article

Health implications of α_1-antitrypsin deficiency in Sub-Sahara African countries and their emigrants in Europe and the New World

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Purpose: To determine the frequencies of the protease inhibitor (PI) deficiency alleles of α_1-antitrypsin deficiency (AAT Deficiency) in indigenous populations in 12 countries in Sub-Sahara Africa because of their potential impact on the health in these populations with regard to the high risk for development of liver and lung disease. In addition, to discuss the unique susceptibility of these populations and emigrants to Europe and the New World to the adverse health effects associated with exposure to environmental microbes, chemicals, and particulates. **Methods:** Detailed statistical analysis of the 24 control cohort databases from genetic epidemiological studies by others were used to estimate the allele frequencies and prevalence for the two most common deficiency alleles PIS and PIZ and to estimate the numbers at risk in each of the local Sub-Sahara populations as well as those who have emigrated from these countries to Europe and the New World. **Results:** The present study has provided evidence for the presence of both PIS and PIZ in the general populations of Nigeria, Republic of South Africa, and Somalia, the PIS allele in Angola, Botswana, Cameroon, Mozambique, Namibia, and the Republic of Congo, and only the PIZ allele in Mali. **Conclusion:** AAT Deficiency is found in both the Black and "Colored" populations in many of the Sub-Sahara countries in Africa, providing evidence for the presence of AAT Deficiency in such populations in Europe and in the New World. Such populations should be screened for AAT Deficiency and made aware of their unique susceptibility to exposure to chemical and particulate agents in the environment. ***Genet Med* 2005:7(3):175–184.**

Key Words: *α_1-antitrypsin deficiency, PI subtypes, Sub-Sahara Africa, genetic epidemiology, indigenous populations, environmental health*

α_1-Antitrypsin deficiency (AAT Deficiency) is one of the most common serious hereditary disorders in the world, because it affects all major racial subgroups, and there are an estimated 120.5 million carriers and deficient subjects in the countries surveyed worldwide.[1] The present article deals with the application of the American Thoracic Society/European Respiratory Society Statement "Standards for the Diagnosis and Management of Individuals AAT Deficiency"[2] as they might be applied to the indigenous Sub-Sahara populations in their native countries (Angola, Botswana, Cameroon, Democratic Republic of the Congo, Gambia, Mali, Mozambique, Namibia, Nigeria, Republic of South Africa, Republic of the Congo, and Somalia) as well as immigrants in various countries in Europe and the New World.

AAT Deficiency was believed to be primarily a disease affecting Whites from Northern Europe,[3] and there is concern that when members of these non-White ethnic groups present, for example, with asthma, allergies, or chronic obstructive pulmonary disease, that they may not be tested for AAT Deficiency. It is the intent of this article to review the evidence that indigenous populations in Sub-Sahara countries are at risk and to provide a statistical analysis of the overall database that permits estimates of allele frequencies, prevalences, and the numbers of carriers and deficiency allele combinations for the two most prevalent deficiency alleles PIS and PIZ. In addition, environmental health issues associated with this disease are reviewed in terms of occupation and environmental exposures relevant to these indigenous populations.

AAT is a 52-kD α_1-glycoprotein composed of 394 amino acid residues and 3 asparagine-linked complex carbohydrate side chains.[4] The AAT gene locus is located on the long arm of chromosome 14, has been mapped to chromosome 14q31-32.3,[5] and is organized in three noncoding (Ia, Ib, and Ic) exons and four (II, III, IV, and V) coding exons.[6] Recently, it was reported that AAT resides within a cluster of 11 different serpin genes within the 14q32.1 region, including two novel α_1-anti-

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proteinase–like gene sequences, a kallistatin-like sequence, and two recently identified serpins that had not been mapped previously to 14q32.1.[7]

AAT is produced mainly by hepatocytes and secreted into the blood where it acts as a circulating serine protease inhibitor (PI) whose principal substrate is neutrophil elastase (NE).[8] The normal gene is designated PIM, and about 100 normal and defective genetic variants are recognizable by isoelectric focusing (IEF).[9] The two most frequent deficient alleles are PIS, which expresses approximately 50% to 60% of AAT, and PIZ, which expresses approximately 10% to 20% of AAT.[5,10–12] In clinical practice, most (95%) of AAT Deficiency–related diseases are linked with PIZZ phenotype.

AAT Deficiency is a heritable autosomal recessive metabolic disease that results in the synthesis and secretion of a defective AAT. Some of abnormal AAT is retained as pathologic polymers within the endoplasmic reticulum of the hepatocytes, resulting in a low plasma concentration. This deficit is usually insufficient to ensure lifetime protection of the lung from the proteolytic damage of NE, resulting in early onset of panlobular pulmonary emphysema in adults, especially in habitual tobacco smokers.[13–15] In addition, this deficit also can result in the development of neonatal cholestasis that may progress to infant and juvenile cirrhosis. It also can result in slowly progressive liver disease in up to 40% to 50% of the adults due to a pathologic aggregation of abnormal AAT polymers in hepatocytes.[16,17] AAT Deficiency is also suspected to promote asthma,[18] bronchiectasis,[19] systemic vasculitis,[20] relapsing panniculitis,[21,22] and lung and liver cancer.[23] In addition, other diseases such as rheumatoid arthritis,[24] intracranial arterial dissections,[25] multiple sclerosis,[26] and other diseases have been suspected to be related to AAT Deficiency. Although some published reviews indicate that both carriers and deficiency allele combinations for the PIS and PIZ defective alleles (namely PIMS, PIMZ, PISS, PISZ, and PIZZ phenotypes) are at risk for all of these adverse health effects,[27–46] clear scientific evidence of the relationship among AAT Deficiency and some of these diseases listed above remains to be established.[2]. Although all five phenotypic classes of carriers (PIMS and PIMZ) and the deficiency allele combinations (PISS, PISZ, and PIZZ) are suspected to predispose subjects to a variety of other adverse health effects, the only definitive evidence for lung and liver disease and cancer, however, is with the PIMZ, PISZ, and PIZZ phenotypes with the level of risk being much higher in the latter phenotypic class.[2]

It has already been acknowledged that knowledge of AAT Deficiency prevalence in every community is essential for enhancing awareness of this disorder among healthcare givers and the general public.[9] It also important due to unique sensitivity AAT Deficiency imparts for the adverse health effects associated with exposure to environmental biological, chemical, and particulate agents.[47] All of this information is critical for planning health policy and financial medical resources, and to their utilization by the scientific community, governments, and the pharmaceutical industry.

For indigenous populations, and other residents resulting from admixture with early European settlers, living in these twelve Sub-Sahara countries as well as immigrants from these countries now residing in Europe and the New World, it is important to realize that some individuals are at risk for AAT Deficiency.

The present article focuses on the prevalences of the two major deficiency alleles PIS and PIZ and numbers of carriers (PIMS and PIMZ) and deficiency allele combinations (PISS, PISZ, and PIZZ) at risk for AAT Deficiency in each country. The implications of these data for screening and detection programs for AAT Deficiency on Black populations in Sub-Sahara African countries and in Europe and the New World are discussed.

MATERIALS AND METHODS

Definition of the term "Black"

Only in South Africa are the populations cited as Blacks, Coloreds (resulting from admixture and intermarriage with early European settlers), and Whites. In all other Sub-Sahara African countries, the term "Black" applies to various racial subgroups ranging from indigenous tribal Blacks as well as those that have resulted from admixture with early Arab and European traders and settlers. The term "Black" is also used for immigrants from these twelve countries to Europe and the New World and also includes those whose genome may be more Arab or European in content than indigenous Sub-Sahara African Black.

Sources of the control cohort data used in the present study

The articles used in the present study were obtained through a variety of sources and have been discussed in earlier publications.[1,48,49] In many cases, the studies reported were performed by the same investigators using the same phenotyping techniques as were used in comparable studies on control cohort populations in various countries in Europe.

Estimating allele frequencies of PIM, PIS, and PIZ

The formulas developed by Dr. Bustillo for developing estimates of the allele frequencies and 95% confidence intervals were discussed in an earlier article.[49]

Development of a "Precision Factor Score" of statistical reliability for each control cohort

To assess the statistical reliability of each survey, we have developed a new statistical approach to calculate the coefficient of variation (cv) for PIS and PIZ frequencies in each control cohort as discussed in an earlier publication.[48] The reliability of a PFS value depends both on the magnitude of 95% Confidence Interval (which is closely related to the sample size), and also to the PIS and PIZ frequencies found.

RESULTS

Overview

A total of 24 cohorts, having a total of 4718 individuals, have been collected from database searches on each of these 12 countries in Sub-Sahara Africa. These 24 are distributed as follows: one each from Angola, Botswana, Cameroon, Democratic Republic of the Congo, Gambia, Mali, Mozambique, and Somalia; two each from Namibia and the Republic of the Congo; three from Nigeria; and nine from the Republic of South Africa. The individual control cohort database for each of the 12 countries is given in Tables 1 through 5. Summary data of the prevalence of each of the five phenotypic classes for 12 countries are showed in Tables 6, and the estimates of the numbers in each of the five phenotypic classes are given for four of the countries in Table 7.

Angola, Botswana, Cameroon, Democratic Republic of the Congo, Gambia, Mali, Mozambique, and Somalia

Only a single cohort exists for each of these eight countries with the size of individual cohorts ranging from 88 for Botswana to 701 for Gambia as shown in Table 1. In addition, the PF Score means vary from 1.4 for Botswana to 11.2 for Gambia as a direct reflection of the difference in the size of the individual cohorts.

The detailed presentation on the characteristics of the type of population studied, the ethnic subgroup, the method of phenotypic analysis, and the deficiency allele frequencies for PIS and PIZ with 95% confidence intervals is given in Table 1.

For Botswana, the calculated total prevalence was 1 in 11.5 individuals, with none for phenotype PIMZ, none for PISZ, and none for PIZZ. The total number of carriers and deficiency phenotypes was 136,523, with 0 PIMZ, 0 PISZ, and 0 PIZZ. The remaining 136,523 AAT Deficiency phenotypes (100%) were PIMS and PISS not currently considered at risk.

For Gambia, the calculated total prevalence was zero, with none for phenotype PIMZ, none for phenotype PIZZ, and none for phenotype PIZZ. The total number of carriers and deficiency phenotypes was zero in a total population of 1,501,050, with none for phenotype PIMZ, none for phenotype PISZ, and none for phenotype PIZZ. None of the remaining AAT Deficiency phenotypes (0%) were PIMS and PISS not currently considered at risk.

Namibia, Nigeria, and the Republic of Congo

There are two cohorts for Namibia, three for Nigeria, and two for the Republic of the Congo ranging from 60 for Namibia to 350 for Nigeria as shown in Table 2. In addition, the PF Score means vary from 1.3 for Namibia to 3 for Nigeria as a

Table 1.
Gene frequencies of PIZ and PIZ (per 1000) and prevalence of Pi phenotypes MM, MS, MZ, SS, SZ and ZZ in 8 control cohorts in Angola, Botswana, Democratic Republic of the Congo, Gambia, Mali, Mozambique, and Somalia

Author, year, reference	Region, ethnic subgroup	No., type, method, PF Score	Allele frequency (per 1,000)		Calculated prevalence of PI phenotypes 1/× (Hardy-Weinberg Equilibrium statistics)					
			PIS	PIZ	MM	MS	MZ	SS	SZ	ZZ
Angola[50]	Southern Angola, Sekele	101, HUP, IEF, 1.6	188 (138–250)	0 (0–18)	1.5	3.3 2–5)	$>1 \times 10^6$	28 (18–52)	$>1 \times 10^6$	$>1 \times 10^6$
Botswana[50]	Ngwato, General population	88, HUP, IEF, 1.4	45 (21–91)	0 (0–21)	1.2	12 (6–27)	$>1 \times 10^6$	484 (121–2,207)	$>1 \times 10^6$	$>1 \times 10^6$
Cameroon[67]	Tikar, General population	266, HUP, IEF, 4.3	5.6 (1.5–17.8)	0 (0–7)	1	89 (28–349)	$>1 \times 10^6$	31,447 (3,149–470,761)	$>1 \times 10^6$	$>1 \times 10^6$
Democratic Republic of the Congo[68]	Bantu	132, HUP, CAAE, 2.1	0 (0–14)	0 (0–14)	1	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$
Gambia[69]	West Kiang District, Keneba Mandinka Blacks	701, HUP, IEF, 11.2	0 (0–3)	0 (0–3)	1	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$
Mali[53]	Bani-Niger Region, Bozo Blacks	102, HUP, IEF, 1.6	0 (0–18)	10 (2–39)	1	$>1 \times 10^6$	52	$>1 \times 10^6$	$>1 \times 10^6$	10,404
Mozambique[54]	Blacks	274, HUP, CAAE, 4.4	2 (0–12)	0 (0–7)	1	$>1 \times 10^6$	275	300,304	$>1 \times 10^6$	$>1 \times 10^6$
Somalia[57]	Mogadishu, Blacks	347, HUP, IEF, 3.5	17 (9–31)	12 (5–24)	1	30	45	3,345	2,509	7,526

No., Number of subjects; Type: HUP, Healthy unrelated persons (includes blood donors, workers, controls, subjects not clearly specified, etc); Method: IEF, isoelectrofocusing; CAAE, crossed antigen-antibody electrophoresis; PF Score, Precision factor score.

Table 2.
Gene frequencies of PIZ and PIZ (per 1000) and prevalence of PI phenotypes MM, MS, MZ, SS, SZ, and ZZ in five control cohorts in Namibia, Nigeria, and Republic of the Congo

Author, year, reference	Region, ethnic subgroup	No., type, method, PF Score	Allele frequency (per 1000)		Calculated prevalence of PI phenotypes 1/× (Hardy-Weinberg Equilibrium statistics)					
			PIS	PIZ	MM	MS	MZ	SS	SZ	ZZ
Namibia										
50	Kung, Blacks	97, HUP, CAAE, 1.6	216 (162–282)	0 (0–19)	1.63	3	$>1 \times 10^6$	21	$>1 \times 10^6$	$>1 \times 10^6$
50	Dama, Blacks	60, HUP, CAAE, 1.0	33 (11–88)	0 (0–30)	1.07	16	$>1 \times 10^6$	900	$>1 \times 10^6$	$>1 \times 10^6$
Nigeria										
70	Blacks	114, HUP, IEF, 1.8	0 (0–16)	0 (0–16)	1.00	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$
55	Blacks	100, HUP, IEF, 1.6	0 (0–18)	5 (0–32)	1.01	$>1 \times 10^6$	101	$>1 \times 10^6$	$>1 \times 10^6$	40,000
71	Blacks	350, HUP, IEF, 3	103	4	1.25	5	131	95	1,134	54,444
Republic of the Congo										
72	Covette area, Beti and Bateke	164, HUP, IEF, 1.4	0 (0–21)	0 (0–21)	1.00	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$
72	Pool area, Bateke and Babenga	73, HUP, IEF, 0.6	39 (10–118)	0 (0–47)	1.08	13	$>1 \times 10^6$	642	$>1 \times 10^6$	$>1 \times 10^6$

No., Number of subjects; Type: HUP, Healthy unrelated persons (includes blood donors, workers, controls, subjects not clearly specified, etc); Method: IEF, isoelectrofocusing; CAAE, crossed antigen-antibody electrophoresis; PF Score, Precision factor score.

direct reflection of the difference in the size of the individual cohorts of 157 for Namibia and 1128 for Nigeria.

The detailed presentation on the characteristics of the type of population studied, the ethnic subgroup, the method of phenotypic analysis, and the deficiency allele frequencies for PIS and PIZ with 95% confidence intervals is given in Table 2.

For Namibia, the calculated total prevalence was 1 in 3.7 individuals, with none for phenotype PIMZ, none for phenotype PISZ, and none for phenotype PIZZ. The total number of carriers and deficiency phenotypes was 523,364, with none for phenotype PIMZ, none for phenotype PISZ, and none for phenotype PIZZ. The remaining 523,364 AAT Deficiency phenotypes (100%) were PIMS and PISS not currently considered at risk.

For Nigeria, the calculated total prevalence was 1 in 8.4 individuals, with 1 in 167 for phenotype PIMZ, 1 in 2,209 of PISZ and 1 in 79,524 of PIZZ. The total number of carriers and deficiency phenotypes was 15,849,672, with 802,206 PIMZ, 60,607 PISZ, and 1,684 PIZZ. The remaining 14,985,175 AAT Deficiency phenotypes (94.5%) were PIMS and PISS not currently considered at risk.

For the Republic of the Congo, the calculated total prevalence was 1 in 59.5 individuals, with none of phenotype PIMZ, one in none of phenotype PIZZ, and none of phenotype PIZZ. The total number of carriers and deficiency phenotypes was 49,651, with none of phenotype PIMZ, none of phenotype PISZ, and none of phenotype PIZZ. The remaining 49,651 AAT Deficiency phenotypes (100%) were PIMS and PISS not currently considered at risk.

Republic of South Africa

A total of 11 cohorts exist for the Republic of South Africa with a total sample size of 1254 and a mean PF Score of 2.2. The results for each of the four major racial subgroups (Blacks, Whites, Coloreds, and Indians) described by the authors[50,51] are shown in Table 3. The data represent studies on five different indigenous Blacks: Zulu, Xhos, Tswana, Ndebele, and Venda tribes,[50] and the Pedi tribe.[51] Two of the other three ethnic subgroups were Coloreds and Whites from Pretoria,[51] and Indians with no data reported, and with estimates based on studies on this same population in India.[52]

The detailed presentation on the characteristics of the type of population studied, the ethnic subgroup, the method of phenotypic analysis, and the deficiency allele frequencies for PIS and PIZ with 95% confidence intervals is given in Table 3.

The number of individuals studied was 1,254 in a total population of 42,768,678 inhabitants. The four major ethnic subgroups

Table 3.
Gene frequencies of PIZ and PIZ (per 1000) and prevalence of PI phenotypes MM, MS, MZ, SS, SZ, and ZZ in 11 control cohorts in the Republic of South Africa

Author, year, reference	Region, ethnic subgroup	No., type, method, PF Score	Allele frequency (per 1000)		Calculated prevalence of PI phenotypes 1/× (Hardy-Weinberg Equilibrium statistics)					
			PIS	PIZ	MM	MS	MZ	SS	SZ	ZZ
Blacks										
50	Zulu	88, HUP, IEF, 1.4	80 (46–132)	0 (0–21)	1.18	7	$>1 \times 10^6$	158	$>1 \times 10^6$	$>1 \times 10^6$
50	Xhosa	164, HUP, IEF, 2.6	34 (18–61)	0 (0–11)	1.12	16	$>1 \times 10^6$	889	$>1 \times 10^6$	$>1 \times 10^6$
50	Tswana	119, HUP, IEF, 1.9	80 (50–124)	0 (0–15)	1.19	7	$>1 \times 10^6$	157	$>1 \times 10^6$	$>1 \times 10^6$
50	Ndebele	61, HUP, IEF, 1	33 (11–87)	0 (0–30)	1.09	16	$>1 \times 10^6$	930	$>1 \times 10^6$	$>1 \times 10^6$
50	Venda	173, HUP, IEF, 2.8	14 (5–35)	0 (0–11)	1.04	35	$>1 \times 10^6$	4,789	$>1 \times 10^6$	$>1 \times 10^6$
51	Pedi	127, HUP, 1 IEF✲1.	4 (0–25)	12 (3–37)	1.15	136	136	64,516	32,258	64,516
Coloreds										
51	Pretoria, coloreds	100, HUP, 6 IEF, 2.	45 (22–86)	20 (6–54)	1.19	12	27	494	556	2,500
Whites										
50	Johnnesburg, Whites	102, HUP, IEF, 2.4	49 (25–91)	15 (4–46)	1.14	11	36	416	694	4,624
51	Pretoria, Whites	320, HUP, IEF, 5.1	34 (22–52)	23 (14–39)	1.13	15	23	846	621	1,820
Indians										
52	Parojas	100, HUP, IEF, 1.6	0 (0–18)	0 (0–18)	1.04	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$
52	Binjhals	105, HUP, IEF, 1.7	0 (0–17)	0 (0–17)	1.09	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$	$>1 \times 10^6$

No., Number of subjects; Type: HUP, Healthy unrelated persons (includes blood donors, workers, controls, subjects not clearly specified, etc); Method: IEF, isoelectrofocusing; PF Score, Precision factor score.

consisted of Blacks with a total population of 32,162,046, Whites with a total population of 5,8916,540, Coloreds with a total population of 3,678,106, and Indians with a total population of 1,111,986. The total numbers in each of these four major subgroups was used to develop weighted mean values for the whole country as presented in Tables 4, 5, and 6.

For the Republic of South Africa total population (Table 4), the calculated total prevalence was 1 in 13 individuals, with 1 in 180 for phenotype PIMZ, 1 in 4,613 for phenotype PISZ, and 1 in 119,061 for phenotype PIZZ. The total number of carriers and deficiency phenotypes (Table 5) was 3,444,340, with 406,910 for phenotype PIMZ, 17,649 for phenotype PISZ, and 4,132 for phenotype PIZZ. The remaining 3,015,649 AAT Deficiency phenotypes (87.6%) were PIMS and PISS not currently considered at risk.

DISCUSSION

Overview

A total of 24 cohorts, having a total of 4718 individuals, have been collected from database searches on each of these 12 Sub-Sahara African countries. The tabulation in Table 4 demonstrates that both the PIS and PIZ alleles are found in Nigeria, Republic of South Africa, and Somalia. In addition, the PIS allele was found Angola, Botswana, Cameroon, Mozambique, Namibia, and the Republic of Congo. It is also of interest that only the PIZ allele was found in Mali.[53] This tabulation demonstrates, however, very striking differences among the prevalences of carriers and deficiency allele combinations for PIS and PIZ within Sub-Sahara Africa, ranging from 2 per 1000 for Mozambique[54] to 188 per 1000[50] for Angola for PIS, and 4 per 1000[55,56] in Nigeria to 12 per 1000[57] for Somalia for PIZ.

Origin of the PIS and PIZ alleles in 9 of the 12 Central and South African countries

The history of each of the 12 countries under discussion can be readily found in various encyclopedias (e.g., http://www.nationmaster.com). Most of these countries were colonized by groups of Europeans from various countries starting as early, for example, as in the year 1482 with the Portuguese colonization of northern Angola. This colonization included the pur-

Table 4.
Data summaries of PIZ and PIZ gene frequencies and prevalence of PI phenotypes for carriers and deficiency allele combinations with 95% CI in each of the 12 Sub-Sahara countries in Africa

	Allele frequency		Calculated prevalence of Pi phenotypes: 1/× (Hardy-Weinberg Equilibrium statistics)					
Country	PIS × 1000	PIZ × 1000	MS	MZ	SS	SZ	ZZ	Total
Angola	188	0	3	0	28	0	0	3
	(138–250)	(0–18)	(2–5)	(0–32)	(16–52)	(0–110)	(0–3,054)	(3–3)
Botswana	45	0	12	0	484	0	0	12
	(21–91)	(0–21)	(6–27)	(0–25)	(121–2,207)	(0–266)	(0–2,324)	(12–12)
Cameroon	6	0	89	0	31,447	0	0	89
	(1–18)	(0–7)	(28–349)	(0–72)	3,149–470,761)	(0–4,060)	(0–20,943)	(89–89)
Democratic Republic of the Congo	0 (0–999)	0 (0–36)	0 (0–36)	0 (0–36)	0 (0–5,194)	0 (0–2,597)	0 (0–5,194)	0 (0–15 × 10^6)
Gambia	0	0	0	0	0	0	0	<0.001
	(0–3)	(0–3)	(0–190)	(0–190)	(0–144,827)	(0–72,414)	(0–144,827)	(0–406,913)
Mali	0	10	0	52	0	0	10,404	51
	(0–18)	(2–39)	(0–28)	(13–306)	(0–3, 114)	(0–720)	(667–346,064)	(51–51)
Mozambique	18	0	275	0	300,304	0	0	274
	(0–12)	(0–7)	(43–5,311)	(0–75)	(7,224–110 × 10^6)	(0–6,334)	(0–22,217)	(272–26)
Namibia	147	0	4	0	47	<0.001	0	4
	(110–192)	(0–12)	(3–6)	(0–48)	(27–82)	(0–223)	(0–7,331)	(4–4)
Nigeria	64	3.6	9	167	245	2,209	79,524	8
	(51–80)	(1–10)	(7–12)	(59–535)	(156–391)	(643–8,695)	(10,600–774,253)	(8–9)
Republic of the Congo	8 (3–23)	0.0 (0–8)	60 (22–189)	0 (0–65)	14,042 (1,893–136,500)	0 (0–2,806)	0 (0–16,640)	60 (59–60)
Republic of South Africa (Blacks)	37 (28–48)	1 (0–4)	14 (11–19)	774 (118–15,044)	735 (439–1,268)	19,845 (2,345–499,375)	2,143,296 (51,086–786 × 10^6	14 (14–14)
Republic of South Africa (Whites)	38 (26–54)	21 (13–34)	14 (10–21)	25 (15–42)	696 (347–1,425)	618 (272–1,444)	2,199 (856–5,852)	9 (9–9)
Republic of South Africa (Coloreds)	45 (22–86)	20 (6–54)	12 (6–26)	27 (10–90)	494 (134–2,044)	556 (108–3,518)	2,500 (346–24,218)	8 (8–8)
Republic of South Africa (Indians)	0 (0–9)	0 (0–9)	0 (0–57)	0 (0–57)	0 (0–12,465)	0 (0–6,232)	0 (0–12,465)	0 (0–301,443)
Republic of South Africa (Total)	37 (28–50)	3 (1–8)	14 (14–14)	180 (178–182)	715 (400–1,296)	4,613 (185–21,101)	119,061 (14,065–1 × 10^6)	13 (13–13)
Somalia	17	12	30	45	3,345	2,509	7,526	18
	(9–31)	(5–24)	(16–56)	(22–97)	(1,048–11,333)	(688–9,913)	(1,807–34,682)	(18–18)

chase from African chiefs of people to work on sugar plantations, etc., in the New World, setting up what evolved into a slave trade involving the local Black population. By the 19th century, Angola was the largest source of slaves for the Americas, including the United States. A logical consequence of this transport could have been the introduction of the PIS allele into the Black population found in the New World!

The history of each of the other eight countries where either the PIZ or the PIZ, or both deficiency alleles, were found in recent genetic epidemiological studies is clouded with the arrival and settlement of these countries either by Arab or European traders and settlers. It is not difficult to imagine that this influx of the defective PIS and PIZ alleles, particularly from the European gene pool, could account for some portion of the prevalences of these deficiency alleles in the general populations in each of these countries. In the latter cases, the term "Black" may well be used for inhabitants resulting from admixture with other non-Black groups from other North African Arab or African countries or from early European settlers from Portugal, Great Britain, France (Huguenots), and the Nether-

Table 5.
Summaries of the estimates of the numbers of carriers and deficiency allele combinations of PIZ and PIZ in the Republic of South Africa

Country	Total population	Calculated numbers[a] of carriers and deficiency allele combinations at risk			Calculated numbers[a] of carriers and deficiency allele combinations for PIS		Total numbers of PIS and PIZ phenotypes
		MZ	SZ	ZZ	MS	SS	
Republic of South Africa (Blacks)	32,162,046	41,536	1,621	15	2,242,959	43,757	2,329,888
Republic of South Africa (Whites)	5,816,540	230,755	9,407	2,646	410,232	8,361	661,401
Republic of South Africa (Coloreds)	3,678,106	134,619	6,621	1,471	302,892	7,448	453,051
Republic of South Africa (Indians)	1,111,986	0	0	0	0	0	0
Republic of South Africa (Weighted means)	42,768,678	237,907	17,649	359	3,070,103	59,820	3,377,460

[a]Hardy-Weinberg Equilibrium statistics

Table 6.
Summaries of the estimates of the numbers of carriers and deficiency allele combinations of PIZ and PIZ in four countries in sub-Sahara Africa

Country	Total population	Calculated numbers[a] of carriers and deficiency allele combinations at risk			Calculated numbers[a] of carriers and deficiency allele combinations for PIS		Total number of PIS and PIZ phenotypes
		MZ	SZ	ZZ	MS	SS	
Mali	11,626,219	225,730	0	1,117	0	0	226,848
Nigeria	123,337,822	739,028	55,834	1,551	13,302,506	502,508	14,601,428
Republic of South Africa	42,768,678	237,907	17,649	359	3,070,103	59,820	3,377,460
Somalia	8,025,190	179,687	3,199	1,066	269,530	2,399	455,892
Total	185,757,909	1,382,352	76,682	4,093	16,642,139	564,727	18,661,628

[a]Hardy-Weinberg Equilibrium statistics

Table 7.
Environmental agent exposures that may be hazardous to patients with AAT Deficiency

Environmental Hazard	Occupation
Liquid and solid chemicals	Beauticians, chemical plant workers, gas station attendants, painters
Toxic fumes and gases	Airport personnel, bus, cab, and truck drivers, fumigators, dry cleaners, factory workers, indigenous tribal members, industrial and household cleaning personnel, manicurists, welders
Organic wastes and/or particulates	Agricultural workers, dental workers, farmers, miners, textile workers, indigenous tribal members
Pathogens	Physicians, dentists, teachers, nurses and other health care personnel, sales personnel, restaurant and hotel wait staffs

Adapted from ref. 47.

lands. During the 18th century, for example, admixture and intermarriage between Khoikhoi slaves and European settlers in the Republic of South Africa began to create what became later known as the "Colored" population in that country.

The introduction of the Arab and European gene pools into Sub-Sahara Africa, however, does not appear to provide an adequate explanation for the presence of the PIZ deficiency allele in the Bani-Niger Region indigenous Bozo Blacks in Mali. In addition, this explanation is inadequate to account for the presence of the PIS deficiency allele in the indigenous Kung and Dama Blacks in Namibia, the indigenous Zulu, Xhosa, Tswana, Ndebele, Venda, and Pedi Blacks in the Republic of South Africa, and the indigenous Bateke and Babenga Blacks in the Republic of the Congo. It appears that if admixture resulting from contact with European settlers occurred in these indigenous African tribal cultures that it was rare or did not occur at all (e.g., see http://www.nationmaster.com).

Consideration should be given to the possibility that these deficiency alleles may have had a completely different mode of origin in each of these indigenous and distinct Black tribal cultures. It is also possible that the codons that gave rise to each of these deficiency alleles in the AAT gene have high spontaneous mutation rates and that the deficiency alleles in these different African populations are the result of independent spontaneous mutations during the course of their ancient and independent histories.

Estimates of the size of the Black populations at risk for AAT Deficiency

Beyond the estimate of 1.4 million Blacks at risk for AAT Deficiency given in Table 6 for Mali, Nigeria, Republic of South Africa, and Somalia, it is possible to estimate the sizes of the Black populations, for example, in North America. The Black

population in the United States of America is estimated at 36 million,[49] and that of the Black and a mixed population in Canada could be as high as 10 million (http://www.nationmaster.com). Comparable data on the number of Blacks and a mixed population in England and various countries on the continent would certainly increase this combined number to something > 70 million. Such estimates are important for the recognition of these populations as being at risk for AAT Deficiency when they present, for example, with allergies, asthma, and/or COPD so that physicians in general practice, and particularly pulmonary physicians, will order a test for AAT Deficiency.

We present these data and this analysis with the intention of modifying the standard of practice for the detection and treatment of AAT Deficiency[2] to include populations that have not been considered at risk in the past.[9] It is becoming clear not only for the White populations, but also the "Black" populations of various countries in Europe and the New World, that AAT Deficiency is not a rare disease, but one that is rarely diagnosed.[47]

Limitations of the present genetic epidemiological database

The most important aspect of these tabulations was the evidence for significantly high frequencies of the PIZ allele in the Bozo Black population of Mali (10 per 1000),[53] the less defined Black populations of Nigeria (3.6 per 1000),[55,56] the Blacks in Somalia (12 per 1000),[57] as well as in the Black (1 per 1000) and Colored (20 per 1000) populations of the Republic of South Africa.[51]

It is noteworthy, however, that for many of these countries, many have only a single cohort with a small number of subjects. Because the database for some of these countries was limited both in the number of cohorts and in their size, caution must be exercised with regard to the values of the PIZ and PIZ alleles in these areas. These countries were included in the overall tabulation of Sub-Sahara Africa, however, as a demonstration of the need for further and more comprehensive genetic epidemiological studies.

Adverse health effects of the deficiency alleles PIS and PIZ

There is not general acceptance of the adverse health effects associated with the PIZ deficiency allele as indicted in the ATS/ERS Standards document.[2] As a result, we have treated the PIMS and PISS phenotypic classes as "not currently considered at risk." However, recent review articles[27,35] and research articles[58,59] provide documentation that both carriers (PIMS and PIMZ) and deficiency allele combinations (PISS, PISZ, and PIZZ) may be at risk for various adverse health effects.

The adverse health effects associated with being a carrier of the PIS deficiency allele were reviewed in 1989,[35] and they included cirrhosis,[39] multiple sclerosis,[26] chronic "cryptogenic" liver disease,[30] and malignant hepatoma.[30] In addition, there are more recent reports that the PIMS phenotype can be associated with hepatic dysfunction during the first 6 months of life[41] to cryptogenic cirrhosis between ages 1 month and 18 years,[43] and intracranial arterial dissections.[25]

In other publications, PIMZ carriers were found to be more prone to the development of COPD[42] and to chronic liver failure in adults.[44] In addition, carriers for both defective alleles have been found to be at risk for the development of asthma[31] and to alcoholic toxic cirrhosis.[60] The fact that carriers for various metabolic diseases such as early vascular disease in homocystinuria, hyperammonemic episodes in ornithine transcarbamylase deficiency, presenile cataracts in galactosemia, etc.,[61] as well as for AAT Deficiency,[27,35] are at risk for adverse health effects has been well documented.

New research initiatives are needed to gain a better understanding of the differences in the adverse health effects associated with the same five phenotypic classes of AAT Deficiency in different individuals associated with the two most prevalent deficiency alleles PIS and PIZ. Equally important is the need to investigate any differences associated with the expression of this genetic disease in different racial subgroups. Such an approach may well resolve apparent differences in the adverse health effects reported in the medical literature on each of the five phenotypic classes of the PIS and PIZ deficiency alleles. These issues are particularly important for the Black and Colored populations identified as carriers of the PIS deficiency allele in the present study as well as the more adverse health effect–documented PIZ deficiency allele.

Environmental health issues relating to AAT Deficiency in Black populations

Cigarette smoking is the greatest health hazard for residents of South Africa with a smoking prevalence, for example, of 49% among Coloreds, followed by Whites and Indians (at 37% and 28%, respectively), and Blacks at 23%.[73] The unique susceptibility of AAT Deficiency for chronic obstructive pulmonary disease (COPD) was demonstrated in 1986[42] and was conformed in a series of studies demonstrating that cigarette smoking was a risk factor for FEV_1 decline and emphysema.[14,62–64] Occupational exposures of concern may include a variety of work situations that expose workers with AAT Deficiency to hazardous agents. In Sub-Sahara Africa, of equal concern is the smoke from wood burning fires used for cooking and heating by members of indigenous African tribes. Relatively undocumented in the peer-reviewed medical literature is concern for those affected by AAT Deficiency for exposure to various hazardous biological, chemical, and particulate environmental agents.[58,65] Such agents could include liquid and solid chemical substances, toxic fumes and gases, organic wastes and particulates, and viral and bacterial pathogens.[47] Worker groups known to be exposed to such agents are given in Table 7. The collection of detailed information on occupation personal lifestyle activities is critical for the effective management of individuals with AAT Deficiency. In addition, the role of polymorphisms in the human genome in modifying the effects of environmental exposures to toxic agents has been discussed in a recent review in a broader context.[66]

CONCLUSIONS

Despite the previously mentioned limitations, the development of the present database demonstrates that a large number of individuals are at risk for adverse health effects related to AAT Deficiency in 9 of the 12 countries in Central and South Africa: Angola, Botswana, Mali, Mozambique, Namibia, Nigeria, Republic of South Africa, Republic of the Congo, and Somalia. There are many geographic areas in each of these 12 countries where there is a total lack of genetic epidemiological data providing an opportunity for the development of studies in the general population in those unexplored regions.

Using the information on the total populations in 4 of these 12 countries and the estimates of the gene frequencies for PIM, PIS, and PIZ, it is possible to estimate the numbers of carriers and deficiency allele combinations for only 4 of the 12 countries as tabulated in Table 6. This analysis suggests that a total of 18,651,358 individuals are at risk for adverse effects of AAT Deficiency in the total population of 170,988,205 for these four countries. It is important to note, however, that the predominant phenotype in each of these four countries is PIMS, and that the only definitive evidence for lung and liver disease is with the PIMZ, PISZ, and PIZZ phenotypes with the level of risk being highest in the latter phenotypic class.

Application of the "Standards for the diagnosis and management of individuals with α_1 antitrypsin deficiency" in Sub-Sahara Africa

Despite the previously mentioned limitations, the development of the present database demonstrates that a large number of individuals are at risk for adverse health effects related to AAT Deficiency in Sub-Sahara Africa with the highest risk for residents of Angola, Namibia, Nigeria, Republic of South Africa, and Somalia where prevalence of AAT Deficiency is high. There are, however, many geographic areas in each of these five countries where there is a total lack of genetic epidemiological data, providing an opportunity for the development of studies in the general population in those unexplored regions

Our data on indigenous populations in Central and South Africa, although limited in size, demonstrate that it is important that those non-Whites who present with allergies, asthma, and/or chronic bronchitis be tested for AAT Deficiency. This is important for indigenous populations in their home countries as well as those who have emigrated both to Europe and to various countries in the New World. In some countries in Europe and the New World there is no category of "Coloreds" and all individuals of African ancestry are classified as "Black" however light their skin color and lack of typical African features.

Many of these individuals in Sub-Sahara Africa have resulted from admixture and intermarriage with early settlers from the British Isles and all of the four countries in Southern Europe in Sub-Sahara Africa. In each of these situations, this mingling of the African, White, Arab, and Hispanic gene pools has resulted in the transfer of high prevalences for both of deficiency alleles PIS and PIZ into these original Sub-Sahara African populations when immigrants from the countries settled in Europe and the New World. This new class of Blacks in Europe and the New World can be found in every occupational category ranging from the most unskilled to the most highly skilled professions. Thus, the present database impacts the practical application of standard of care, diagnosis, and treatment[2] of AAT Deficiency not only for residents of each of these sub-Sahara African countries but also for immigrants in various countries in Europe and in the New World.

Because the presence of both PIS and PIZ in indigenous populations in Sub-Sahara African countries will affect the application of the American Thoracic Society/European Respiratory Society Statement "Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency,"[2] more extensive and comprehensive genetic epidemiological studies in these 12 countries as well as others in these regions of Africa should be both encouraged and supported.[67–72]

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