 1:5,500 (Kim & Kim, 2012). Although, the relatively numerous individuals with DSD in Ecuador may be a sign of consanguinity, since several conditions in DSD have an autosomal recessive inheritance. In a study of non-malformed liveborn infants, Ecuador has a consanguinity rate of 1.25% (Liascovich, Rittler, & Castilla, 2001). Alvarez, Quintero, and Ceballos (2011) reported Ecuadorian consanguineous marriages represented 2.8% of total marriages while in USA, it was estimated to be 0.2%–0.5% (Liascovich et al., 2001). For instance, the most frequent cause of female virilization is congenital adrenal hyperplasia, which is a group of autosomal recessive disorders. As the reports are based on small series of patients, this hypothesis should be considered cautiously (Bashamboo & McElreavey, 2014).

In relation to defined translocations, the most frequent reported here is t(13;14), a Robertsonian translocation. This structural arrangement occurs in approximately 1:1,000 newborns (Song et al., 2016) and accounts for ~75% of acrocentric chromosome fusions (Scriven, Flintner, Braude, & Ogilvie, 2001). Although, genomic information in carriers is complete and does not comprise their health and lifespan, they have the possibility to produce

**TABLE 4** Chromosomal polymorphisms in the registry

Polymorphisms	Number	Percentages
1qh+	16	3.40
2qh+	1	0.21
9qh+	87	18.47
9qh+ (mosaic)	2	0.42
9qh-	2	0.42
13ps+	2	0.42
13pstk+	1	0.21
14pstk+	1	0.21
15ps+	5	1.06
15pstk+	6	1.27
16qh+	33	7.01
21ps+	7	1.49
21pstk+	1	0.21
22pstk+	4	0.85
22pvar	1	0.21
Yqh+	178	37.79
Yqh-	65	13.80
Chromosomes Supernumerary	3	0.64
+mar	11	2.34
+mar (mosaic)	44	9.34
Triploidy	1	0.21
TOTAL	471	100.00

unbalanced gametes, which increase the risk of infertility (Song et al., 2016). If one partner carries a translocation, genetic counseling should be offered to inform them the probabilities of their offspring to carry any chromosomal imbalance or to be advised to undergo assisted reproduction (Scriven et al., 2001). According to the Ecuadorian Society of Reproductive Medicine, the first IVF baby was born in 1992 in Guayaquil and until 2007 eight IVF private clinics have opened (Roberts, 2016).

Referring to polymorphisms, the highest percentage (37.79%) belongs to Yqh+ polymorphism, which indicates an increase in length of the heterochromatin on the long arm of the Y chromosome. This heterochromatin is formed by tandemly repeated sequences that do not encode proteins, therefore karyotypes with this polymorphisms are reported as normal similarly as Bhasin (2005) did. However, several studies have frequently identified Yqh+ polymorphisms in couples with recurrent miscarriages or male infertility supported by the following evidence (Cathrine, Chinnaswami, & Mahalingam, 2015; Madon, Athalye, & Parikh, 2005; Sahin et al., 2008; Wang et al., 2017). Heteromorphisms can alter synapsis of X and Y chromosomes during meiosis (Sahin et al., 2008). Genes required for viability and fertility may reside in the heterochromatin region (Madon et al., 2005). Increased heterochromatin can silence nearby gene

expression by position-effect variegation (Minocherhomji et al., 2008). Conversely, Dong et al., (2013) studied family members of infertile individuals with Yqh± polymorphism and did not find any link as they were also found also in fertile family members. There are other factors that contribute to reproduction failure apart from Y heterochromatin size. Since there are other factors that contribute to reproductive failure, the function or direct clinical significant of Y polymorphisms is uncertain and still controversial (Tempest & Simpson, 2017).

Down syndrome and infertility/recurrent miscarriages were the two major clinical reasons to perform cytogenetic analysis in infant-children and adult group respectively. Reproductive problems like infertility and recurrent miscarriages can be caused by either autosomes or sex chromosomes abnormalities. Such abnormalities can be structural or numerical. In females, TS is the leading contributor to female infertility (Al-Alawi, Goud, Al-Harasi, & Rajab, 2016). In males, Klinefelter syndrome and Y chromosomes microdeletions are genetic causes that impair normal sperm production. Carriers of translocation and other chromosomal rearrangements are at an increased risk of miscarriages due to unbalanced chromosomal information inherited to their offspring (Song et al., 2016).

In this study, a conclusive finding of chromosomal disorders or polymorphisms was obtained in 20.9% of patients with diverse clinical indications. In Latin America, the prevalence of chromosomal abnormalities in invasive prenatal diagnosis varies from 2.8% (Cuba) (Méndez-Rosado et al., 2014), 14.0% (Colombia) (Fandiño-Losada, Lucumí-Villegas, Ramírez-Cheyne, Isaza-De Lourido, & Saldarriaga, 2018), 30% (Mexico) (Gómez-Puente, Esmer-Sánchez, & Quezada-Espinoza, Martínez-de Villarreal, 2012) up to 31% (Chile) (Vargas et al., 2016), which includes pregnancies with advanced maternal age, atypical ultrasound findings, parental carriage of chromosome alterations, abnormal maternal serum markers by invasive diagnostic testing. An expected higher frequency of chromosomal abnormalities, 69.5%, that causes spontaneous abortion was informed in Peruvian study (Quiroga de Michelena et al., 2007). Latin American studies that karyotyped malformed or alive newborns, stillbirths and adults seeking for genetic counselling evidenced frequencies of chromosomal alterations that are mostly close to ours; 4.3% (Chile) (Nazer et al., 2003), 20% (Armas García et al., 2016) (Mexico), 29.3% (Brazil) (Duarte et al., 2004), 29.3% (Mexico) (Hernández-Herrera et al., 2014). A relatively comparable study that includes Cuban individuals with heterogeneous clinical indications for cytogenetic test using peripheral blood, detected 14% of altered karyotypes including polymorphisms (Blanco Pérez, Mitjans Torres, & Miñoso Pérez, Socarrás Gómez, 2013). Frequent differences of chromosomal abnormalities may reflect different inclusion criteria for patients karyotype selection,



**TABLE 5** Molecular biology techniques applied to characterize several cases

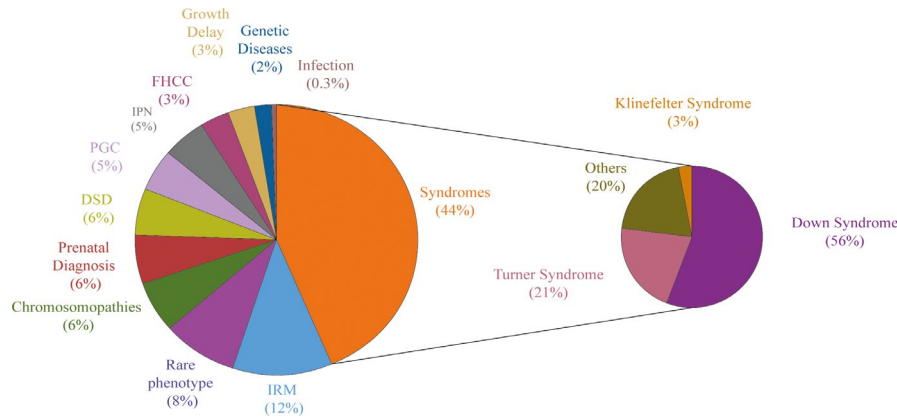
Cases	No	CP	CGH	FISH	GMA	MLPA	PCR-based		
							Exon	SRY	STR
Deletions/duplications	8		X						
Disorders of sex development	33							X	
Disorders of sex development	3							X	X
Disorders of sex development	1								X
Down syndrome	2							X	
Genetic Disease	1							X	
Genetic Disease	1						X		
Infectious Disease	1							X	
Infertility	2							X	X
Infertility	2							X	
Klinefelter syndrome	1								X
Marker chromosome identification	1								X
Partial trisomy	1								X
Partial Trisomy	3					X			
Rare phenotype	1							X	
Rare phenotype	1							X	X
Ring Chromosome	2			X	X				
Situs Inversus	1			X	X			X	
Translocation	1				X				
Translocation	2	X		X	X				
Translocation	1			X	X	X			
Turner syndrome	3							X	
Turner syndrome with translocation	1			X	X				
Chromosomopathy	1								X
Chromosomopathy	1							X	
Total	75	1	1	5	6	2	1	12	8

Abbreviations: CGH, Comparative Genomic Hybridization; CP, Chromosome painting; GMA, Genetic mapping array; FISH, fluorescence in situ hybridization; MLPA, multiplex ligation-dependent probe amplification; PCR, polymerase chain reaction; SRY, SRY gene analysis; STR, short tandem repeats.

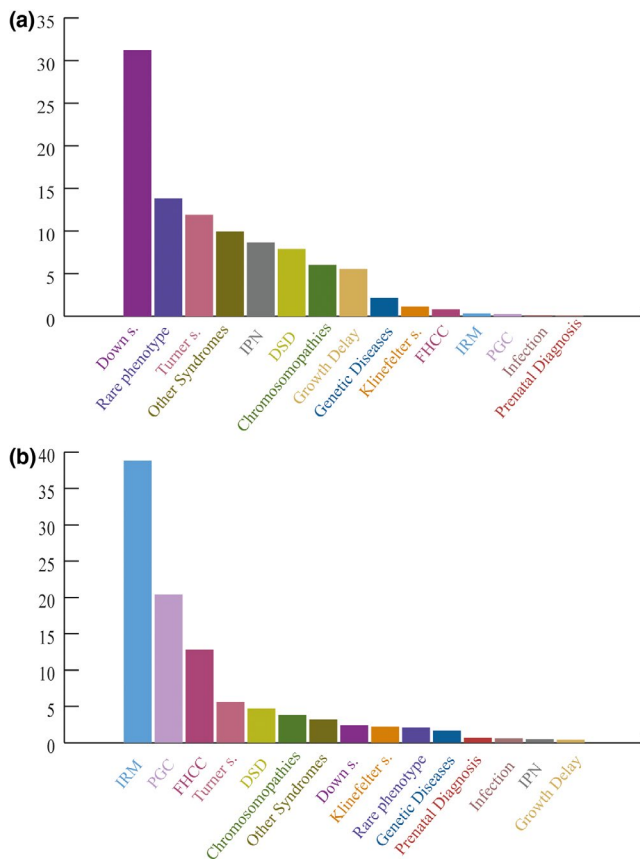
the population where the studied group came from and the alterations described. DS, Edwards syndrome, Patau syndrome, and TS were the most frequent abnormalities reported in other registers. As reported in our study DS was the first chromosome abnormality listed in all registers, followed by trisomy 18 and 13 in most to them (Armas García et al., 2016; Duarte et al., 2004; Fandiño-Losada et al., 2018; Gimeno-Martos et al., 2016; Hernández-Herrera et al., 2014; Nazer et al., 2003; Paz-y-Miño et al., 1998; Wellesley et al., 2012). DS and TS often evidenced great karyotype variability (Duarte et al., 2004; Gimeno-Martos et al., 2016), which emphasized the importance of differential cytogenetic diagnosis confirmation. The rest of

structural autosome rearrangements were similarly scarce and varied (Duarte et al., 2004; Gimeno-Martos et al., 2016; Gómez-Puente et al., 2012).

The common algorithm to diagnose if a patient, who exhibits dysmorphic features, has a chromosomal disorder starts with cytogenetic analysis. If the karyotype is not conclusive, molecular techniques are applied according to the case. For example, an autosomopathy initially reported by Paz-y-Miño, Cumbal, Araujo, and Sánchez (2012a) as add(8)(p23), was re-labeled as t(2;8)(p16.3;p23.1), after identifying that the additional segment in the short arm of chromosome 8 belongs to chromosome 2 and mapping the translocation breakpoints using genetic mapping arrays and FISH. In



**FIGURE 2** Clinical Indications for Cytogenetic Testing. The two most common reasons physicians ask for cytogenetic tests are Down syndrome and Infertility/Recurrent Miscarriages, followed by rare phenotypes. DSD, Disorders of Sexual Differentiation; FHCC, Family history of congenital diseases or chromosomopathies; IPN, Intellectual, psychomotor delays and/or neurobehavioral alterations; IRM, Infertility and/or recurrent miscarriages; PGC, Preconceptional Genetic Counselling



**FIGURE 3** Clinical Indications for Cytogenetic Testing by Age Group. (a) 0–17 years (infants-children) (b) 18–80 years (adults). DSD, Disorders of Sexual Differentiation; FHCC, Family history of congenital diseases or chromosomopathies; IPN, Intellectual, psychomotor delays and/or neurobehavioral alterations; IRM, Infertility and/or recurrent miscarriages; PGC, Preconceptional Genetic Counselling

ring chromosome syndromes, arrays were applied to detect breakpoints at either telomere regions and if there was any significant genetic material loss, which provides a clue for the clinical signs (Paz-y-Miño et al., 2018). Another case

worth mentioning, is one that by conventional cytogenetic an extra chromosomal region was detected in 14p, but with MLPA and genetic mapping arrays this region was matched to chromosome 9 genetic material. This was then registered as der(14)t(9;14)(p13.1;q11.2) (Leone et al., 2019). With a precise location of the chromosomal regions affected, it will be easier to match one or more genes to the phenotype of the patient and even elucidate the function of unknown genes. Other techniques as CGH can also be used to define deletions or duplications ranged between 3–5 Mb, while FISH and MLPA analyses can be applied to detect the chromosome of origin which comprises the microdeletion or duplication (Gómez-Puente et al., 2012; Wellesley et al., 2012). To identify single genes or polymorphism PCR is ideal. Regularly, patients with disorders of sex development are PCR-tested to detect *SRY* presence. Karyotyping is a genetic diagnosis method widely used, while molecular techniques are mainly used for research and scientific publication. Recently, few public services are combining clinical diagnosis with genetic approaches but is not a routine procedure.

## 5 | CONCLUSION

The publication of the Ecuadorian National Registry of chromosomal abnormalities and polymorphisms provides a baseline of cytogenetic data in Ecuador. This work aims to promote timely genetic diagnosis that can better inform management and family planning decisions. Finance support and application of a diagnosis algorithm that combines cytogenetics and modern molecular techniques could improve diagnosis to have a greatest impact on patient well-being.

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## CONFLICT OF INTEREST

None declared.

## AUTHORS CONTRIBUTION

César Paz-y-Miño: conceived the idea, coordinated, wrote manuscript and followed up with the development of the article. Verónica Yumiceba karyotyped, collected and processed data and wrote the manuscript. Germanía Moreta, Rosario Paredes, Mónica Ruiz, Ligia Ocampo, Arianne Llamas Paneque, Catalina Ochoa Pérez, Juan Carlos Ruiz-Cabezas, Jenny Álvarez Vidal, Idarmis Jiménez Torres, Ramón Vargas-Vera, Fernando Cruz, Víctor Hugo Guapi N., Martha Montalván, Sara Meneses Álvarez, Maribel Garzón Castro, Elizabeth Lamar Segura, María Augusta Recalde Báez, María Elena Naranjo, Nina Tambaco Jijón, María Sinche, Pedro Licuy, Ramiro Burgos and Fabián Porrás-Borja karyotyped and provided patients' data. Andy Pérez-Villa karyotyped and contributed in writing edition. Isaac Armendáriz-Castillo, Jennyfer M. García-Cárdenas, Santiago Guerrero, Patricia Guevara-Ramírez, Andrés López-Cortés, Ana Karina Zambrano participated in writing edition. Paola E. Leone collected the data and contributed in writing and formatting. All authors have approved the final manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the results of this study are available from the corresponding author, César Paz-y-Miño, upon reasonable request.

## ORCID

César Paz-y-Miño  <https://orcid.org/0000-0002-6693-7344>

Verónica Yumiceba  <https://orcid.org/0000-0001-6998-7913>

Rosario Paredes  <https://orcid.org/0000-0003-4438-5603>

Arianne Llamas Paneque  <https://orcid.org/0000-0002-7161-1787>

Ramón Vargas-Vera  <https://orcid.org/0000-0002-1922-8983>

Andy Pérez-Villa  <https://orcid.org/0000-0001-6758-4299>


Isaac Armendáriz-Castillo  <https://orcid.org/0000-0003-2636-2707>

Jennyfer M. García-Cárdenas  <https://orcid.org/0000-0001-9035-7668>

Santiago Guerrero  <https://orcid.org/0000-0003-3473-7214>

Patricia Guevara-Ramírez  <https://orcid.org/0000-0002-4829-3653>

Andrés López-Cortés  <https://orcid.org/0000-0003-1503-1929>

Ana Karina Zambrano  <https://orcid.org/0000-0003-4102-3965>

Paola E. Leone  <https://orcid.org/0000-0003-3351-2275>

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