

Therapeutic Advances in Respiratory Disease

<http://tar.sagepub.com>

Ethnic differences in alpha-1 antitrypsin deficiency in the United States of America

Frederick J. de Serres, Ignacio Blanco and Enrique Fernández-Bustillo

Ther Adv Respir Dis 2010; 4; 63

DOI: 10.1177/1753465810365158

The online version of this article can be found at:

<http://tar.sagepub.com/cgi/content/abstract/4/2/63>

Published by:



<http://www.sagepublications.com>

Additional services and information for *Therapeutic Advances in Respiratory Disease* can be found at:

Email Alerts: <http://tar.sagepub.com/cgi/alerts>

Subscriptions: <http://tar.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.co.uk/journalsPermissions.nav>

Citations <http://tar.sagepub.com/cgi/content/refs/4/2/63>

Ethnic differences in alpha-1 antitrypsin deficiency in the United States of America

Frederick J. de Serres, Ignacio Blanco and Enrique Fernández-Bustillo

Ther Adv Respir Dis

[2010] 4(2) 63–71

DOI: 10.1177/

1753465810365158

© The Author(s), 2010.
Reprints and permissions:
<http://www.sagepub.co.uk/journalsPermissions.nav>

Abstract:

Background: Our earlier publications have demonstrated that alpha-1 antitrypsin (AAT) deficiency is not a rare disorder in the United States with at least 33,728 PI*ZZ homozygote individuals at risk.

Method: Using data on the prevalences of the two most common deficiency alleles PI*S and PI*Z in the five major individual ethnic subgroups in the United States, the numbers of heterozygotes for PI*MS and PI*MZ, and compound heterozygotes/homozygotes for PI*SS, PI*SZ and PI*ZZ have been determined for each ethnic subgroup.

Results: When the data for the prevalence of AAT deficiency in individual cohorts are displayed as a function of ethnic subgroup, striking differences are found in the numbers in each of the five phenotypic classes of PI*S and PI*Z. This type of analysis has demonstrated striking differences in the risk for AAT deficiency in each of these five ethnic subgroups. This analysis as a function of ethnic subgroup also has demonstrated that there are higher numbers of each of the five PI*S and PI*Z deficiency classes, namely PI*MS, PI*SS, PI*MZ, PI*SZ and PI*ZZ.

Conclusions: This analysis has demonstrated that the highest risk for AAT deficiency is found in Whites, followed by Hispanics and Blacks with the lowest prevalence among Mexican Americans and no risk among Asians. The numbers for those at risk for AAT deficiency in the United States are well documented and in the present analysis there are, for example, a total of 48,904 PI*ZZ homozygotes at risk. The critical question for our healthcare professionals is 'When will the medical community acknowledge that AAT deficiency is a prevalent and well-documented human genetic disorder and develop appropriate mechanisms for early diagnosis, medical follow-up and treatment both in the United States and worldwide?'

Keywords: alpha-1 antitrypsin deficiency, ethnic subgroups, genetic epidemiology, SERPINA1, PI phenotypes

Introduction

Alpha-1 antitrypsin (AAT) is a 52-kDa alpha-1-glycoprotein that acts as a circulating serine proteinase inhibitor (PI) and permeates most body tissues where it acts as an inhibitor of a range of proteolytic enzymes [Brantly *et al.* 1988]. Although its primary function is to inhibit neutrophil elastase, AAT has a broad spectrum of anti-inflammatory and connective tissue repair functions [Janciauskiene *et al.* 2007]. AAT gene is subject to mutations in the five-exon gene at q31-32.1 on the long arm of chromosome 14. About 100 genetic variant PI phenotypes of AAT have been identified and classified to date according to the PI nomenclature that assesses

AAT mobility by isoelectrofocusing. The predominant normal variant is called M (medium mobility) and, thus, the predominant normal phenotype is MM. The two most prevalent deficiency alleles are PI*S (Glu²⁶⁴→Val) and PI*Z (Glu³⁴²→Lys). S and Z proteins are abnormal proteins, which fail to fold properly and tend to polymerize in hepatocytes, being retained in the endoplasmic reticulum of the liver. Thus, 90% of Z and 40–50% of S proteins are retained in the hepatocytes, where are normally degraded by the proteasome. The severe mutation Z distorts the relationship between the reactive center loop and a β -sheet A, allowing the reactive center of one AAT molecule to lock into the A sheet of a

Correspondence to:
Frederick J. de Serres, PhD
Center for the Evaluation of Risks to Human Reproduction, National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709-2233, USA
deserres@bellsouth.net

Ignacio Blanco, MD
Respiratory Diseases Branch, Hospital Valle del Nalon, 33920 Langreo, Principado de Asturias, Spain

Enrique Fernández-Bustillo, PhD
Bio-statistics Unit, Hospital Central de Asturias, 33006 Oviedo, Principado de Asturias, Spain

second molecule to form a dimer, which may then form chains of polymers. The rate of polymer formation for S protein is much slower if compared with that of the Z variant, resulting in less retention and milder plasma deficiency [Lomas, 2005]. Liver deposits and decreased secretion of AAT to blood can result in serious lung diseases in adults (i.e. chronic obstructive pulmonary disease [COPD]) and liver diseases in infants, children, teenagers and adults (ranging from neonatal hepatitis to hepatic cirrhosis and hepatocarcinoma). Other diseases related to AAT deficiency are systemic vasculitis type Wegener and necrotizing panniculitis [Brantly *et al.* 1988]. The most common phenotypes are six combinations of M, S and Z alleles, namely MM, MS, SS, MZ, SZ and ZZ. Serum levels for these phenotypes are: MM 100% (range 80–120%); MS 80% (75–85%); SS 60% (45–70%); MZ 60% (50–70%); SZ 40% (30–45%); and ZZ 15% (10–20%). AAT serum levels less than 35% of the normal levels of AAT, 50 mg/dl or 11 μ M, are associated with an increased risk for pulmonary emphysema. Therefore, most of the pathology related to AAT deficiency is linked to the Z allele, and in clinical practice 96% of AAT deficiency patients have a ZZ phenotype. The remaining 4% belongs mostly to SZ, and other rare deficiency (i.e. Mmalton and Siyama) or null phenotypes [Lomas, 2005; Needham and Stockley, 2004; Stoller *et al.* 2003a, 2003b; Brantly *et al.* 1988].

AAT deficiency is an underdiagnosed condition worldwide. Recent guidelines from both the World Health Organization [WHO, 1997, 1996], National Heart, Lung, and Blood Institute Registry [Eden *et al.* 2003], and the American Thoracic Society/European Respiratory Society [Stoller *et al.* 2003a, 2003b] recommend the establishment of screening programs for the detection of AAT deficiency in patients with COPD, because the detection of coexisting AAT deficiency could lead to family screening, appropriate management (including lifestyle changes such as quitting smoking and replacement therapy in selected cases), and specific counseling for these patients and families [Stoller *et al.* 2003a, 2003b].

In our earlier paper [de Serres *et al.* 2007], we have discussed the adverse health effects associated with AAT deficiency and the prevalences of this human genetic disorder in 55 countries worldwide. There is little doubt that it is the

most prevalent human genetic disorder known to man in many parts of the world with good estimates of the numbers at risk in individual countries worldwide [de Serres *et al.* 2006a, 2005, 2003a, 2003b; Blanco *et al.* 2005, 2004, 2001a, 2001b; Luisetti and Seersholm, 2004; de Serres, 2002; Hutchison, 1998]. This disorder is also suspected to make carriers for the PI*S and PI*Z deficiency alleles as well as compound heterozygotes/homozygotes especially susceptible to environmental chemical and particulate exposure [de Serres, 2003].

Our previous estimates of the numbers at risk for AAT deficiency in the United States was based on a summation of 38 genetic epidemiological studies on five different ethnic subgroups [de Serres *et al.* 2003b]. In the present paper, we have revised the estimates of the total populations in each of these five major ethnic subgroups based on the most recent United States total population estimate in the 2008 CIA FactBook [CIA, 2008]. Using these numbers the overall database was subdivided to investigate the prevalence of AAT Deficiency in each subgroup as well as to determine the number of heterozygotes (PI*MS and PI*MZ) and the numbers of heterozygotes/homozygotes (PI*SS, PI*SZ and PI*ZZ) in each ethnic subgroup.

Methods

Using the estimate of the total United States population of 303,824,646 individuals [CIA, 2008] and the methodology described in our earlier publications [de Serres *et al.* 2003b], we have used the data on genetic epidemiological studies for each ethnic subgroup in the United States to determine the numbers of heterozygotes (PI*MS and PI*MZ) as well as the numbers of heterozygotes/homozygotes (PI*SS, PI*SZ and PI*ZZ) in each ethnic subgroup with 95% confidence intervals on all estimates. The epidemiological studies performed by others, and the number of patients in the total cohorts of these five major ethnic subgroups, are given in Table 5 of our earlier manuscript [de Serres *et al.* 2003b]. These genetic epidemiological studies performed by others were performed on patients self-identified as Asian, Hispanic, Mexican American, Black or White. All of these individuals constitute what might be considered the normal patient population in the United States. None of the data collected [de Serres *et al.* 2003b] include tests on such subgroups as Native Americans, immigrants from the Far East, etc., since no such data on

those residing in the United States exist in the peer-reviewed medical literature.

Thus, the purpose of the present manuscript is to determine whether there are any differences in the numbers in each of the five phenotypic classes for AAT deficiency *as a function of ethnic subgroup as self-defined by individual patients.*

Results

The number of cohorts in each of the five ethnic subgroups and our estimates of the prevalence of the two major deficiency alleles PI*S and PI*Z with 95% confidence intervals is given in Table 1.

The different allele frequencies for PI*S and PI*Z in Table 1 demonstrate the striking difference between the prevalences of the PI*S and PI*Z deficiency alleles among these five major ethnic subgroups. The highest PI*S frequencies were found in Hispanic Americans (50 per 1000), Mexican Americans (41 per 1000) and White Americans (31 per 1000). The PI*S phenotype was rare among Black Americans (about 11 per 1000) and nonexistent among Asian Americans. On the other hand, the highest PI*Z frequencies were found among White Americans (15 per 1000), followed by Hispanic Americans (9 per 1000), and were rare or nonexistent in the remaining populations.

The next step was to determine the numbers of normal individuals (PI*MM) as well as the two classes of carriers (PI*MS and PI*MZ) and the three classes of heterozygotes/heterozygotes (PI*SS, PI*SZ and PI*ZZ), for each of these five ethnic subgroups along with 95% confidence intervals for all estimates in a total United States population of 303,824,646 individuals [CIA, 2008] as illustrated in Table 2.

The data in Table 2 show the numbers in all six phenotypes when the 38 cohorts are combined as

well as individually for each of these five ethnic subgroups (along with 95% confidence intervals) for all estimates in a total United States population of 303,824,646 individuals [CIA, 2008].

The values in Table 2 provide information on the numbers in the five different carrier and deficiency allele combinations for the database where all five ethnic subgroups are combined (United States Phenotype Original) [de Serres, 2003] as well as individually for each of the five ethnic subgroups. The final set of data gives the numbers when the numbers in each of the five phenotypic classes of the five ethnic subgroups are added and the total numbers recalculated. In the case of the three deficiency allele combinations, namely PI*SS, PI*SZ and PI*ZZ, when these five ethnic subgroup numbers are added, the summations (United States Phenotype Totals) are considerably higher than when all of the data on the five ethnic subgroups are combined (United States Phenotype Original). Thus, this analysis has also demonstrated that there are higher numbers at risk for COPD in the United States White American population than demonstrated in our earlier publication [de Serres *et al.* 2006b].

The present analysis demonstrates that a total of 48,904 PI*ZZ individuals were estimated for the whole US population, with 91.6% being White Americans, 7.8% Hispanic Americans, and 0.5% Black Americans. Neither Mexican nor Asian Americans showed any PI*ZZ individuals. This same distribution trend was found with PI*SZ and PI*MZ phenotypes among the populations studied. In general, the present analysis demonstrates a gradient of deficiency phenotypes (from maximum to minimum): White > Hispanic > Black > Mexican > Asian Americans.

The values in Table 3 provides information on the prevalences of the different carrier and

Table 1. Number of cohorts and allele frequencies for PI*M, PI*S and PI*Z for each of five major ethnic subgroups in the United States.

Ethnic subgroup	Cohorts No.	PI*M	95% CI	PI*S	95% CI	PI*Z	95% CI
Asian Americans	2	1.0000	0.9995–1.0000	0.0000	0.0000–0.0003	0.0000	0.0000–0.0003
Black Americans	6	0.9834	0.9771–0.9880	0.0111	0.0074–0.0164	0.0026	0.0010–0.0058
Hispanic Americans	3	0.9314	0.9086–0.9490	0.0503	0.0354–0.0707	0.0091	0.0037–0.0208
Mexican Americans	2	0.9542	0.9277–0.9716	0.0408	0.0242–0.0663	0.0000	0.0000–0.0091
White Americans	25	0.9534	0.9432–0.9478	0.0316	0.2988–0.3341	0.0149	0.0138–0.0162
Totals	38	0.9472	0.9444–0.9498	0.0307	0.0287–0.3288	0.0144	0.0130–0.0159

Table 2. Estimates of the numbers in each of the six phenotypic classes for each of five major ethnic subgroups in the United States of America based on a total population of 303,824,646 individuals (CIA FactBook July 2008 estimate).

Ethnic subgroup	Total	PI*MM	95%CI	PI*MS	95%CI	PI*MZ	95%CI	PI*SS	95%CI	PI*SZ	95%CI	PI*ZZ	95%CI
United States Original	38	281,971,873	281,034,424–282,873,138	13,561,679	13,539,116–13,583,335	6,167,748	6,157,487–6,177,597	163,065	146,257–181,772	148,322	140,469–169,862	33,728	33,728–39,683
Current study													
Asian Americans	2	13,459,432	13,450,110–13,459,255	0	0.00000–0.00000	0	0.00000–0.00000	0	0.00000–0.00001	0	0.00000–0.00002	0	0.00000–0.00001
Black Americans	6	37,984,556	37,539,522–38,303,718	852,848	847,838–856,424	196,811	195,655–197,636	4,787	2,135–4,743	2,209	600–1,333	255	42–238
Hispanic Americans	3	40,584,724	38,737,560–42,004,497	4,341,316	4,241,370–4,416,599	789,330	771,158–803,018	116,097	57,497–229,186	42,217	12,094–135,152	3,838	636–19,925
Mexican Americans	2	4,563,243	4,323,759–4,719,845	388,612	378,277–395,224	0	0.00000–0.00000	8,274	2,983–21,836	0	0.000–5,983	0	0.000–410
White Americans	25	180,559,073	179,702,062–181,383,637	12,022,075	11,993,510–12,049,494	5,688,929	5,675,412–5,701,904	200,115	178,967–223,707	189,392	164,983–217,347	44,811	38,023–52,792
United States Phenotype Totals	38	277,151,028		17,604,851		6,675,070		329,273		233,818		48,904	

deficiency allele combinations for the database where all five ethnic subgroups are combined (United States Original) as well as individually for each of the five ethnic subgroups. The final set of data gives the prevalences of the two carrier phenotypes and the three deficiency allele phenotypes when the numbers in each of the five phenotypic classes of the five ethnic subgroups are added and the prevalences recalculated. The present analysis demonstrates that as a whole, 1 in each 17 Americans carries either the PI*S and/or PI*Z congenital AAT deficiency. A total PI*ZZ prevalence of 1 in every 6211 individuals was estimated for the whole US population, with the following distribution in the four populations studied: White Americans 1/4472, Hispanic Americans 1/11,954, Black Americans 1/153,000, and nonexistent in the Mexican and Asian American populations. This relatively high PI*ZZ prevalence among White Americans is similar to that calculated for many Central Europe countries [de Serres *et al.* 2007, 2005, 2003a].

The numbers at risk for AAT deficiency in the United States

In an earlier paper [de Serres *et al.* 2003b], we calculated the numbers at risk for AAT deficiency in the United States by combining the database on all 38 cohorts consisting of genetic epidemiological studies on five different ethnic subgroups. In the present paper, we have updated these estimates by using the most recent data on the size of the population using the July 2008 CIA FactBook Estimate [CIA, 2008]. If, as in our original paper [de Serres *et al.* 2003b], we consider that only the homozygotes/heterozygotes for AAT deficiency are at risk [Stoller *et al.* 2003b], then (in the first line of Table 1), the total number is 345,115 (163,065 + 148,322 + 33,728). If, however, we add up the numbers from the estimates for each of the five ethnic subgroups (bottom line in Table 1), then the number at risk is 611,995 (329,273 + 233,818 + 48,904).

The numbers in each of the six phenotypic classes when we combine all 38 cohorts represent mean values for the five United States populations at risk for AAT deficiency. However, when the five ethnic subgroups are calculated individually, the total number of heterozygotes (PI*MS and PI*MZ) and heterozygotes/heterozygotes (PI*SS, PI*SZ and PI*ZZ) at risk for AAT deficiency in the United States are considerably higher. If we combine the numbers in the latter three phenotypic classes (bottom line in Table 1),

Table 3. Estimates of the prevalence (1/X) in each of the six phenotypic classes for each of five major ethnic subgroups in the United States of America based on a total population of 303,824,646 individuals (CIA FactBook July 2008 estimate).

	Values of 1/x									
	PI*MS	95%CI	PI*MZ	95%CI	PI*SS	95%CI	PI*SZ	95%CI	PI*ZZ	95%CI
United States Original	17	17–17	36	38–37	1,863	2,077–1,671	2,048	2,163–1,789	9,008	9,008–7,656
Current Study										
Asian	0	0–0	0	0–0	0	0–0	0	0–0	0	0–0
Americans										
Black	46	46–46	198	200–198	8,155	18,287–8,232	17,670	65,066–29,289	153,142	926,024–164,383
Americans										
Hispanic	11	11–10	58	59–0	395	798–200	1,087	339–3,793	11,954	2,303–72,133
Americans										
Mexican	13	13–13	0	0–0	600	1,663–227	0	0–829	0	0–12,104
Americans										
White	17	17–17	35	35–1,014	1,001	1,120–896	1,058	1,215–922	4,472	5,271–3,796
Americans										
United States Totals	17		48		922		1,299		6,211	

there is a striking difference between these two approaches of individuals at risk ($611,995 - 345,115 = 266,880$).

The number of individuals of PI*ZZ phenotype alone of 48,904 individuals is considerably higher than any previous estimate [Stoller *et al.* 2003a, 2003b]. The best estimates of the numbers of PI*ZZ individuals actually detected in the United States population has been given as about 5,000 individuals (see <http://www.alpha-1-foundation.org/>), at least a 10-fold difference between the numbers at risk as demonstrated above and those actually identified and treated. The present analysis demonstrates that 48,904 PI*ZZ individuals are estimated for the whole US population, with 91.6% White Americans, 7.8% Hispanic Americans and 0.5% Black Americans. Neither Mexican nor Asian Americans showed any PI*ZZ individuals. This same distribution trend was found by PI*SZ and PI*MZ AAT deficiency phenotypes among the populations studied. In general there is a gradient (from maximum to minimum): White > Hispanic > Black > Mexican > Asian Americans.

Discussion

Concerns about either the size of the individual ethnic subgroup cohorts or consistency with results of our earlier studies on different ethnic populations worldwide

Asians. The Asian database consists of only two cohorts that indicate that neither deficiency allele

(PI*S or PI*Z) is found in the two populations evaluated. These data are totally consistent with our earlier studies on Asian populations in China, Mongolia, Japan and South Korea [de Serres *et al.* 2006a] that show a striking absence of both deficiency alleles in these four countries. The two cohorts in Table 1 consist of 6,912 individuals: 6,860 in Oahu, HI, and 52 in San Francisco, CA.

Black Americans. The six-cohort database of Black Americans demonstrates that both the PI*S and PI*Z alleles are found in these portions of the indigenous American population. Both alleles are found in various countries in different regions in Africa [de Serres *et al.* 2005], and also in the early slave-owner gentry populations usually derived from different European countries where both PI*S and PI*Z are known to be prevalent [de Serres *et al.* 2003a; Blanco *et al.* 2001b]. The six cohorts of Black Americans consist of 1,174 individuals: 549 in Brooklyn, NY, 96 in Pittsburgh, PA, 77 in New York City, NY, 62 in Houston, TX, 204 in St. Louis, MO, and 186 in Long Beach, CA.

Hispanic Americans

The three-cohort database of Hispanic Americans demonstrates that both the PI*S and PI*Z alleles are found in this portion of the indigenous American population. In the United States, these individuals are derived predominantly from those individuals who emigrated from Spain (see <http://www.u-s-history.com/pages/h436.html>) and who settled in Southern

Florida as well as other parts of the United States. Emigration from many other provinces in Spain also occurred and the data in Table 1 are entirely consistent with our earlier studies on the prevalences of PI*S and PI*Z in Spain [de Serres *et al.* 2007, 2003a; Blanco *et al.* 2004]. The three cohorts consist of 328 individuals: 103 in Brooklyn, NY, another of 178 individuals in Brooklyn, NY and 47 in New York City, NY.

Mexican Americans. The Mexican American population is derived from interaction of early Spanish explorers carrying the PI*S allele predominantly but also the PI*Z allele [Blanco *et al.* 2004, 2001b] mating with Amerindians (usually Aztec, Mayan, Incas, Olmec, Yaqui, Zapotec, etc.; (see <http://www.indigenpeople.net/americas/southam/> and http://www.search.com/reference/Indigenous_peoples_of_the_Americas) and similar native Americans who have migrated north through Mexico and, with some intermarriage with the local ethnically mixed Mexican/Hispanic population, into various states in the United States (see http://nacts.asu.edu/North_American_Migration/Map5a) [Fonseca-Perez *et al.* 1996; Marini *et al.* 1993; Simoes *et al.* 1989; Goedde *et al.* 1984, 1980]. The two-cohort database on Mexican Americans indicates the presence of the PI*S allele but not the PI*Z allele in a cohort of 202 individuals: 127 in Long Beach, CA and 75 in Los Angeles, CA, both cities with very high Mexican American populations.

White Americans. The largest 25-cohort database consists of White Americans derived primarily from emigration to the United States from various countries in Europe [de Serres *et al.* 2003a; Blanco *et al.* 2001b; Hutchison, 1998]. This cohort demonstrates the presence of both the PI*S and PI*Z deficiency alleles. The 25 cohorts consist of a total of 19,193 individuals: 1,458 in Cleveland, OH, 192 in Pittsburgh, PA, 92 in Salt Lake city, UT, 904 in Minneapolis, MN, 283 in Brooklyn, NY, 1,380 in Long Beach, CA, 2,285 in St Louis, MO, 2,944 in Tucson, AZ, 500 in Rochester, NY, 1,026 in Baltimore, MD, 930 in Rochester, NY, 632 in Cleveland, OH, 257 in Philadelphia, PA, 1,380 in Sepulveda, CA, 212 in Rochester, NY, 114 in Rochester, NY, 114 in Rochester, NY, 930 in Rochester, NY, 890 in Rochester, NY, 1,018 in Rochester, NY, 498 in Rochester, NY, 270 in Rochester, NY, 260 in Rochester, NY, 310 in Portland, OR, 240 in Philadelphia, PA, and 188 in Philadelphia, PA.

Comparison of the numbers at risk for AAT deficiency in the United States with other countries worldwide

The present analysis of genetic epidemiological studies on AAT deficiency in the five major ethnic subgroups in the United States indicates differences in the prevalence of the PI*S and PI*Z deficiency alleles in each ethnic subgroup. Most important are the data in Table 1 (bottom line) that indicate that there are 17,604,851 PI*MS individuals, 6,675,070 PI*MZ individuals, 329,273 PI*SS individuals, 233,818 PI*SZ individuals and 48,904 PI*ZZ individuals in the current United States population.

In a recent publication, we used the data on genetic epidemiological studies performed by others on 69 countries worldwide to develop estimates for these same five phenotypic classes for the 2007 total world population of 4,688,304,652. The results were as follows: PI*MS is 125,260,653 (105,917,993–160,351,348), PI*MZ is 28,596,350 (19,929,593–52,816,942), PI*SS is 2,702,584 (1,971,570–3,932,470), PI*SZ is 902,996 (651,675–1,756,218) and PI*ZZ is 163,673 (97,104–403,295). It is easy to see that the population of the United States is responsible for a major portion of these five world phenotypic classes.

It is important to note that these are estimates based on genetic epidemiological studies performed by different research groups and possibly provide only a glimpse of the potential differences in the prevalences of these two deficiency alleles in each ethnic subgroup.

These data demonstrate that AAT deficiency is not just a genetic disorder that affects Europeans [de Serres *et al.* 2007] and our current database for the prevalence of AAT deficiency worldwide has important implications for the identification of those at risk and treatment of individuals [Eden *et al.* 2003; Stoller *et al.* 2003b] who may present with asthma, allergies [Eden *et al.* 1997; Colp *et al.*, 1993; Niggemann and Albani, 1989; Szczeklik *et al.* 1974] or COPD [de Serres *et al.* 2006b].

Careful examination of the data in Table 3 demonstrates that the prevalences of the different phenotypes vary markedly among the ethnic subgroups. When the individual prevalences for each one of the five phenotypic classes are calculated

and added up the prevalences are very different from when all of the data are combined. The bottom line in Table 1 gives us a better estimate of the prevalences of each of these five phenotypic classes. When the estimate for PI*SS, PI*SZ and PI*ZZ are combined, the prevalence of all three phenotypic classes is 1/496 instead of 1/880. Somewhat surprising is the estimate for the combination of these same three phenotypic classes for Hispanic Americans where the combined prevalence is 1/283. The present analysis demonstrates that calculated as a whole 1 out of every 17 Americans carries PI*S and/or PI*Z congenital AAT deficiency. A total PI*ZZ prevalence of 1 out of every 6211 individuals was estimated for the whole US population, with the following distribution in the four populations studied: White Americans 1/4,472, Hispanic Americans 1/11,954, Black Americans 1/153,000, and non-existent in Mexican and Asian Americans. This relatively high ZZ prevalence among White Americans is similar to that calculated for many Central Europe countries [de Serres *et al.* 2003a, 2007].

Adverse health effects associated with heterozygotes and heterozygotes/homozygotes for AAT deficiency

In the present paper, we have also demonstrated that the risk for heterozygotes and heterozygotes/homozygotes for AAT deficiency varies markedly between these five ethnic subgroups and that very large numbers of individuals in the present population of 303,824,646 individuals are at risk. The present results extrapolated to populations of Whites in other parts of the world clearly indicate that there are much larger populations at risk worldwide [de Serres *et al.* 2007].

The critical question for our healthcare professionals is “When will the medical community acknowledge that AAT deficiency is a prevalent and well-documented human genetic disorder and develop appropriate mechanisms for early diagnosis, medical followup and treatment both in the United States and worldwide?”

Conflict of interest statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

- Blanco, I., Bustillo, E.F. and Rodriguez, M.C. (2001a) Distribution of alpha-1-antitrypsin PI*S and PI*Z frequencies in countries outside of Europe: a meta-analysis. *Clin Genet* 60: 431–441.
- Blanco, I., Fernandez, E. and Bustillo, E. (2001b) Alpha-1-antitrypsin Pi Phenotypes S and Z in Europe: an analysis of the published surveys. *Clin Genet* 60: 31–41.
- Blanco, I., Fernandez-Bustillo, E., de Serres, F.J., Alkassam, D. and Menendez, C.R. (2005) PI*S and PI*Z alpha-1-antitrypsin deficiency: estimated prevalence and number of deficient subjects in Spain. *Med Hypotheses* 64: 759–769.
- Blanco, I., Fernandez-Bustillo, E., de Serres, F.J., Alkassam, D. and Rodríguez Menéndez, C. (2004) PI*S and PI*Z alpha-1-antitrypsin deficiency: estimated prevalence and number of deficient subjects in Spain. *Med Clin (Barc)* 123(20): 761–765.
- Brantly, M.L., Paul, L.D., Miller, B.H., Falk, R.T., Wu, M. and Crystal, R.G. (1988) Clinical features and history of the destructive lung disease associated with alpha-1-antitrypsin deficiency of adults with pulmonary symptoms. *Am Rev Respir Dis* 138: 327–336.
- CIA (2008) 2008 CIA FactBook. <https://www.cia.gov/library/publications/the-world-factbook/index.html/>
- Colp, C., Pappas, J., Moran, D. and Lieberman, J. (1993) Variants of alpha-1-antitrypsin in Puerto Rican children with asthma. *Chest* 103: 812–815.
- de Serres, F.J. (2002) Worldwide racial and ethnic distribution of alpha(1)-antitrypsin deficiency—summary of an analysis of published genetic epidemiologic surveys. *Chest* 122: 1818–1829.
- de Serres, F.J. (2003) Alpha-1 antitrypsin deficiency is not a rare disease, but a disease that is rarely diagnosed. *Environ Health Perspect* 111(16): 1851–1854.
- de Serres, F.J., Blanco, I. and Fernandez-Bustillo, E. (2003a) Genetic epidemiology of alpha-1 antitrypsin deficiency in southern Europe: France, Italy, Portugal and Spain. *Clin Genet* 63: 490–509.
- de Serres, F.J., Blanco, I. and Fernandez-Bustillo, E. (2003b) Genetic epidemiology of alpha-1 antitrypsin deficiency in North America and Australia/New Zealand: Australia, Canada, New Zealand and the United States of America. *Clin Genet* 64: 382–397.
- de Serres, F.J., Blanco, I. and Fernandez-Bustillo, E. (2005) Health implications of alpha1-antitrypsin deficiency in Sub-Sahara African countries and their emigrants in Europe and the New World. *Genet Med* 7: 175–184.
- de Serres, F.J., Blanco, I. and Fernandez-Bustillo, E. (2006a) Estimated numbers and prevalence of PI*S and PI*Z deficiency alleles of alpha-1-antitrypsin deficiency in Asia. *Eur Respir J* 28: 1091–1099.
- de Serres, F.J., Blanco, I. and Fernandez-Bustillo, E. (2007) PI*S and PI*Z alpha-1 antitrypsin deficiency

- worldwide. a review of existing genetic epidemiological data. *Monaldi Arch Chest Dis* 67: 184–208.
- de Serres, F.J., Blanco, I. and Fernandez-Bustillo, E. (2006b) Estimating the risk for alpha-1-antitrypsin deficiency among COPD patients: evidence supporting targeted screening. *COPD: J Chronic Obstruct Pulm Dis* 3: 133–139.
- Eden, E., Hammel, J., Rouhani, F.N., Brantly, M.L., Barker, A.F., Buist, A.S. *et al.* (2003) Asthma features in severe alpha-1-antitrypsin deficiency: experience of the National Heart, Lung, and Blood Institute Registry. *Chest* 123: 765–771.
- Eden, E., Mitchell, D., Mehlman, B., Khouli, H., Nejat, M., Grieco, M.H. *et al.* (1997) Atopy, asthma, and emphysema in patients with severe alpha-1-antitrypsin deficiency. *Am J Respir Crit Care Med* 156: 68–74.
- Fonseca-Perez, T., Gonzalez-Coira, M. and Arias, S. (1996) Pi locus (alpha-1-antitrypsin allelic frequencies in an Andean Venezuelan population. *Gene Geogr* 10: 65–74.
- Goedde, H.W., Benkmann, H.G., Flatz, G., Bienzle, U. and Kroeger, A. (1980) Alpha-1-antitrypsin subtypes in the populations of Germany, Ecuador, Afghanistan, Cameroon, and Saudi-Arabia. *Z Morphol Anthropol* 70: 341–346.
- Goedde, H.W., Rothhammer, F., Benkmann, H.G. and Bogdanski, P. (1984) Ecogenetic studies in Atacameno Indians. *Hum Genet* 67: 343–346.
- Hutchison, D.C. (1998) Alpha 1-antitrypsin deficiency in Europe: geographical distribution of Pi types S and Z. *Respir Med* 92: 367–377.
- Janciauskiene, S.M., Stevens, T. and Blanco, I. (2007) New insights into the biology of alpha 1-antitrypsin and its role in chronic obstructive pulmonary disease. *Curr Respir Med Rev* 3: 147–158.
- Lomas, D.A. (2005) Molecular mousetraps, alpha 1-antitrypsin deficiency and the serpinopathies. *Clin Med* 5: 249–257.
- Luisetti, M. and Seersholm, N. (2004) Alpha-1-antitrypsin deficiency. 1: Epidemiology of alpha-1-antitrypsin deficiency. *Thorax* 59: 164–169.
- Marini, E., Moral, P., Petralanda, I., Pacheco, M., Sandiumenge, T., Succa, V. *et al.* (1993) Serum protein markers in the Piaroa Indians of Amazonia (Venezuela). *Hum Hered* 43: 232–238.
- Needham, M. and Stockley, R.A. (2004) Alpha-1-antitrypsin deficiency. 3: Clinical manifestation and natural history. *Thorax* 59: 441–445.
- Niggemann, B. and Albani, M. (1989) [Bronchial asthma and homozygous alpha-1-antitrypsin deficiency (Pizz) in 3 members of a family]. *Klin Padiatr* 201: 412–415.
- Simoes, A.L., Kompf, J., Ritter, H., Luckenbach, C., Zischler, H. and Salzano, F.M. (1989) Electrophoretic and isoelectric focusing studies in Brazilian Indians: data on four systems. *Hum Biol* 61: 427–438.
- Stoller, J.K., Snider, G.L. and Brantly, M.L. (2003a) American Thoracic Society/European Respiratory Society Statement: Standards for the diagnosis and management of individuals with alpha-1-antitrypsin deficiency. *Am J Respir Crit Care Med* 168: 818–855.
- Stoller, J.K., Snider, G.L., Brantly, M.L., Fallat, R.J., Stockley, R.A., Turino, G.M. *et al.* (2003b) Genetic testing for alpha-1-antitrypsin deficiency – ethical, legal, psychologic, social, and economic issues. *Am J Respir Crit Care Med* 168: 874–900.
- Szczeklik, A., Turowska, B., Czerniawska-Mysik, G., Opolska, B. and Nizankowska, E. (1974) [Alpha-1 antitrypsin level and phenotype Pi in healthy subjects and patients with asthma]. *Pol Arch Med Wewn* 52: 283–290.
- WHO (1996) AAT deficiency. World Health Organization: Geneva.
- WHO (1997) [Alpha 1-Pi deficiency. World Health Organization]. *Pneumologie* 51: 885–918.