Colombia: A Diverse Country

Colombia is a country located in the northwest corner of South America (Fig. 1). Initially founded in 1717 as the Viceroyalty of New Grenada, it underwent many transitions in its government and territory after winning its independence from Spain in 1819, finally becoming the Republic of Colombia in 1886 (CIA, World Fact Book: https://www.cia.gov/library/publications/the-world-factbook/geos/co.html).

Known officially as the Republic of Colombia, it shares borders with Venezuela and Brazil to the east; with Peru and Ecuador to the south; and with Panama to the Northwest; it also shares maritime borders with Nicaragua, Honduras, Jamaica, Dominican Republic, Haiti, and Costa Rica. Colombia is in a unique position in South America, possessing coasts on both Oceans; it borders the Caribbean Sea between Venezuela and Panama and the Pacific Ocean between Ecuador and Panama (CIA, World Fact Book).

It has a total land area of 1,138,910 square km, which makes it slightly less than twice the size of Texas. Its gross domestic product (GDP) was 378.4 billion in 2013. Colombia’s growth was 4.7% in 2013, which was above the regional average of 3.7%. The World Bank considers Colombia a middle power and is part of the CIVETs group of six leading emergent markets (Schulz 2010). Colombia is also one of 17 megadiverse countries in the world. It is considered the most biodiverse by square kilometer (Declaración de Cancún: http://www.inecc.gob.mx/descargas/ai/con199328.pdf) and has the largest number of endemisms (species not found anywhere else) (Convention on Biological Diversity: http://www.cbd.int/countries/index.countries=co). Colombia hosts 10% of all species in the world, including 10% of all mammals, 14% of amphibian species, and 20% of birds; it has 32 terrestrial biomes and 314 types of ecosystems (SIB Colombia: http://www.sibcolombia.net/web/sib/cifras).

Colombia has suffered from asymmetric low-intensity armed conflict for nearly 60 years; the conflict has decreased considerably since the year 2000 owing to governmental efforts to curb the violence (CIA, World Fact Book). Its life expectancy is 74, on par with the regional standard.

Population Diversity

Colombia is the third most populous country in Latin America with 47 million people as of 2014 (Departamento Administrativo Nacional de Estadística, DANE: https://www.dane.gov.co). The population of this ethnically diverse country is composed of three major groups: the descendants of its indigenous people (Amerindians), European immigrants (mostly Spanish), and Africans originally brought as slaves. Later waves of immigration in the 20th century would bring individuals from the Middle East and Romani populations, although these represent a small minority. There were also waves of German immigrants around both world wars.

Colombia is second only to Brazil in terms of number of indigenous tribes. Its indigenous peoples, composed of over 80 tribes, speak over 66 different languages; each tribe has its own values, believes, customs and religious, and artistic expressions (Aristizabal 2000). Among the indigenous peoples, two tribes currently count among their members over 100,000 individuals; the Nasa and Wayuu. Many of the tribes count less than 100 individuals with some on the verge of extinction such as the Taiwano, Pisamira, Makaguaje, and Bara (Aristizabal 2000). The Amerindian population is located in the plains, Amazonian jungle and in some regions of the Colombian Andes.

The Afro-Colombian population is descendant of slaves brought from Senegal, Ivory Coast and Mali during the early 16th century and for the most part settled along the
Pacific coast of the country with a minority settling in the Caribbean coast and Islands. Raizal is the name given to individuals of a separate ethnic Afro-Caribbean group that populates the islands north of Colombia (San Andres y Providencia); they speak English Creole and have distinct religious beliefs (Pasaporte Colombiano: https://
Healthcare in Colombia

After an overhaul to the Colombian national constitution in 1991, Law 100 of 1993 was created; the purpose of the law was to dramatically expand health coverage to the population, entitling all citizens, irrespective of their ability to pay, to comprehensive health benefits (Gideon and Villar Uribe 2009). In Colombia, citizens can participate in one of two regimens: the contributory regime, which covers workers who meet a threshold of minimum monthly income; and the subsidized regime, which covers the poor. Financing is carried out through payroll tax contributions (Gideon and Villar Uribe 2009). Benefit packages are tiered based on the regime individuals belong to, for the contributory regime, the POS (Plan Obligatorio de Salud) includes all levels of care, for the subsidized regime, the POSS (Plan Obligatorio de Salud Subsidiado), covers mostly low-complexity care and catastrophic illness. In Colombia, individuals are free to choose from a variety of insurers; ownership of these health-promoting entities (EPS, Entidad Promotora de Salud) can be public, private, or mixed. It is important to note that the Colombian Constitutional Court matched both benefit packages, POS and POSS, in 2009 (Judgment T-230/09 Corte Constitucional de Colombia: http://www.corteconstitucional.gov.co/relatoria/2009/T-230-09.htm).

Despite major efforts to expand healthcare coverage to all Colombian citizens (before 1993, health care coverage was 26%, in 2006 it was 96%), health care delivery continues to be disparate and the provision of services unequal. The quality of health care for the poor tends to fall behind accepted standards of care and there are concerns of pervasive, widespread corruption in the system (America Economia Magazine: http://www.worldcrunch.com/world-affairs/the-corruption-at-the-heart-of-colombia-039-s-health-care-system/colombia-health-care-corruption-privatization/c1s9 688/#.VMK4ksaA3dm). It is a stark contrast: While Colombia has reached near-universal health insurance coverage and has grown as a destination for the health tourism industry with some of the best hospitals in Latin America (Ranking Revista America Economia: http://rankings.americaeconomia.com/mejores-clinicas-hospitales-2014/ranking/), some of the population has little or no access to adequate health care. In terms of quality and coverage, the rural areas in the non-Andean regions suffer the most.

In 2002, Colombia had 58,761 physicians, 23,950 nurses, and 33,951 dentists. In 2005, Colombia had 1.1 physicians per 1000 population as compared to an average of 1.5 for Latin America (Library of Congress, Colombia: http://lcweb2.loc.gov/frd/cs/cotoc.html). General government spending of health care in Colombia
Figure 2. Physical map of Colombia showing a rough distribution of its populations. (1) Atlantic and Pacific coasts have the highest density of Afro-Colombian populations; (2) Andean highlands; (3) Amazonian region, with the highest density of Amerindian populations. Not pictured are the Islands of San Andres and Providencia (Source: Embassyworld.com).
accounted for 20% of total government expenditure in 2005 (World Bank: http://www.worldbank.org/en/country/colombia). The burden of health care in Colombia is caused by chronic conditions with 75% of reports of morbidity and mortality related to ongoing, untreated medical conditions. The top five causes of morbidity in Colombia for women for all age groups were mental disorders, hypertensive disease, birth trauma, low birth weight, and glaucoma. (Cendex: http://cendex.javeriana.edu.co). In terms of reproductive health, the average fertility rate is 2.1, the rate being higher in rural areas and lower near urban centers (Encuesta Nacional de Demografía y Salud, 2010: http://www.profamilia.org.co/encuestas/Profamilia/Profamilia/index.php?option=com_content&view=article&id=62&Itemid=9). The average age at first birth is 21 years and the median interval between births is 48 months. Prenatal care is carried out in 97% of pregnancies and deliveries were carried out in a hospital in 95% of cases (Encuesta Nacional de Demografía y Salud, 2010). Although the maternal mortality rate has been falling, it is still far from goal at 72.9 per 100,000 live births, the leading cause of death is hypertensive disease of pregnancy (21%), followed by obstetric complications (14%), and maternal sepsis (7%) (DANE, 2009).

Genetic testing in Colombia is not covered by the mandatory health plan (POS, Plan Obligatorio de Salud) but patients can demand testing through legal action for protection of the right to health and life that must be solved expeditiously by judges against the health insurer (EPS), which will eventually be reimbursed by the government. Referrals to see a Clinical Geneticist are only covered by some EPS.

Although Colombia does not currently count with a rare disease program, work is being done in establishing one. The current census for patients with rare diseases is 13,168. A recently passed law (Law 1392 of 2010) enshrines guarantees of medical care and social protection for individuals with an orphan disease. The definition of orphan disease in the Colombian legislature is a medical condition with prevalence lower than 1 in 2,000 (Corte Constitucional de Colombia). There is a list of all conditions considered rare, ultra-rare and orphan in Colombia, the list is updated every 2 years (Ministerio de Salud y Proteccion Social, http://www.cuentadealtocosto.org/index.html: http://www.cuentadealtocosto.org/patologias/HUERFANAS/docs/generales/Resolucion-0430-2013.pdf).

Genetic Disorders in Colombia

We have evidence from the pre-Columbian era on the recognition of certain disorders from the Tumaco-La Tolita culture, a group of Amerindians settled in what is now the Colombian and Ecuador coast circa the year 600 bc. A collection of clay figurines have preserved in incredible detail the representation of what are thought to be prevalent genetic syndromes in the population at that time, such as: Morquio, Down syndrome, and Treacher-Collins (Museo del Oro) (Fig. 3).

Colombia shows a characteristic pattern of prevalence of certain disorders based on ethnic distribution of some of its population, high prevalence of consanguinity and geographic isolation (the Andes Mountains have limited mobility of certain populations and isolated them to certain regions). The regions of Boyaca, Santander, and Antioquia see a higher incidence of several autosomal recessive conditions due to the high degree of consanguinity in rural regions. The prevalence of consanguinity in the country is the third highest in South America after Brazil and Venezuela at 1.30%, the majority of these matchings are between first cousins (Liascovich et al. 2001). No discussion on the effects of inbreeding in Colombia would be complete without referencing the work of Gabriel García Márquez. In his seminal book “Cien años de Soledad (One hundred years of solitude)”, Gabo (an affectionate nickname) writes about a large, multigenerational pedigree, that of the Buendía family in the fictitious town of Macondo (Márquez 1967). The themes of geographic isolation, inbreeding and incest are pervasive.

Figure 3. Tumaco-La Tolita clay figurine purportedly showing a patient with Morquio syndrome (Source: Museo Del Oro, Colombia).
throughout the novel and weigh heavily in the mind of the author. Mental illness, fetal demise, congenital anomalies, dysmorphic features, and intellectual disability are all attributed in the novel as a direct or indirect consequence of consanguineous mating. The book ends describing the birth of a child with a caudal appendage (“pigtail” in the novel) product of a consanguineous mating between nephew and aunt bringing with it the end of the lineage (Castilla and Adams 1996).

Not many epidemiological studies have been carried out calculating the prevalence or cataloging the number of genetic conditions in Colombia, but data exist on conditions that are considered to be present in higher numbers within the Colombian population. Off the northwest coast of Colombia, the island of Providencia has a higher than average prevalence of sensorineural deafness, in general nonsyndromic deafness and in particular Waardenburg syndrome. The prevalence on the island is five cases per 1000, of which 65% are considered genetic. This is thought to be due to a founder effect. (Instituto Colombiano de Cultura Hispanica: http://www.banrepcultural.org/blaavirtual/geografia/geografia/index.htm). Colombian investigators initially described Roberts’s syndrome, a rare disorder characterized by severe limb and facial abnormalities after noticing an unusually high number of cases outside Bogota (Vega et al. 2005). These individuals shared a common ancestor in the 18th century and were pivotal in finding the causal gene, ESCO2. Since then several other cases have been described, there are thought to be ~150 cases worldwide, several of them in Colombia.

Huntington’s disease is endemic in a small town in the northwestern part of the country, in the state of Atlántico; the town of Juan de Acosta contains the second largest population of patients with Huntington’s disease in the world. The condition can be traced back to one of its founders, Lucas Echeverria who emigrated from Spain in 1790, generations of consanguineous matings lead to the extensive number of affected members with the condition (El Espectador: http://www.elspectador.com/noticias/salud/enfermedad-rara-mas-comun-juan-de-acosta-articulo-478109). There are over 25 multigenerational families affected. Lastly, in Valle del Cauca, there is a cluster of 200 children affected with an autosomal recessive form of vitamin D-dependent rickets (Giraldo et al. 1995).

It is important to comment on a well-characterized and studied population within Colombia, that of the Paisas in the Antioquia region. As mentioned before, this community has a higher incidence of genetic disease owing to its geographical isolation and higher degree of consanguinity. The Paisas arose from several founder families, their genomes shaped by the admixture of Amerindian women and Caucasian (Spanish) men (Arcos-Burgos and Muenke 2002). This makes the Paisa population an excellent target as a genetic isolate for linkage and genome-wide association studies (GWAS); such studies have been carried out for a variety of conditions, such as ADHD (Arcos-Burgos et al. 2010), bipolar disorder (Kremer et al. 2010), Tourette syndrome (Scharf et al. 2013), benign hereditary chorea (Perez-Poveda et al. 2005), and facial clefting (Camargo et al. 2012). One of the most severe forms of early onset Alzheimer can be seen in this population due to a founder mutation, p.Glu280Ala in the PSEN1 gene (Acosta-Baena et al. 2011). Other conditions described in the Paisas with a strong genetic component are multiple sclerosis, rheumatoid arthritis, Sjogren syndrome, and schizophrenia (Arcos-Burgos and Muenke 2002).

Other groups have carried out studies to calculate the prevalence of genetic disorders but these are far fewer and do not represent a concerted effort, for instance, the prevalence of mucopolysaccharidosis in Colombia is around two cases per 100,000, with type IV (Morquio syndrome) being the most common and type VII (Sly) being the least frequent (Gomez et al. 2012); the allele frequency for hemoglobin S in Choco region (predominantly Afro-Colombian) is 0.5% and 0.15% in Valle Del Cauca (Instituto Colombiano de Cultura Hispánica). The prevalence of cystic fibrosis in Colombia is thought to be higher than one in 12,000 although the authors of the study acknowledge that this is likely an underestimate given the high percentage of undiagnosed cases, significant delay in diagnosis (4 years average in Colombia) and early mortality of patients with CF (average range in Colombia is 2–25) (Vasquez et al. 2010).

Studies looking at the rate of congenital malformations and chromosomal abnormalities are even more limited. A study performed in Bogota and Cali, two of the biggest cities in the country, showed that the congenital malformation rate was 2.08%. Of these, cardiac malformations (13%), poly/syndactyly (10%), and multiple congenital anomalies (8%) were the three most common disorders (Garcia et al. 2014). Data from the ECLAMC initiative (Latin-American Collaborative Study of Congenital Malformations)-VIDEMCO group (Epidemiological Vigilance of Congenital malformations in Colombia) showed that the percentage of live birth infants with major malformations was 1.9% and the percentage of stillbirths with major malformations was 10% (Nazer and Cifuentes 2011). The same study showed that the most common malformations detected in Colombia among live birth infants were as follows: polydactyly (36%), club feet (24%), congenital cardiomyopathy (16%), hydrocephalus (13%), and cleft lip (13%). Of mention, there was a cluster of sirenomelia and cyclopia cases in Cali in 2008; in total, there were...
eight cases in a 165-day period. The cases were suspected of being related to heavy metal exposure for families that live downstream from the municipal landfill (Castilla et al. 2008). Microtia carries a similar prevalence as in other countries; most of the documented cases of microtia in Colombia are grade II and are associated with low birth weight. (Garcia-Reyes et al. 2009)

Genetics Services in Colombia

Genetic services in Colombia are rendered in the great majority of cases by Academic institutions in the main cities: Bogota, Medellin, Cali, and Barranquilla.

Colombia has a state laboratory but it is limited in funding and resources, most if not all testing is performed in private laboratories (according to the Colombian Association of Human Genetics, there were at least 17 laboratories able to perform clinical molecular testing, and 12 laboratories able to perform cytogenetic testing), most of the laboratories doing genetic testing are affiliated with an Academic institution or are private for-profit companies. Testing is comprehensive and includes a variety of molecular techniques to include next-generation sequencing, preimplantation genetic diagnosis, and pharmacogenomics. Cytogenetic laboratories offer karyotypes, FISH, and chromosomal microarrays. Biochemical laboratories offer plasma amino acids, acylcarnitine profile, urine organic acids, and extensive menus of specialized biochemical testing.

There are organized efforts by patients for some genetic conditions, for instance, there is a Colombian Foundation for Cystic Fibrosis (https://es-es.facebook.com/FundacionColombianaParaFibrosisQuistica), which helps patients obtain appropriate care and treatment; the Colombian league for hemophiliacs (http://colhemofilicos.org.co); the association for lysosomal storage disorders (http://www.acopol.org.co/web/), Huntington’s disease (http://fuhcol.blogspot.com/), and cleft lip and palate. There are also associations for individuals with congenital blindness, congenital deafness, and NF1.

Colombia has formal genetics training for medical professionals (physicians) in the form of a residency program that lasts 3 years; there are also master level courses that basic scientists can take. Physicians who complete a training program are boarded as Clinical geneticists. Genetics is also part of the medical school curriculum and students at the major academic institutions get exposure to a variety of patients with genetic conditions. There are no genetic counselors (GC) training in Colombia, the clinical geneticists, pediatricians, or Obstetricians/gynecologists do all counseling. The Colombian Society of Genetics is tasked with advancing the field, they host a conference every 2 years; trainees, resident, and faculty are encouraged to submit their work in the form of abstracts and lectures.

Reproductive Law and Newborn Screening

Abortion is illegal in Colombia except in certain conditions: (1) In cases of rape; (2) When the pregnancy poses a health risk to the mother, or (3) Severe congenital malformation. Reform to reproductive rights in Colombia was a consequence of a high profile case in the country, that of Marta Gonzales. While pregnant Ms. Gonzales was diagnosed with cervical cancer, radiotherapy was denied since it would terminate the pregnancy. Ms. Gonzales eventually delivered a healthy baby girl but the cancer had metastasized, she died less than 2 years later. The case served as a flashpoint for reproductive rights (Sentence C-355 of 2006, Colombian Constitutional Court).

Colombia started a pilot newborn screening program in 1986 for congenital hypothyroidism (Carrillo, 1986), only more recently (1999) have efforts to institute a more broad NBS program have taken place. The current coverage is ~36% with most samples coming from cord bloods. The program is decentralized and funded by three separate components of the health care system, as part of the mandatory program, only congenital hypothyroidism is screened for, other conditions offered on request include: PKU, galactosemia, congenital adrenal hyperplasia, biotinidase deficiency, hemoglobinopathies, and fatty acid oxidation disorders (Borrajo 2007).

More extensive NBS panels similar to ones offered in the United States can be obtained through in-house testing at private laboratories, although this testing is expensive and thus out of reach for most of the population.

Final Remarks

The field of medical genetics is growing in Colombia; this is represented in the growing numbers of clinical geneticists, the wider variety of services, and the increasing availability and complexity of genetic testing offered to the public. It is encouraging that there are ongoing efforts to care and protect individuals with rare and orphan conditions, including expensive treatments that these patients would otherwise not be able to cover. The country still needs to address the delivery of care to underserved populations, work on increasing the number of newborns screened for inborn errors of metabolism, and the number of conditions screened for, and lastly increase the number of nonclinician genetics professionals. The rate-limiting step for many of these goals will be the availability of government funding.
Conflict of Interest
None declared.

References
Acosta-Baena, N., D. Sepulveda-Falla, C. M. Lopera-Gomez, M. C. Jaramillo-Elorza, S. Moreno, D. C. Aguirre-Acevedo, et al. 2011. Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer’s disease: a retrospective cohort study. Lancet Neurol. 10:213–220.
Arcos-Burgos, M., and M. Muenke. 2002. Genetics of population isolates. Clin. Genet. 61:233–247.
Arcos-Burgos, M., M. Jain, M. T. Acosta, S. Shively, H. Stanescu, D. Wallis, et al. 2010. A common variant of the latrophilin 3 gene, LPHN3, confers susceptibility to ADHD and predicts effectiveness of stimulant medication. Mol. Psychiatry 15:1053–1066.
Aristizabal, S. 2000. La diversidad etnica y cultural de Colombia: un desafio para la educacion. Pedagogia y Saberes 15:55–66.
Borja, G. J. 2007. Newborn screening in Latin America at the beginning of the 21st century. J. Inherit. Metab. Dis. 30:466–481.
Camargo, M., D. Rivera, L. Moreno, A. C. Lidral, U. Harper, M. Jones, et al. 2012. GWAS reveals new recessive loci associated with non-syndromic facial clefting. Eur. J. Med. Genet. 55:510–514.
Carrillo, J. C. 1986. Deteccio´ n de hipotiroidismo conge´ nito en Colombia. Acta Ped Col 4:31–38.
Carvajal-Carmona, L. G., I. D. Soto, N. Pineda, D. Ortiz-Barrientos, C. Duque, J. Osquina-Duque, et al. 2000. Strong Amerind/white sex bias and a possible Sephardic contribution among the founders of a population in northwest Colombia. Am. J. Hum. Genet. 67:1287–1295.
Castilla, E. E., and J. Adams. 1996. Genealogical information and the structure of rural Latin-American populations: reality and fantasy. Hum. Hered. 46:241–255.
Castilla, E. E., P. Mastroiacovo, J. S. Lopez-Camelo, W. Saldañariga, C. Isaza, and I. M. Orioli. 2008. Sirenomelia and cyclopia cluster in Cali, Colombia. Am. J. Med. Genet. A 146a: 2626–2636.
Garcia, M. A., L. Imbachi, P. M. Hurtado, G. Gracia, and I. Zarante. 2014. Ultrasound detection of congenital anomalies in 76,155 births in the cities of Bogota and Cali, 2011–2012. Biomedica 34:379–386.
Garcia-Reyes, J. C., M. A. Caro, P. Vega, J. C. Osipna, A. M. Zarante, and I. Zarante. 2009. Epidemiology and risk factors for microtia in Colombia. Acta Otorrinolaringol. Esp. 60:115–119.
Gideon, U., and M. Villar Uribe. 2009. Colombia’s Universal Health Insurance System. Health Aff. 28:853–863.
Giraldo, A., W. Pino, L. F. Garcia-Ramirez, M. Pineda, and A. Iglesias. 1995. Vitamin D dependent rickets type II and normal vitamin D receptor cDNA sequence. A cluster in a rural area of Cauca, Colombia, with more than 200 affected children. Clin. Genet. 48:57–65.
Gomez, A., R. Garcia, and F. Suarez. 2012. Estimacion de las frecuencias de las mucopolisacaridosis y analisis de agrupamiento espacial en los departamentos de Cundinamarca y Boyaca. Biomedica 32:602–609.
Kremeyer, B., J. Garcia, H. Muller, M. W. Burley, I. Herzberg, M. V. Parra, et al. 2010. Genome-wide linkage scan of bipolar disorder in a Colombian population isolate replicates Loci on chromosomes 7p21-22, 1p31, 16p12 and 21q21-22 and identifies a novel locus on chromosome 12q. Hum. Hered. 70:255–268.
Liasovich, R., M. Rittler, and E. E. Castilla. 2001. Consanguinity in South America: demographic aspects. Hum. Hered. 51:27–34.
Márquez, G. G. 1967. Cien anos de soledad. Buenos Aires, Editorial Sudamericana.
Nazer, H. J., and O. L. Cifuentes. 2011. Congenital malformations in Latin America in the period 1995–2008. Rev. Med. Chil. 139:72–78.
Perez-Poveda, J. C., L. G. Palacio, and M. Arcos-Burgos. 2005. Description of an endogamous, multigenerational and extensive family with benign hereditary chorea from the Paisa community. Rev. Neurol. 41:95–98.
Sanchez-albornoz, N. 1987. Emigration from the Iberian Peninsula to America. Bol Asoc Demogr Hist 5:36–40.
Scharf, J. M., D. Yu, C. A. Mathews, B. M. Neale, S. E. Stewart, J. A. Fagerness, et al. 2013. Genome-wide association study of Tourette’s syndrome. Mol. Psychiatry 18:721–728.
Schulz, N.-S. 2010. The third wave of development players. Policy Brief, FRIDE, 1–6.
Vasquez, C., R. Aristizabal, and W. Daza. 2010. Fibrosis quistica en Colombia. Neumologia Pediatrica 5:44–50.
Vega, H., Q. Waisfisz, M. Gordillo, N. Sakai, I. Yanagihara, M. Yamada, et al. 2005. Roberts syndrome is caused by mutations in ESCO2, a human homolog of yeast ECO1 that is essential for the establishment of sister chromatid cohesion. Nat. Genet. 37:468–470.
Yunis, J. J., L. E. Acevedo, D. S. Campo, and E. J. Yunis. 2013. Geno-geographic origin of Y-specific STR haplotypes in a sample of Caucasian-Mestizo and African-descent male individuals from Colombia. Biomedica 33:459–467.