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ORIGINAL ARTICLE

Estimates of PI*S and PI*Z Alpha-1 antitrypsin deficiency alleles prevalence in the Caribbean and North, Central and South America

F.J. de Serres[1], I. Blanco[2], E. Fernández-Bustillo[3]

ABSTRACT: ***Estimates of PI*S and PI*Z Alpha-1 antitrypsin deficiency alleles prevalence in the Caribbean and North, Central and South America. F.J. de Serres, I. Blanco, E. Fernández-Bustillo.***

Background. **AAT deficiency is not a rare disease, but one of the most common congenital disorders increasing susceptibility of individuals with this deficiency to both lung and liver disease as well as other several adverse health effects. Studies to develop accurate estimates of the magnitude of this genetic disorder in any given country is critical for the development of screening programs for detection, diagnosis, and treatment of those individuals and/or families at risk. In the present study, estimates of the prevalence of the two major deficiency alleles PI S and PI Z were estimated for 25 countries in the Caribbean and North, Central, and South America to supplement our previous studies on 69 countries worldwide.**

Method. **Using data on the prevalence of the two most common deficiency alleles PI S and PIZ in the mother countries that provided the majority of immigrants to these 25 countries, as well as genetic epidemiological studies on various genetic subgroups indigenous to the Caribbean and North, Central and South America it was possible to develop new formulas to estimate the numbers in each of five phenotypic classes, namely PI MS, PI MZ, PI SS, PI SZ and PI ZZ for each country.**

Results. **When these 25 countries were grouped into six different geographic regions, the present study demonstrated striking differences when comparisons were made in numeric tables, maps and figures. Highly significant numbers of individuals at risk for AAT Deficiency were found in both the European, Mestizo and Mulatto populations for most of the 25 countries studied in the Caribbean and North, Central and South America.**

Conclusions. **Our studies demonstrated striking differences in the prevalence of both the PIS and PIZ alleles among these 25 countries in the Caribbean and North, Central and South America and significant numbers of individuals at risk for adverse health effects associated with AAT Deficiency in a given country. When these data are added to the results from our earlier studies on 69 countries, we now have data on AAT Deficiency in 94 of the 193 countries worldwide listed in the CIA FactBook.** ***Monaldi Arch Chest Dis 2009; 71: 3, 96-105.***

Keywords: alpha-1 antitrypsin deficiency, PI subtypes, PI phenotypes, genetic epidemiology, SERPINA1.

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Introduction

In previous studies, we have used existing genetic epidemiological data on AAT Deficiency collected by others and published in the peer-reviewed medical literature on 69 countries worldwide both to develop estimates of the prevalence of these two deficiency alleles and to use them to obtain estimates of the percentages of the total population in each country in each of the five major deficiency phenotypic classes, namely: PI MS, PI MZ, PI SS, PI SZ and PI ZZ. This present analysis has made use of the most recent estimates of the total population of each country and our estimates of the prevalence of PI S and PI Z for contributed by immigrants primarily from Portugal and Spain in each of these 25 countries in North and South America.

The present analysis has provided estimates of the numbers at risk for AAT Deficiency for each of these 25 countries as well as updated estimates for Canada and the United States in the Caribbean and North, Central, and South America. These 25 countries in addition to the 69 countries in our prior publications, brings to a total of 94 countries out of a possible 193 countries worldwide (https://www.cia.gov/cia/publications/factbook/index.html/) where there are genetic epidemiological studies on AAT Deficien-

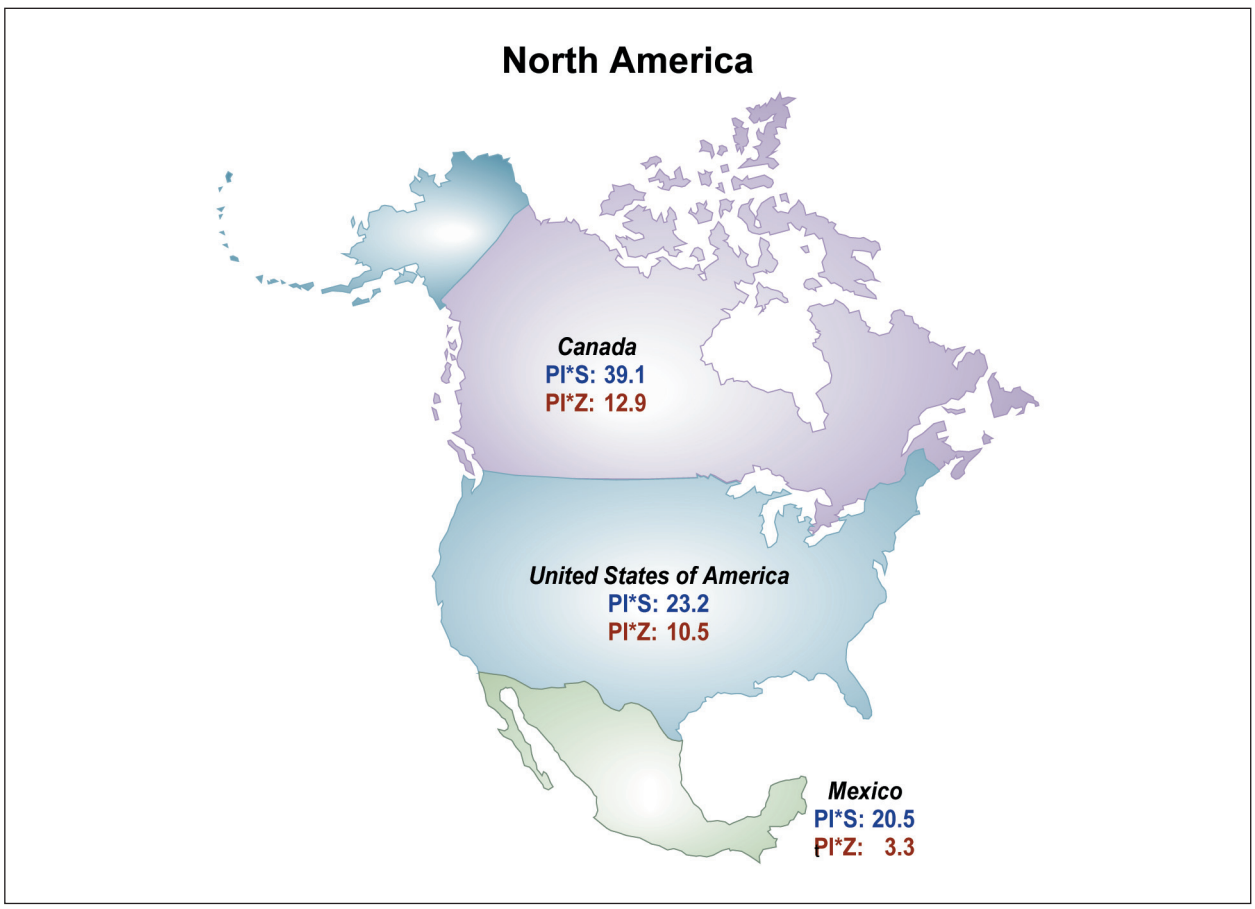

Fig. 1. - Prevalence of the PI S and PI Z deficiency alleles in North America (Canada and United States data from [6])

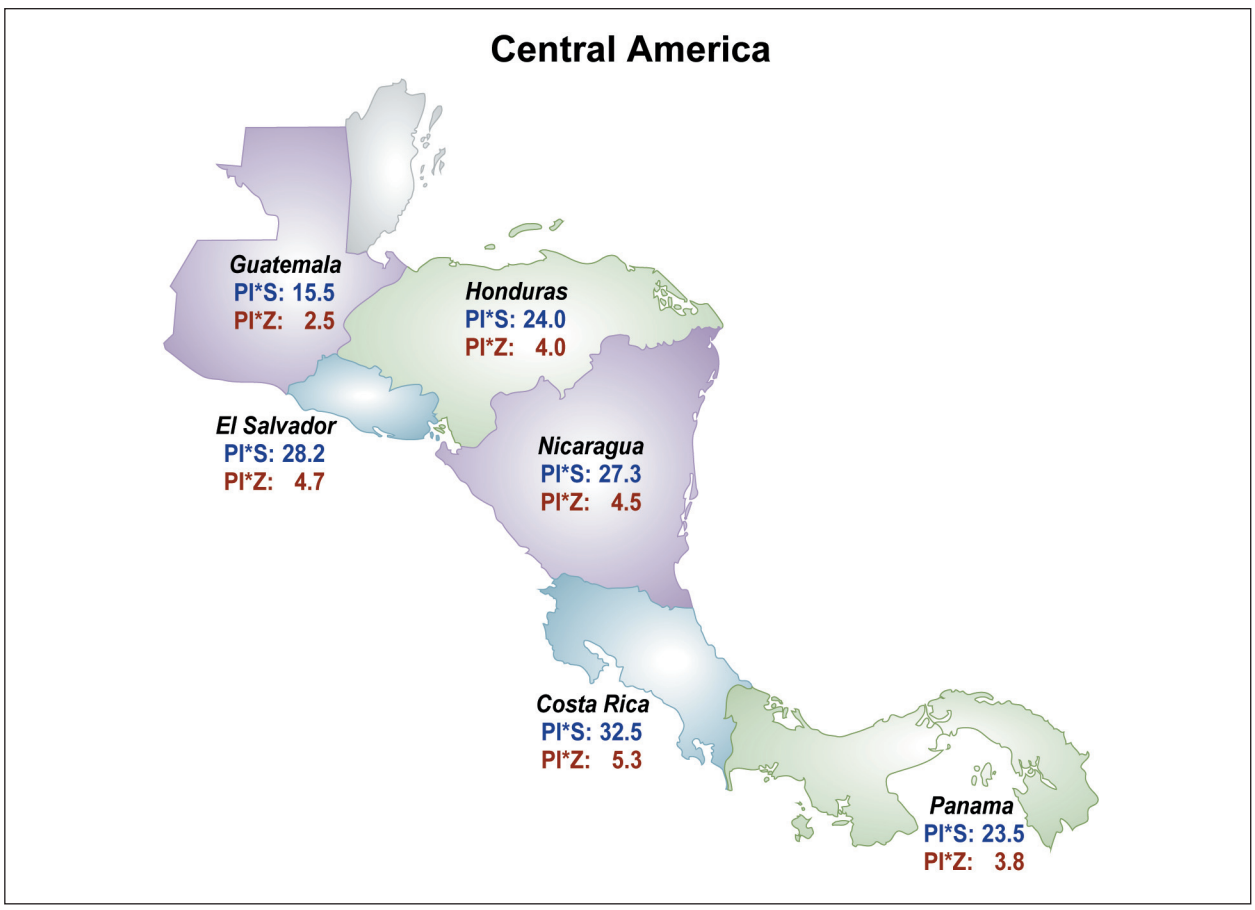

Fig. 2. - Prevalence of the PI S and PI Z deficiency alleles in Central America

cy. The present study provides estimates of the numbers at risk for AAT Deficiency in these 25 countries in the Caribbean, and North, Central and South America. as well as providing an update on the numbers at risk in Canada and the United States as described earlier.

This unique database of AAT Deficiency in these 94 countries worldwide has resulted in estimates of the numbers at risk in each of these countries for a particular human genetic disease. We also have compared the numbers in each of these five phenotypic classes of the total populations from one country to another and demonstrated striking differences among countries in the same geographic region in the Caribbean, North, Central and South America. Such information is critical for a better understanding of the spread of this disease into different counties worldwide.

The prevalence data for these 94 countries suggests that AAT deficiency may be one of the most common serious single-locus human genetic diseases in the world. It is not a rare disorder, but a human disease that is relatively unknown and as a result is too rarely diagnosed and treated.

Methods

Estimates of the total population in each country

Estimates of the total population of each country as of July 2008 were obtained from the CIA FactBook site (https://www.cia.gov/cia/publications/factbook/index.html).

Source of the estimates genetic epidemiological studies for PI S, and PI Z, and estimates of the prevalences for each of these two major deficiency alleles

Estimates of the percentages of the PI S and PI Z alleles in different ethnic subgroups were made as illustrated in tables 1 and 2 using data both from the present and our previous studies on African, European and Asian cultures as well as genetic epidemiological studies on various genetic subgroups indigenous to the Caribbean and North, Central and South America.

Allele frequencies of PI M, PI S, and PI Z in these 25 countries were estimated as follows:

Table 1.

Population	**Reference**	**Prevalence X 1,000**	
		PI S	**PI Z**
Spain (general population)	[1, 2, 5]	104.1	17.3
Italy (general population)	[2, 5, 17]	30.2	7.7
Portugal (general population)	[2, 5]	128.7	13.8
France (general population)	[2, 5]	76.2	12.4
Germany (general population)	[2, 5]	21.3	9.8
Amerindians (Atacameno)	[14]	0.0	0.0
Amerindians (Piaora Indians of Amazonia pop)	[15]	0.0	0.0
Brazilian Amerindians (Macushi and Icana River Indians)	[16]	0.0	0.0
India (general population)	[8]	1.5	0.4
Afro-Americans, from US (NY, Pittsburg, Houston, St Louis, Long Beach)	[4, 6]	11.0	2.5
Mexicans from US (Long Beach, Los Angeles, California)	[4, 6]	40.8	0.0
Mexico (Mestizo Indians)	[16]	2.4	0.0

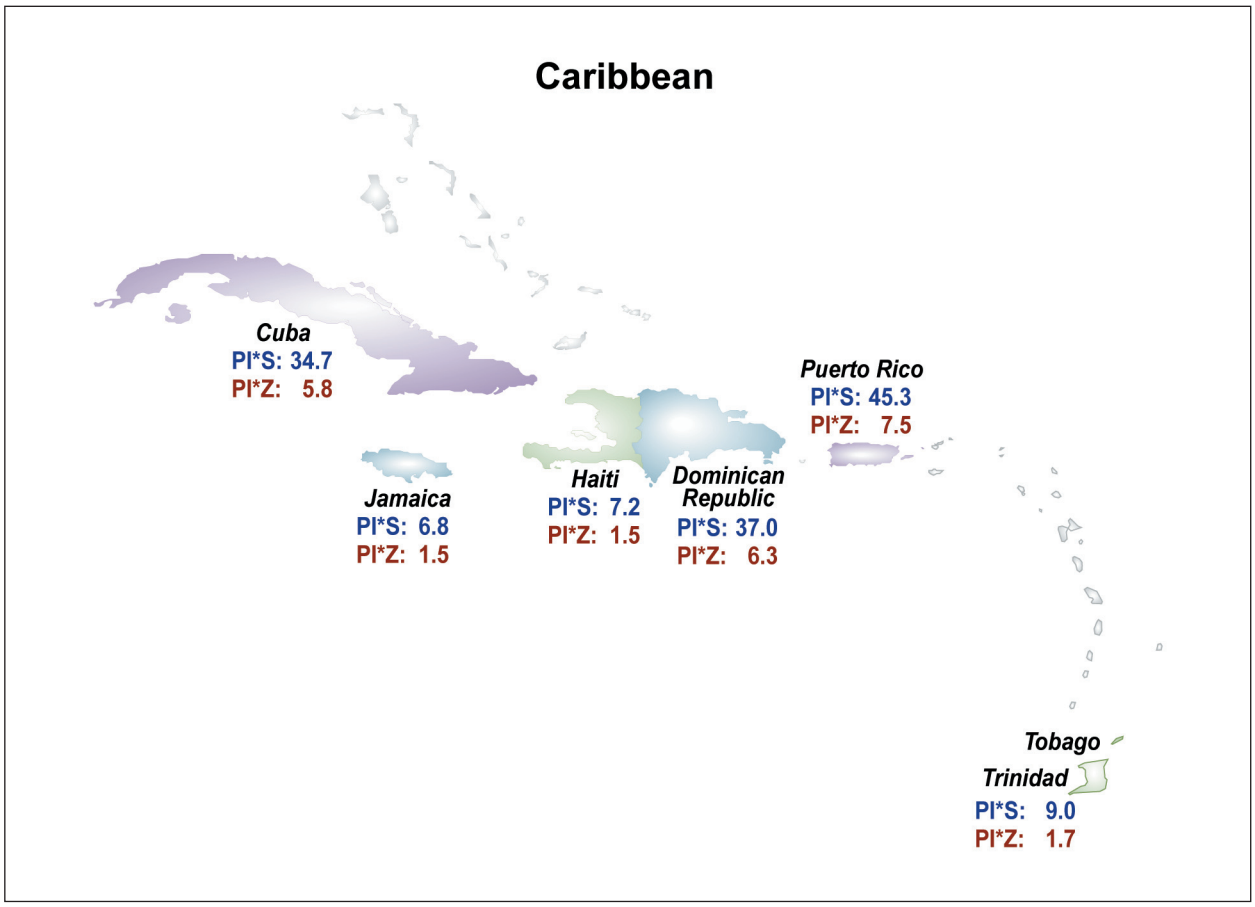

Fig. 3. - Prevalence of the PI S and PI Z deficiency alleles in the Caribbean

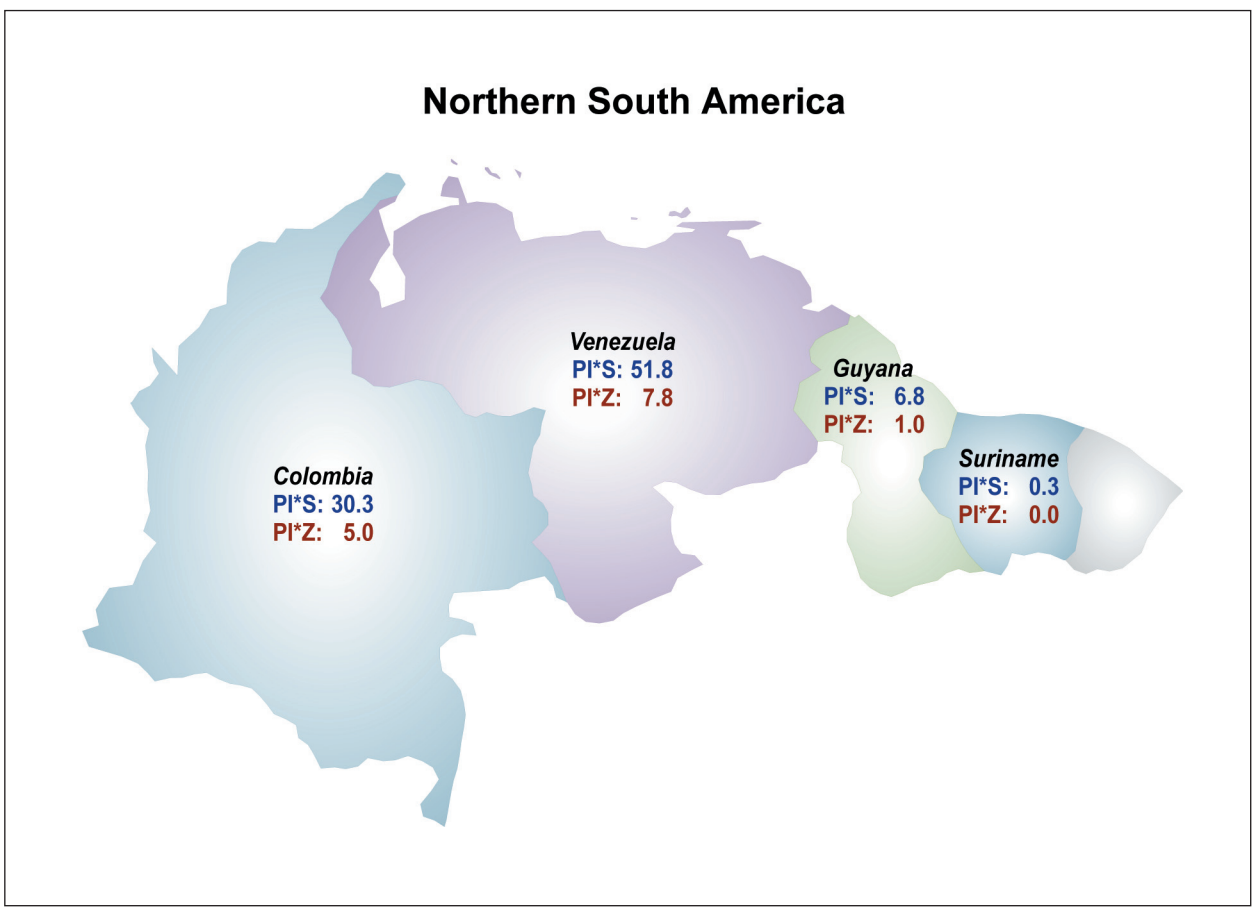

Fig. 4. - Prevalence of the PI S and PI Z deficiency alleles in Northern South America

The gene frequencies of the PI S and PI Z deficiency alleles in these different ethnic populations were used to develop formulas to obtain estimates of the number of the PI S and PI Z alleles in hypothetical populations of 1,000 individuals in each of these 25 countries. These formulas, which varied from country to country, took into account the differences in the ethnic compositions as well as the frequencies of the PI S and PI Z alleles in each of these ethic subgroups as illustrated in table 1. All of these estimates were then extrapolated to theoretical populations of 3,000 individuals in each country as follows:

$$\textit{allele number} \times 3000\ \textit{subjects} = \sum \frac{\textit{ethnic group \%} \times \textit{S or Z allelic frequency}}{100} \times 3$$

The ethnic subgroup composition of each country and estimates of size (%) of each was used to obtain estimates of the numbers of PI S ad PI Z alleles found for each of these 25 countries as given in table 2.

Results

In table 3, The number of the PI S and PI Z deficiency alleles in these theoretical populations of 3,000 individuals were then used to estimate the numbers in each of five phenotypic classes: PI MS, PI MZ, PI MS, PI SZ and PI ZZ in each of the 25 countries in the Caribbean, and North, Central, and South America using methods described in our earlier publications. These estimates of the numbers in each of five phenotypic classes: PI MS, PI MZ, PI MS, PI SZ and PI ZZ with 95% confidence intervals for these 25 countries are grouped into 6 major geographic regions. This makes it possible to compare the estimates for each of the countries within a given geographic region as in our earlier publication on 69 countries worldwide.

Comparison of the numbers in each of the five phenotypic classes of PI S ad PI Z in each of 25 countries in the Caribbean and North, Central and South America grouped into 6 geographic regions

The final comparisons in table 4 were made between the numbers in each of the each of five phenotypic classes: PIMS, PIMZ, PI MS, PI SZ and PIZZ in each of the six geographic regions in the Caribbean and North, Central, and South America. Using Hardy-Weinberg statistical analysis, each estimate is given along with 95% confidence intervals. This tabulation makes it possible to compare the numbers in each of these five phenotypic classes both between countries in the same geographic region as well as between different geographic regions.

In table 4, the data for each of the 6 geographic regions are given along with a summary for all of the 25 countries collated as a summary for this portion of the 25 countries in the Caribbean and North, Central, and South America. Of particular interest are the estimates of 25,452,217 for phenotype PI

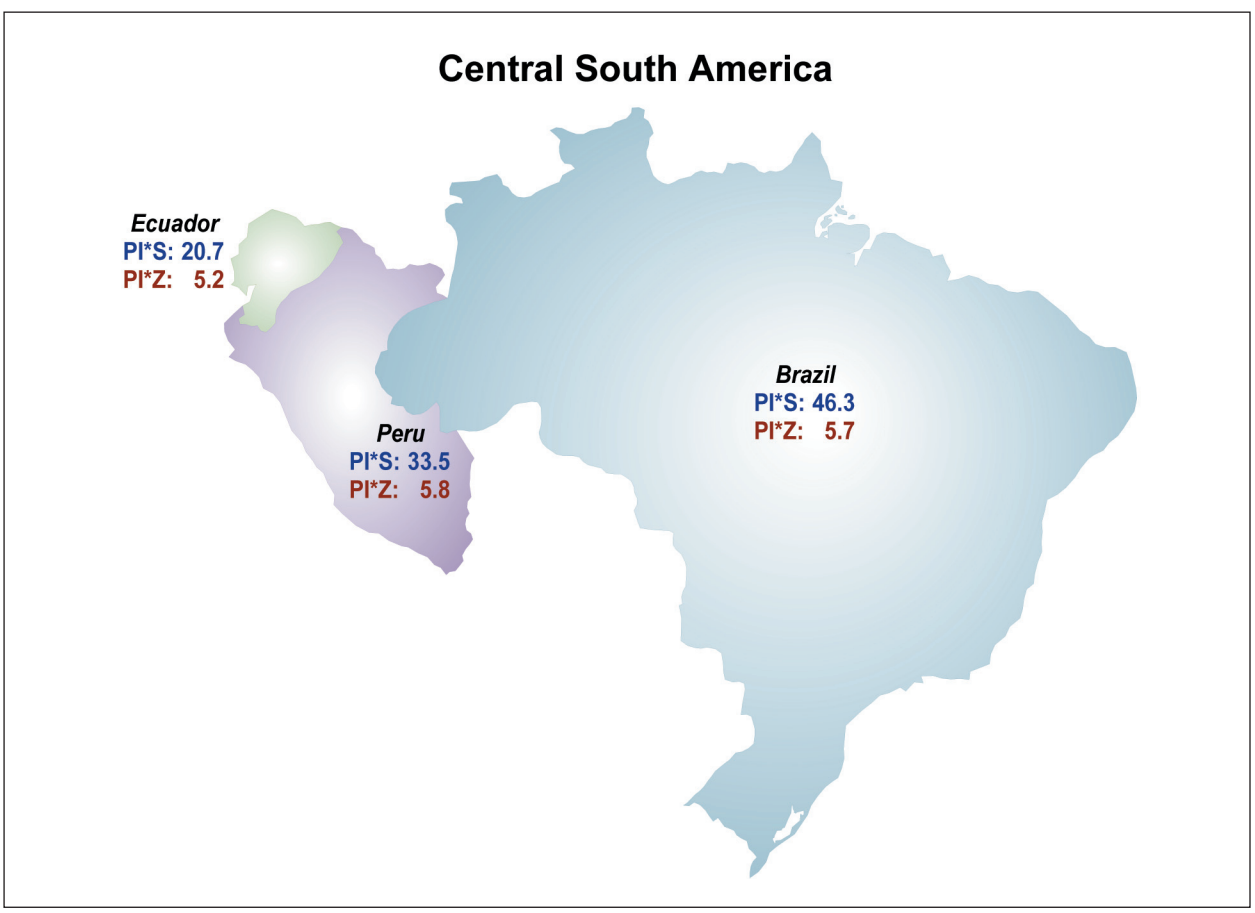

Fig. 5. - Prevalence of the PI S and PI Z deficiency alleles in Central South America

Table 2. - Estimates of the allele number of the deficiency alleles PI S and PI Z in a population of 3,000 individuals in different countries in the Caribbean, and North, Central, and South America

COUNTRY	POPULATION	Ethnic subgroup and estimates of size (%) of each									2009Σ	Allele Number			
		SPANISH	ITALIAN	PORTUGUESE	AMERINDIAN	INDIAN	AFRO AMERICANS	MEXICAN	MESTIZO	MULATTO		PIS x 1000	PIZ x 1000	PIS x 3000	PIZ x 3000
ARGENTINA	40,913,584	48.5	48.5		1.5				1.5		100	65.9	12.3	198	37
BOLIVIA	9,775,246	15			55				30		100	31.2	5.2	94	16
BRAZIL	191,908,598	0.7		53.7	0.9		6.2			38.5	100	92.7	11.5	278	34
CHILE	16,601,707	50			50						100	52.1	8.7	156	26
COLOMBIA	45,644,023	21			3		4		58	14	100	60.5	10.1	182	30
COSTA RICA	4,253,877	30				3	3		64		100	64.9	10.8	195	32
CUBA	11,451,652	37					12			51	100	69.2	11.8	208	35
DOMINICAN REP.	9,650,054	16							84		100	60.4	10.0	181	30
ECUADOR	14,573,101	7			25		3		65		100	41.4	6.9	124	21
ELSALVADOR	7,185,218	9			1				90		100	56.2	9.3	169	28
GUATEMALA	13,276,517				40.6				59.4		100	30.9	5.1	93	15
GUAYANA	772,298			7	7	50	36				100	13.7	2.1	41	6
HAITI	9,035,536	2.5					95			2.5	100	14.5	3.1	43	9
HONDURAS	7,792,854	1			7		2		90		100	48.1	8.0	144	24
JAMAICA	2,825,928				2.2		91.2		4	2.6	100	13.6	2.9	41	9
MEXICO	111,211,789	9			30			1	60		100	41.0	6.7	123	20
NICARAGUA	5,891,199	17			5		9		69		100	54.6	9.1	164	27
PANAMA	3,360,474	10			16	4			70		100	46.9	7.8	141	23
PARAGUAY	6,995,655	5							95		100	54.7	9.1	164	27
PERU	29,546,963	15			45		3		37		100	35.2	5.9	106	18
PUERTORICO	3,971,020	80.5			0.4	0.2	8		4	6.9	100	90.7	15.2	272	45
SURINAME	481,267				63	37					100	0.6	0.1	2	0
TRINIDAD &TOBAGO	1,229,953	0.8				40	37.5		1.2	20.5	100	18.0	3.4	54	10
URUGUAY	3,494,382	44	44				4		8		100	63.7	11.8	191	35
VENEZUELA	26,814,843	11	5	5	0.2	0	10.8		68		100	56.0	9.1	168	27
Total	578,657,738														

MS, 4,546,935 for phenotype PI MZ, 301,018 for phenotype PI SS, 108,073 for phenotype PI SZ, and 9,757 for phenotype PI ZZ out of an estimated 578,657.738 inhabitants for these 25 countries.

The results of the present analysis of AAT Deficiency in North and South America clearly indicate that this disease is present in all of these 25 different populations. The present prevalences of the PI S and PI Z deficiency alleles are most probably the result of emigration to these countries from Portugal and Spain with minor contributions in some countries from emigration of populations from several countries in Africa, as well as other countries such as Italy, Germany or France.

Discussion

The primary objective of the present analysis is to demonstrate that the two major deficiency alleles of AAT Deficiency are in widespread distribution worldwide and to expand our original analysis for 69 countries in Asia, Africa, Australia/New Zealand and Europe and North America to 25 countries in the Caribbean and North, Central and South America.

In countries colonized by Europeans in Mexico, the Caribbean and North, Central and South America, PI S and PI Z frequencies are a reflection of the immigrant European Caucasian population frequency (predominantly Spanish and Portuguese with fewer Italian and German immigrants, with high and intermediate values of both genes). Both of the PI S and PI Z alleles are rare or non-existent in Amerindians.

Absent from the peer-reviewed medical literature are detailed studies on genetic epidemiology of AAT Deficiency in different parts of the countries in the current 25 country database as well as precise information on the ethnic composition of the populations studied. This paucity of the genetic epidemiological studies in many regions of a given country makes it impossible, for example, to perform the type of analysis that we reported earlier on 14/20 regions in Italy to investigate the possibility of regional differences within a given country due to the differences in the genetic make-up of the original settlers.

Comparison of the prevalence of the PI S and PI Z deficiency alleles among countries within a given geographic region

By combining the data in table 3 of the numbers of the total population for each of these 25 countries in each of the five phenotypic classes of PI S and PI Z, it makes it possible to compare their prevalence among countries in close proximity. It is evident from comparison of this prevalence in the countries that there can be marked differences in this prevalence between countries in the same geographic region.

In contrast to our previous studies on AAT Deficiency in 69 countries worldwide, both of these deficiency alleles were found in the 25 countries. However, the data in table 3 demonstrate the highest numbers of the PI ZZ phenotype were found in

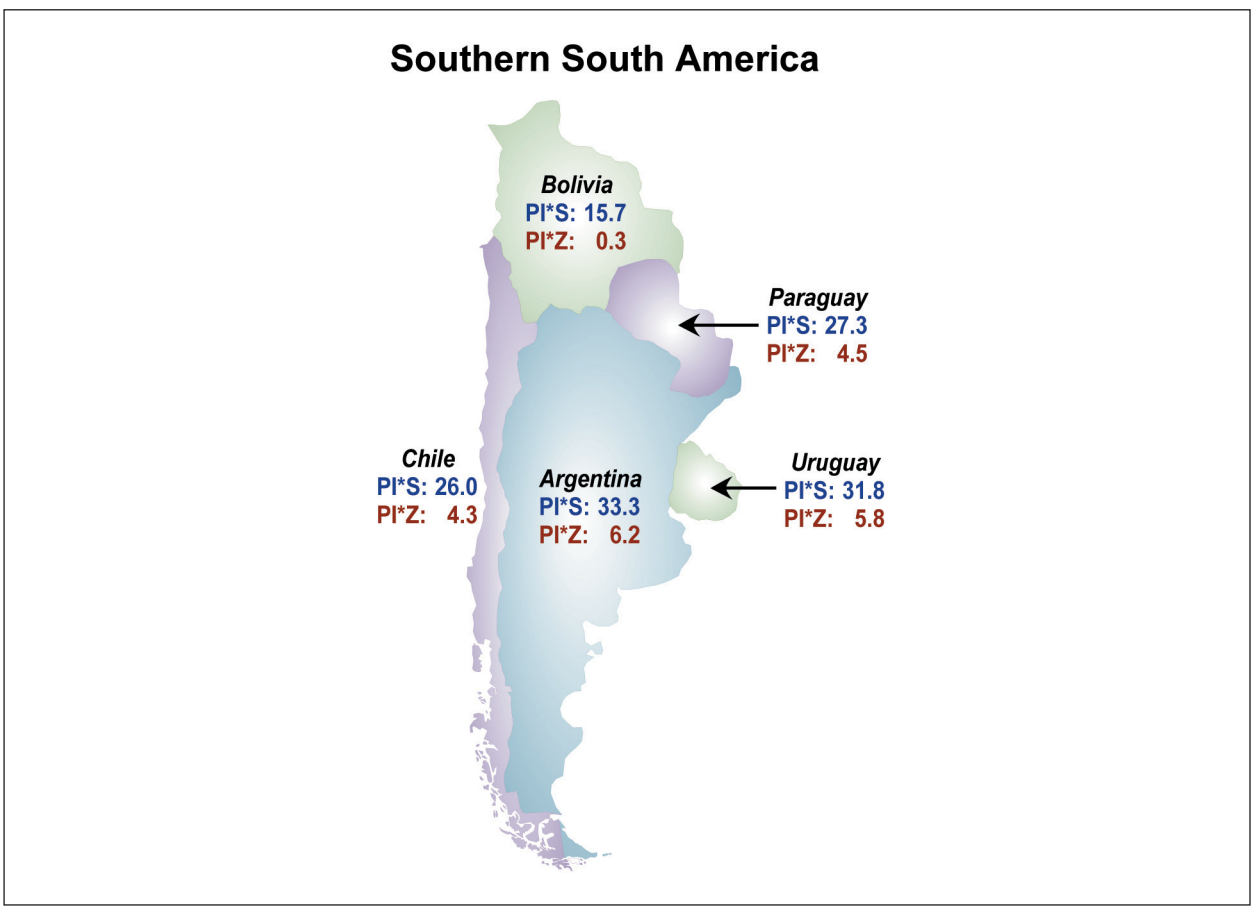

Fig. 6. - Prevalence of the PI S and PI Z deficiency alleles in Southern South America

Table 3. - Data summaries of the numbers of each of the five PI phenotypes for carriers and deficiency allele combinations with 95% CI for 25 countries worldwide

Geographic Region		Number in each of five phenotypic classes with 95% confidence intervals (Hardy-Weinberg statistics)									
No.	Country and total population size	PI MS	95% CI	PI MZ	95% CI	PI SS	95% CI	PI SZ	95% CI	PI ZZ	95% CI
North America	Mexico 111,211,789	**4,451,011**	3,703,729–5,338,200	**723,742**	452,553–,142,897	**46,737**	32,645–66,726	**15,199**	7,978–28,572	**1,236**	487–3,059
Central America	Costa Rica 4,253,877	**266,041**	229,801–307,485	**43,658**	30,216–62,647	**4,493**	3,389–5,945	**1,475**	891–2,422	**121**	59–247
	El Salvador 7,185,218	**391,477**	334,576–457,255	**64,860**	43,733–95,415	**5,700**	4,206–7,708	**1,889**	1,100–3,217	**156**	72–336
	Guatemala 13,276,517	**404,164**	327,149–498,101	**65,188**	37,738–110,506	**3,190**	2,106–4,814	**1,029**	486–2,136	**83**	28–237
	Honduras 7,792,854	**363,583**	306,753–430,134	**60,597**	39,543–91,945	**4,489**	3,225–6,231	**1,496**	832–2,664	**125**	54–285
	Nicaragua 5,891,199	**311,800**	265,859–365,033	**51,333**	34,354–76,053	**4,401**	3,232–5,980	**1,449**	835–2,492	**119**	54–260
	Panama 3,360,474	**153,625**	129,383–182,064	**25,059**	16,196–38,368	**1,856**	1,329–2,586	**605**	333–1,090	**49**	21–115
Caribbean	Cuba 11,451,652	**761,825**	661,030–876,561	**128,192**	90,200–181,062	**13,762**	10,479–18,040	**4,632**	2,860–7,453	**390**	195–770
	Dominican Rep. 9,650,054	**561,745**	482,596–652,761	**93,107**	63,648–135,190	**8,782**	6,550–11,749	**2,911**	1,728–4,867	**241**	114–504
	Haiti 9,035,536	**128,387**	93,860–174,759	**26,872**	13,081–53,093	**464**	249–8 56	**194**	70–520	**20**	5–78
	Jamaica 2,825,928	**38,299**	27,782–52,527	**8,407**	4,093–16,610	**132**	70–247	**58**	21–156	**6**	2–25
	Puerto Rico 3,971,020	**341,017**	301,036–385,723	**56,418**	41,399–76,530	**8,161**	6,441–10,322	**2,700**	1,772–4,096	**223**	122–406
	Trinidad & Tobago 1,229,953	**21,903**	16,577–28,830	**4,056**	2,055–7,741	**100**	57–172	**37**	14–92	**3**	1–12
Northern South America	Colombia 45,644,023	**2,671,230**	2,295,798–3,102,766	**440,313**	300,993–639,333	**41,998**	31,350–56,143	**13,845**	8,220–23,137	**1,141**	539–2,384
	Guyana 772,298	**10,472**	7,597–14,361	**1,532**	621–3,522	**36**	19–68	**11**	3–33	**1**	0–4
	Suriname 481,267	**0**	0-592	**321**	55–1,885	**9**	0–1	**0**	0–1	**0**	0–0
	Venezuela 26,814,843	**1,452,828**	1,241,101–1,697,690	**233,490**	156,253–345,949	**21,023**	15,498–28,455	**6,757**	3,902–11,597	**543**	246–1,182
Central South America	Brazil 191,908,598	**16,858,787**	14,903,263–19,042,138	**2,061,866**	1,442,066–2,929,261	**823,970**	326,065–519,651	**100,773**	63,101–159,876	**6,162**	3,053–12,297
	Ecuador 14,573,101	**586,794**	488,565–703,347	**146,699**	101,002–211,550	**6,224**	4,354–8,873	**3,112**	1,800–5,338	**389**	186–803
	Perù 29,546,963	**1,022,417**	838,779–1,243,496	**173,618**	105,705–281,031	**9,222**	6,258–13,548	**3,132**	1,577–6,124	**266**	99–692
Southern South America	Argentina 40,913,584	**2,594,535**	2,243,427–2,995,633	**484,837**	344,595–678,220	**44,555**	33,682–58,819	**16,652**	10,347–26,633	**1,556**	795–3,015
	Bolivia 9,775,246	**300,676**	243,654–370,151	**51,179**	30,182–85,306	**2,399**	1,588–3,613	**817**	393–1,665	**70**	24–192
	Chile 16,601,707	**837,102**	710,927–983,888	**139,517**	92,636–208,253	**11,223**	8,174–15,373	**3,741**	2,130–6,508	**312**	139–689
	Paraguay 6,995,655	**370,255**	315,701–433,468	**60,957**	40,794–90,311	**5,227**	3,838–7,101	**1,721**	992–2,959	**142**	64–308
	Uruguay 3,494,382	**214,096**	184,649–247,823	**39,232**	27,611–55,402	**3,541**	2,663–4,700	**1,298**	796–2,101	**119**	60–235

Table 4. - Estimates of the number in each of the five phenotypic classes in each of the six regions in the Western Hemisphere

Region	Total	PIMS	95% CI	PIMZ	95% CI	PISS	95% CI	PISZ	95% CI	PIZZ	95% CI
Region 1	111,211,789	4,451,011	4,431,565–4,467,619	723,742	720,580–726,442	46,737	32,645–66,726	15,199	7,978–28,572	1,236	487–3,059
Region 2	41,760,139	2,040,329	1,908,551–2,180,658	335,551	284,338–395,685	26,449	23,229–30,107	8,700	6,922–10,926	715	516–991
Region 3	38,164,143	1,654,007	1,540,764–1,775,114	284,960	239,912 338,185	18,894	16,453–21,690	6,510	5,124–8,265	561	399–787
Region 4	73,712,431	2,368,215	2,140,078–2,619,491	379,637	293,636–489,683	19,765	16,201–24,100	6,337	4,446–9,010	508	305–842
Region 5	236,028,662	10,905,824	9,892,348–12,016,609	2,114,914	1,691,069–2,640,348	133,447	110,377–161,232	51,757	37,737–70,854	5,019	3,226–7,784
Region 6	77,780,574	4,032,831	3,756,238–4,328,487	708,131	597,118–839,066	55,726	48,550–63,941	19,570	15,436–24,790	1,718	1,227–2,403
Western Hemisphere (totals)	578,657,738	25,452,217		4,546,935		301,018		108,073		9,757	

the Region 5 consisting of Brazil, Ecuador and Peru, followed by Regions 6 and 1. The highest number of the PI SS phenotype was also found in Region 5 followed by Regions 6 and 1.

In conclusion, the genetic epidemiological database on the prevalence of the two most common deficiency alleles PI S and PI Z has shown that they both exist in all of the 25 countries in the Caribbean and North, Central and South America. In most countries, individuals with phenotypes that put them at risk for various environmental exposures have not been identified as carriers of the Pi*S or PI*Z deficiency alleles There are cost effective targeted screening approaches that could be used, for example, on white COPD patients to detect such carriers, It is also possible that there is a high prevalence of AAT Deficiency alleles in patients with asthma.

Identification of individuals with AAT Deficiency is critical for management, education and treatment. AAT Deficiency patients comprise a highly susceptible subgroup that is sensitive to tobacco smoking, organic chemical, particulates, and microbes in the environment. It is reasonable to expect that risk could be quite high in particular occupations and professions.

In summary, It is clear that alpha 1-antitrypsin deficiency is not just a disease of Europeans emigrants in these 25 countries, but it also can be found (with a lower frequency) in the Mestizo and Mulatto ethnic subgroups in most of these countries. Unfortunately, it also is clear that most individuals who are carriers of this disease have not yet been identified in any of these 25 countries.

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