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Estimated numbers and prevalence of PI*S and PI*Z deficiency alleles of α_1-antitrypsin deficiency in Asia

F.J. de Serres*, I. Blanco# and E. Fernández-Bustillo¶

ABSTRACT: The current study focuses on updating estimates of the numbers of individuals carrying the two most common deficiency alleles, protease inhibitor (PI)*S and PI*Z, for α_1-antitrypsin deficiency (AT-D) in 20 Asian countries.

A total of 170 cohorts with 31,177 individuals were selected from 20 Asian countries. The total AT-D populations in the countries selected were: 7,264 ZZ; 36,754 SZ; 6,672,479 MZ; 46,492 SS; and 16,881,108 MS. Marked differences among the Asian countries and regions were also found for the prevalence of the deficiency alleles PI*S and PI*Z. These numbers demonstrate that AT-D is not just a genetic disease that affects smaller numbers than various countries, for example, in Europe.

There were marked differences between the prevalence of the PI*S and PI*Z deficiency alleles among these 20 Asian countries as well as among the countries within a given geographic region in Asia. The largest numbers of ZZ phenotypes (3,000–14,000) were in Afghanistan, Pakistan, Saudi Arabia and Thailand; with <1,700 in each of the remaining countries.

KEYWORDS: α_1-Antitrypsin deficiency, α_1-protease, α_1-protease inhibitor, genetic epidemiology, protease inhibitor phenotypes

Although α_1-antitrypsin deficiency (AT-D) is, as a whole, one of the most common hereditary disorders worldwide, AT-D prevalence varies markedly from one country to another [1–4] and affects many different racial subgroups. AT-D can also vary markedly within a given country as illustrated by the differences in the prevalence of protease inhibitor (PI)*S and PI*Z within 14 of the 20 regions in Italy [5]. α_1-Antitrypsin (AT) is the most prevalent proteases inhibitor in human serum, mainly secreted by hepatocytes. The AT gene is highly pleomorphic with ~100 alleles identified to date. Variants are classified according to the PI system, by means of isoelectrofocusing (IEF). Variants that confer an increased risk for developing diseases are those in which deficiency or null alleles are combined in homozygous or heterozygous states that encode plasma AT concentrations of <60%. The majority of a given population has the PI*MM phenotype, which expresses normal serum AT levels. The two most common allelic variants that produce AT-D are PI*Z and PI*S. The range of serum levels of AT, according to phenotype (measured using the purified standard used in the USA Registry), are: PI*MM 20–48 μM; PI*MZ 17–33 μM; PI*SS 15–33 μM; PI*SZ 8–16 μM, and PI*ZZ 2.5–7 μM. It is believed that a level of <11 μM is associated with an increased risk for pulmonary emphysema [6–8].

Most pathology related to AT-D is linked to the Z allele, and in clinical practice 96% of patients have a ZZ phenotype [1, 9, 10]. The remaining 4% mostly belonged to SZ, MZ, and to a lesser extent, other rare deficiency or null phenotypes The risk of developing diseases for PI*SS and PI*MS phenotypes has been the topic of longstanding controversy, but no clear evidence on the relationship among these phenotypes and AT-D associated diseases has been established to date [3, 5, 11].

AT-D is not properly a disease, but a predisposition to develop a number of diseases through life, mainly pulmonary emphysema and several types of liver disease in both children and adults [12, 13].

From a public health perspective, knowledge of the AT-D prevalence in every community is essential [14]. The current study specifically attempts to determine the prevalence and number of subjects carrying the most common defective alleles, PI*S and PI*Z, in Asian countries. The present study estimates the total number of ZZ, SZ and MZ individuals in 20 Asian countries, and goes beyond earlier

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publications, in which only the gene frequencies for PI*M, PI*S, and PI*Z were reported for individual cohorts in individual cities or geographic regions [14].

METHODS

Sources of the control cohort data used in the present study

The present study utilises available data from epidemiological studies, performed by others, to determine the frequencies of deficiency allele combinations for PI*S and PI*Z, in healthy control cohorts of individual case studies from 20 Asian countries: Russia, Israel, Jordan, Saudi Arabia, Afghanistan, India, Iran, Kazakhstan, Nepal, Pakistan, Tajikistan, Indonesia, Malaysia, Singapore, Thailand, China, Japan, Mongolia, Philippines and South Korea.

The database for each of these 20 countries, reported in an earlier paper [1], was expanded with the inclusion of the source of each cohort, as well as a series of previously unpublished genetic epidemiological studies in Russia, China, South Korea, Mongolia and Japan by E.V. Balanovska, and O.P. Balanovsky (Russian Academy of Medical Sciences, Research Centre for Medical Genetics, Moscow, Russia). The present study consists of 170 cohorts with a total number of 31,177 subjects. This expansion provides data on many indigenous populations not included in the original paper [1].

The new data consists of the following additional cohorts: 14 for Russia (2,564 subjects); four for China (2,650 additional subjects); one for Japan (1,807 additional subjects); 17 for Mongolia (505 subjects); and three for South Korea (217 additional subjects).

In addition, the cohort size for several countries has been increased as follows: Israel 1,743 to 2,442; Afghanistan 1,078 to 1,785; Indonesia 724 to 1,105; Singapore 385 to 545; China 4,156 to 6,806; Japan 4,203 to 6,010; and South Korea from 326 to 543. Elimination of some cohorts has reduced the total cohort size of Saudi Arabia from 932 to 801, India from 2,796 to 2,295, and Iran from 1,185 to 1,087.

The data from the individual cohorts for a given country were combined to provide mean frequencies for the PI*M, PI*S and PI*Z alleles. These allele frequencies were then used to calculate the total numbers of individuals in each of the five major phenotypic classes of interest (namely, PI*MS, PI*MZ, PI*SS, PI*SZ and PI*ZZ) in the total population of each of these countries and all of Asia.

The formulas for developing estimates of the allele frequencies, gene prevalence, the numbers of deficiency allele combinations and 95% confidence intervals (CI) were discussed in several earlier papers [4]. Gene frequencies have been expressed as the total number of PI*S and PI*Z, whether in homo- or heterozygotes, per 1,000 genes of all PI-types.

The prevalence of every phenotype has been calculated by applying the Hardy-Weinberg equilibrium statistical formula. The data on the number of individuals in different countries was obtained from the World Factbook database [15].

To assess the statistical reliability of each survey, the coefficient of variation (cv) for PI*S and PI*Z frequencies in each control cohort was calculated. The cv provides an estimate of the precision (or better, the imprecision) of results from each survey. The formulas, developed for estimates of numerical precision factor scores (PFS), form a value scale from 0–12 with which to assess the statistical quality in terms of precision (or imprecision) of each selected survey, and are discussed in earlier papers [4]. The PFS assigned to each individual country is the mean of the PFS given to individual cohorts within that country. They can also be considered an indication of the quality of the cohort database in terms of the total cohort size for each of the 20 countries.

Criteria for selection of studies

Selected studies for the present analysis fulfilled the following criteria: 1) AT phenotyping performed by IEF or antigen-antibody crossed electrophoresis; 2) statistical PFS of two or more; and 3) samples representative of the general population.

Criterion 1: laboratory techniques for the phenotypic identification of PI*S and PI*Z deficiency alleles

In most of the selected surveys, phenotypic characterisation was carried out by means of the IEF method. Starch gel electrophoresis method is a less reliable method. The crossed antigen-antibody electrophoresis method technique is an expensive and time consuming method, and although it does produce reliable results, it has gradually been replaced by IEF.

Criterion 2: screening studies

Surveys in which phenotypes were identified by selecting sera with AT serum levels below normal values were omitted because they could give an excessive number of Z alleles. In addition, they could introduce bias due to moderate deficiency phenotypes, such as MS; SS and MZ could express AT serum concentrations over a given cut off value.

Criterion 3: numerical PFS scale for assessing the statistical quality in terms of precision (or imprecision) of each selected survey

As the cv depends on sample size and the PI*S and PI*Z allelic frequencies, cohorts from countries with excessively high PI*S frequencies will give a deceptively higher PFS than others with much lower PI*S frequencies, but similar or higher PI*Z frequencies. Therefore, PFS should be adapted to different regions and countries, by adjusting the PFS rise by PI*S frequencies. For East Asian countries where both PI*S and PI*Z frequencies are very low, a PFS value of two or more was accepted for selection.

Criterion 4: cohort composition

Only the data of the control group cohort phenotypes in each paper (*i.e.* blood donors, workers, healthy unrelated persons, newborns, school or college students, general population selected at random, *etc.*) were used in the present study. Surveys carried out on hospital-based populations or in patients with AT-D related diseases (*i.e.* lung and liver diseases), were omitted because they could give an excessive number of Z deficient alleles. In addition, some studies carried out in small isolated communities with small sample sizes were rejected due to their low PFS.

TABLE 1 Estimates of the protease inhibitor (PI)*S and PI*Z gene frequency and phenotype prevalence of each of the five phenotypic classes in 20 Asian countries

Region/country	Total population	n#	Calculated frequency × 1000		Calculated prevalence¶			Calculated prevalence¶		Total PI*S and PI*Z calculated prevalence¶
			PI*S	PI*Z	PI*MZ	PI*SZ	PI*ZZ	PI*MS	PI* SS	
North Asia										
Russia	43000000+	2564 (2.4)	3.9 (2.5–6.1)	1.6 (0.7–3.2)	325 (158–701)	82,176 (25434–281313)	410881 (97384–1899529)	130 (82–208)	65741 (26570–166646)	92.6 (92.4–92.7)
Middle East Asia										
Israel	6276883	2442 (2.6)	9.4 (7.0–12.7)	0.6 (0.2–2.0)	824 (258–32040)	86426 (20201–451453)	2650384 (261458–39739458)	54 (40–730)	11273 (6243–20519)	50.2 (49.9–50.5)
Jordan	5759732	424 (6.8)	8.3 (3.6–17.7)	6.8 (0.0–4.3)	0 (0.0–116)	0.0 (0–6499)	0 (0–53075)	61 (28–141)	14676 (3183–762340)	60.8 (60.4–61.2)
Saudi Arabia	26417599	801 (3.1)	31.2 (23.5–41.3)	15.0 (9.8–22.6)	36 (23–560)	4456 (1964–10335)	4456 (1964–10335)	17 (13–23)	1027 (587–1813)	11.3 (11.2–11.3)
Central Asia										
Afghanistan	29928987	1785 (2.0)	7.1 (4.7–10.6)	9.9 (7.0–13.9)	51 (36–73)	7121 (3387–15197)	10172 (5159–20296)	72 (48–109)	19937 (8896–45516)	29.7 (29.7–29.8)
India	1080264388	2295 (2.0)	1.5 (0.6–3.3)	0.4 (0.08–1.8)	1164 (288–6749)	752432 (86531–9911117)	5267025 (324358–175550903)	333 (154–762)	429961 (92338–2238217)	258 (258–259)
Iran	68017860	1087 (3.1)	4.1 (2.0–8.2)	2.8 (1.1–6.3)	182 (79–451)	437624 (9706–220353)	1312852 (25024–793811)	122 (62–250)	58349 (15059–244669)	72.7 (72.5–72.8)
Kazakhstan	15185844	417 (2.0)	0.0 (0.0–4.4)	2.4 (0.4–9.60)	210 (52–1222)	0 (0–11773)	173889 (10798–5793290)	0 (0–114)	0 (0–513410)	209.5 (208.0–211.0)
Nepal	27676547	144 (2.3)	0.0 (0.0–12.7)	0.0 (0.0–12.7)	0 (0–39)	0 (0–3087)	0 (0–6174)	0 (0–39)	0 (0–61740)	0.0 (0–7502698)
Pakistan	162419946	269 (2.5)	11.2 (4.5–25.4)	9.3 (3.4–22.9)	55 (22–152)	4824 (863–32132)	11578 (1915–85176)	46 (20–1140)	8040 (1554–48486)	24.7 (24.7–24.7)
Tajikistan	7163506	262 (2.0)	3.8 (0.7–15.3)	15.3 (7.1–31.1)	34 (16–73)	8581 (1053–106243)	4290 (1035–19749)	134 (33–788)	68644 (4288–2286242)	26.6 (26.5–26.7)
Southeast Asia										
Indonesia	241973879	1105 (2.2)	1.4 (0.3–4.3)	0.0 (0.0–1.7)	0 (0–302)	0 (0–69442)	0 (0–359518)	372 (117–1447)	542678 (53652–8133340)	372 (370–373)
Malaysia	23953136	1886 (5.1)	24.1 (19.6–30.0)	1.3 (0.5–3.3)	389 (156–10640)	15635 (5131–52339)	569119 (92730–4197265)	21 (17–27)	1718 (1136–2611)	20.0 (20.0–20.0)
Philippines	87857473	243 (3.9)	2.1 (0.1–13.30)	0.0 (0.0–7.6)	0 (0–660)	0 (0–4898)	0 (0–17490)	245 (38–4762)	236196 (5693–86672103)	244.8 (244.0–245.6)
Singapore	4425720	545 (4.4)	4.6 (1.7–11.3)	0.0 (0.0–3.4)	0 (0–149)	0 (0–13063)	0 (0–87606)	111 (44–303)	47524 (7792–350137)	110.2 (109.2–111.3)
Thailand	6544371	1064 (3.1)	22.6 (16.9–30.0)	13.2 (8.9–19.2)	40 (27–59)	1685 (866–3324)	5776 (2705–12550)	23 (17–31)	1965 (1108–3521)	14.3 (14.3–14.3)
Far East Asia										
China	1306313812	6806 (5.4)	1.0 (0.6–1.8)	0.0 (0.0–0.3)	0 (0–1855)	0 (0–1040706)	0 (0–13619860)	489 (283–860)	943357 (318085–2909878)	489 (488–489)
Japan	127417244	6010 (12.5)	0.3 (0.06–0.8)	0.2 (0.03–0.7)	3014 (747–17442)	12040033 (937391–269146123)	36120100 (2221831–1203959705)	2009 (630–7789)	16053378 (1581942–240671296)	1205 (1198–1213)
Mongolia	2791272	505 (8.1)	0.0 (0.0–3.7)	0.0 (0.0–3.7)	0 (0–137)	0 (0–37619)	0 (0–75238)	0 (0–137)	0 (0–75238)	0 (0–756673)
South Korea	48422644	543 (2.9)	1.8 (0.3–7.4)	5.5 (2.3–12.6)	93 (40–2310)	49142 (5352–697209)	32761 (6273–197916)	278 (69–1627)	294849 (18266–9824380)	69.3 (69.1–69.5)
Asia	1572802445	31177 (3.4)	5.4 (4.9–6.1)	2.2 (1.8–2.6)	236 (236–236)	42793 (32349–56661)	216530 (153409–306056)	93 (93–93)	33829 (27286–41960)	66.5 (66.5–66.5)

Data are presented as n (95% confidence interval). #: number of subjects (mean precision factor score); ¶: 1/Hardy-Weinberg; +: 2002 population estimate.

TABLE 2 Summary of the estimates of the numbers of carriers and deficiency allele combinations of proteinase inhibitor (PI)*S and PI*Z in 20 Asian countries

Region/country	Total population	Calculated numbers of carriers and deficiency allele combinations					
		PI*MS	PI*MZ	PI*SS	PI*SZ	PI*ZZ	Total
North Asia							
Russia	43000000#	346223 (216650–546213)	138489 (64170–285307)	685 (270–1694)	548 (160–1769)	110 (24–462)	486053 (484695–487415)
Middle East Asia							
Israel	6276883	116737 (86205–157319)	7613 (1959–24310)	557 (306–1005)	73 (14–311)	2 (0–240)	124982 (124297–125670)
Jordan	5759732	94305 (40982–203450)	0 (0–49821)	392 (76–1810)	0 (0–886)	0 (0–109)	94697 (94101–95298)
Saudi Arabia	26417599	1548161 (1148520–2070758)	743117 (481077–1132466)	25734 (14568–44980)	24705 (12204–49197)	5929 (2556–13453)	2347646 (2344781–2350515)
Central Asia							
Afghanistan	29928987	415997 (273872–615384)	582396 (410127–821169)	1501 (658–3364)	4203 (1969–8835)	2942 (1475–5801)	1007040 (1005108–1008976)
India	1080264388	3247546 (1417605–7030198)	927870 (160068–3750994)	2512 (483–11699)	1436 (109–12484)	205 (6–3330)	4179570 (4175572–4183571)
Iran	68017860	559280 (271819–1104114)	372853 (150907–856505)	1166 (278–4517)	1554 (309–7008)	518 (86–2718)	935371 (933490–937256)
Kazakhstan	15185844	0 (0–133745)	72397 (12432–291633)	0 (0–296)	0 (0–1290)	87 (3–1406)	72484 (71959–73013)
Nepal	27676547	0 (0–704252)	0 (0–704252)	0 (0–4483)	0 (0–8966)	0 (0–4483)	0 (0–4)
Pakistan	162419946	3548679 (1420045–8152000)	2957232 (1071401–7342393)	20201 (3350–104532)	33669 (5055–188301)	14029 (1907–84800)	6573809 (6568888–6578734)
Tajikistan	7163506	53431 (9089–216060)	213724 (87791–439737)	104 (3–1670)	835 (67–6800)	1670 (363–6920)	269764 (268,766–270,765)
Southeast Asia							
Indonesia	241973879	650700 (167189–2076689)	0 (0–802242)	448 (30–4510)	0 (0–3485)	0 (0–673)	651146 (649568–652728)
Malaysia	23953136	1120203 (903015–1385149)	61550 (22521–153295)	13941 (9175–21090)	1532 (458–4668)	42 (6–258)	1197268 (1195178–1199360)
Singapore	4425720	40044 (14612–99473)	0 (0–29666)	93 (13–568)	0 (0–339)	0 (0–51)	40137 (39748–40531)
Thailand	6544371	2831674 (2094584–3802513)	1651810 (1109483–2433484)	33297 (18586–59075)	38847 (19690–75612)	11330 (5215–24195)	4566959 (4562920–4571001)
Far East Asia							
China	1306313812	2672334 (1519208–4607922)	0 (0–704191)	1385 (449–4107)	0 (0–1255)	0 (0–96)	2673718 (2670518–2676922)
Japan	127417244	63412 (16358–202180)	42275 (7314–170599)	8 (1–81)	11 (0–136)	4 (0–57)	105709–(105073–106348)
Mongolia	2791272	0 (0–20350)	0 (0–20350)	0 (0–37)	0 (0–74)	0 (0–37)	0 (0–4)
Philippines	87857473	358578 (18451–2322755)	0 (0–1325171)	372 (1–15433)	0 (0–17610)	0 (0–5023)	358950 (357779–360124)
South Korea	48422644	173918 (29771–704549)	521754 (209750–1202266)	164 (5–2651)	985 (69–9047)	1478 (245–7719)	698300 (696675–699928)
Asia	1572802445	16881108 (16865273–16895909)	6672479 (6666220–6678329)	46492 (37484–57641)	36754 (27758–48619)	7264 (5139–10252)	23644097 (23634640–23653558)

Data are expressed as n or n (95% confidence interval). #: 2002 population estimate

FIGURE 1. Comparison of the geographic distribution of the prevalence of the protease inhibitor S deficiency allele for 20 Asian countries.

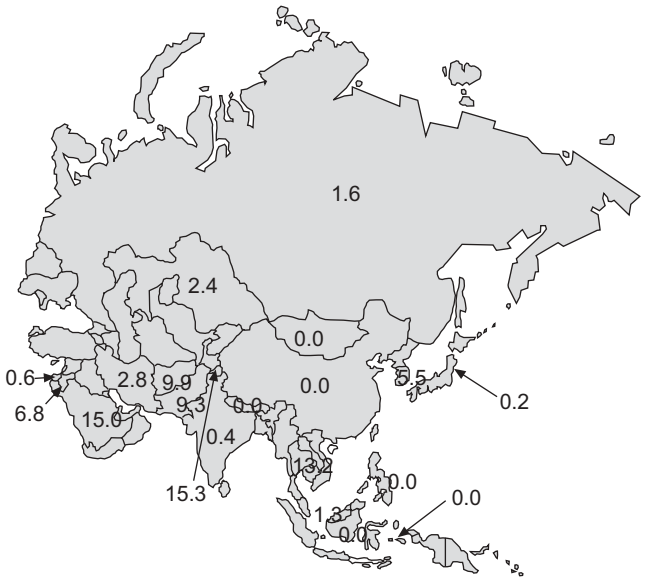

FIGURE 2. Comparison of the geographic distribution of the prevalence of the protease inhibitor Z deficiency allele for 20 Asian countries.

RESULTS

A total of 170 cohorts, comprising 31,177 subjects, were selected from 20 countries in Asia. The individual cohorts from each of these 20 countries were combined into a single cohort for each country. A total cohort population was then developed for all of Asia with a mean PFS value of 10.3 on a 0–12 point scale.

Overview

The 143 control cohorts were distributed as follows: 14 from Russia (E.V. Balanskaya and O. Balansky, unpublished data), 17 from Middle East Asia (12 from Israel [16–20], one from Jordan [21], four from Saudi Arabia [22–25]), 53 from Central Asia (26 from India [26–29], one from Nepal [30], seven from Afghanistan [31–33], five from Iran [34, 35], seven from Kazakhstan [36], one from Pakistan [37], three from Tajikistan [31]), and nine from Southeast Asia (three from Thailand [38–40]), three from Indonesia [41–43], one from Malaysia [40], one from Indonesia [40] and one from the Philippines [40]), and 50 from Far East Asia (23 from China (E.V. Balanskaya and O. Balansky, unpublished data) [29, 44–47], seven from Japan [30, 48–51], 17 from Mongolia (E.V. Balanskaya and O. Balansky, unpublished data), and three from South Korea (E.V. Balanskaya and O. Balansky, unpublished data) [29, 52]).

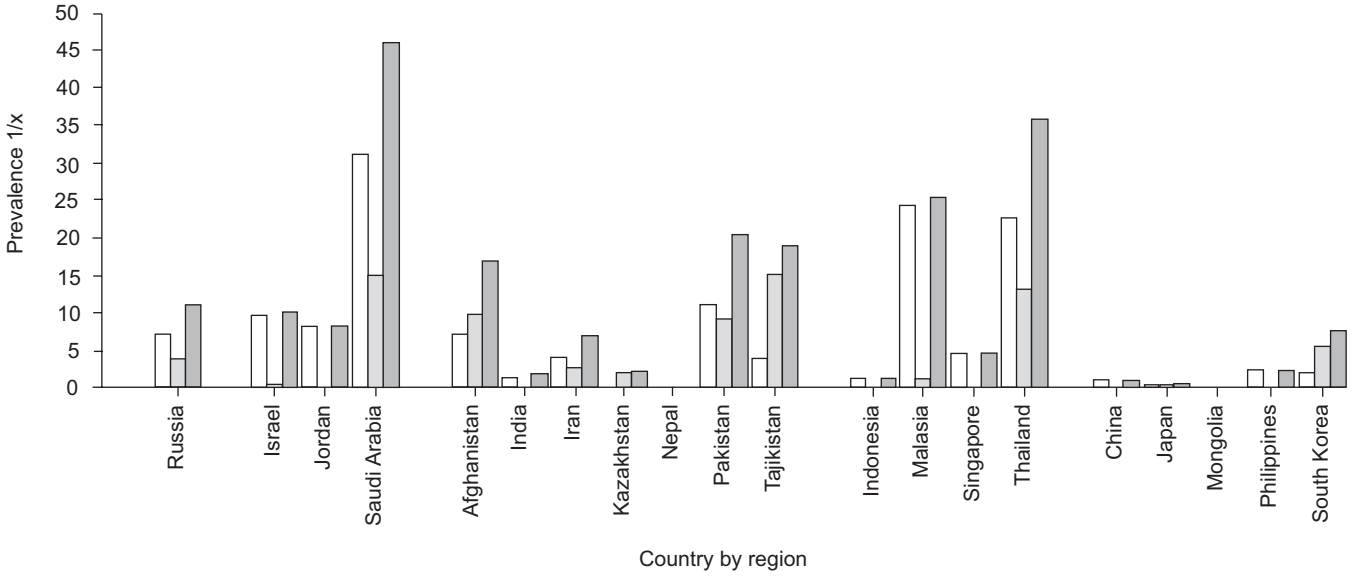

FIGURE 3. Prevalence of the protease inhibitor (PI) deficiency alleles PI*S and PI*Z for 20 Asian countries in selected geographic regions. □: PI*S; ▒:PI*Z; ■: PI*S and PI*Z.

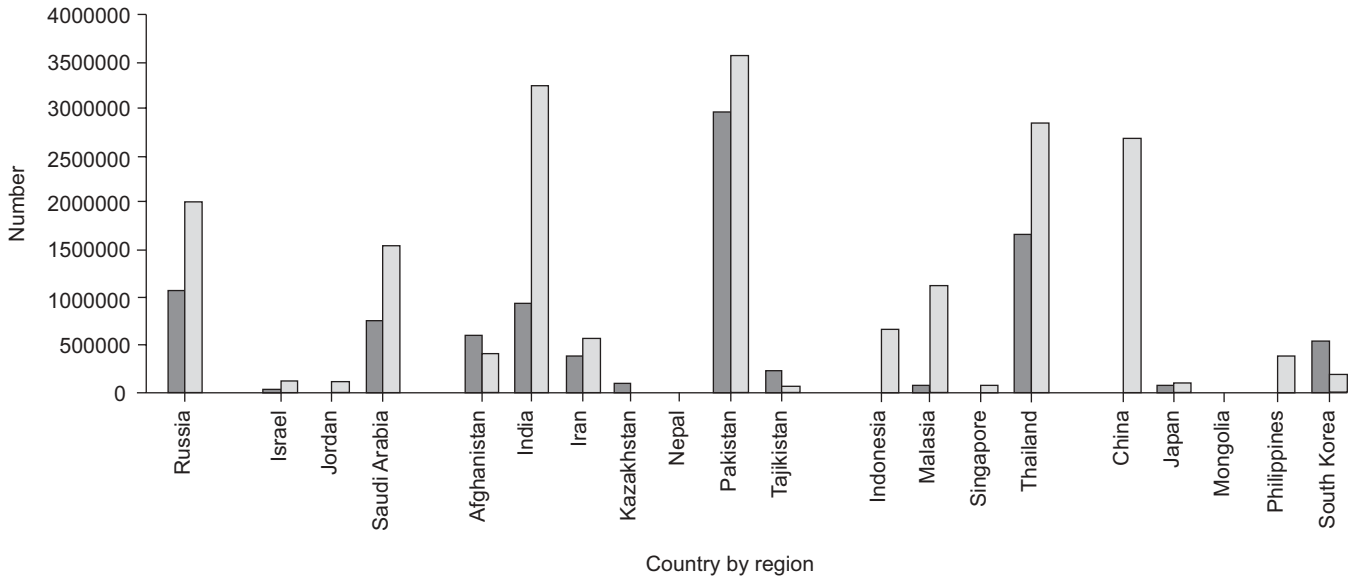

FIGURE 4. Geographical distribution and calculated numbers for protease inhibitor (PI) phenotypes PI*MS (▒) and PI*MZ (■) for 20 Asian countries.

In table 1, calculated statistical values of allele frequencies for PI*S and PI*Z, and the prevalence of the five phenotypic classes of deficiency allele (PI*MZ, PI*SZ, PI*ZZ, PI*MS and PI*SS) are also given, each with 95% CI. The countries are listed according to the five different geographic regions: North-, Middle East-, Central-, Southeast-, and Far East Asia. The final column gives the total prevalence of all five phenotypic classes of the two deficiency alleles PI*S and PI*Z in each of the 20 countries.

Using the data in table 1 and the total populations of each of these 20 countries, the numbers of individuals in each of the five phenotypic classes were calculated using Hardy-Weinberg equilibrium statistics. These calculations are given in table 2 along with 95% CI for each estimate. In addition, in the final column of table 2, the total number of individuals in each of these five phenotypic classes is given for each country.

A comparison of the geographical distribution of the deficiency allele frequencies for PI*S and PI*Z in each of the 20 countries is shown in figures 1 and 2, respectively. The prevalence of these two deficiency alleles in each country is compared in figure 3.

The geographical distribution and calculated numbers for the PI*MS and PI*MZ, PI*SS and PI*SZ, and PI*ZZ and PI*SZ phenotypic classes are shown in figure 4, figure 5 and figure 6, respectively.

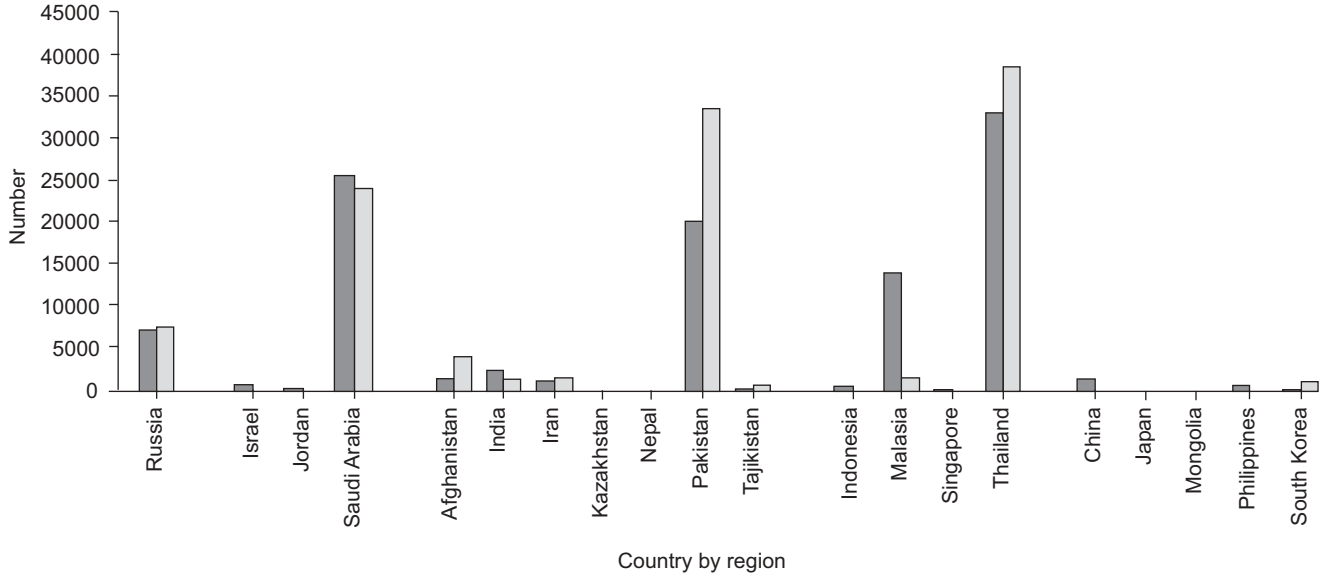

FIGURE 5. Geographical distribution and calculated numbers for protease inhibitor (PI) phenotypes PI*SS (■) and PI*SZ (▒) for 20 Asian countries.

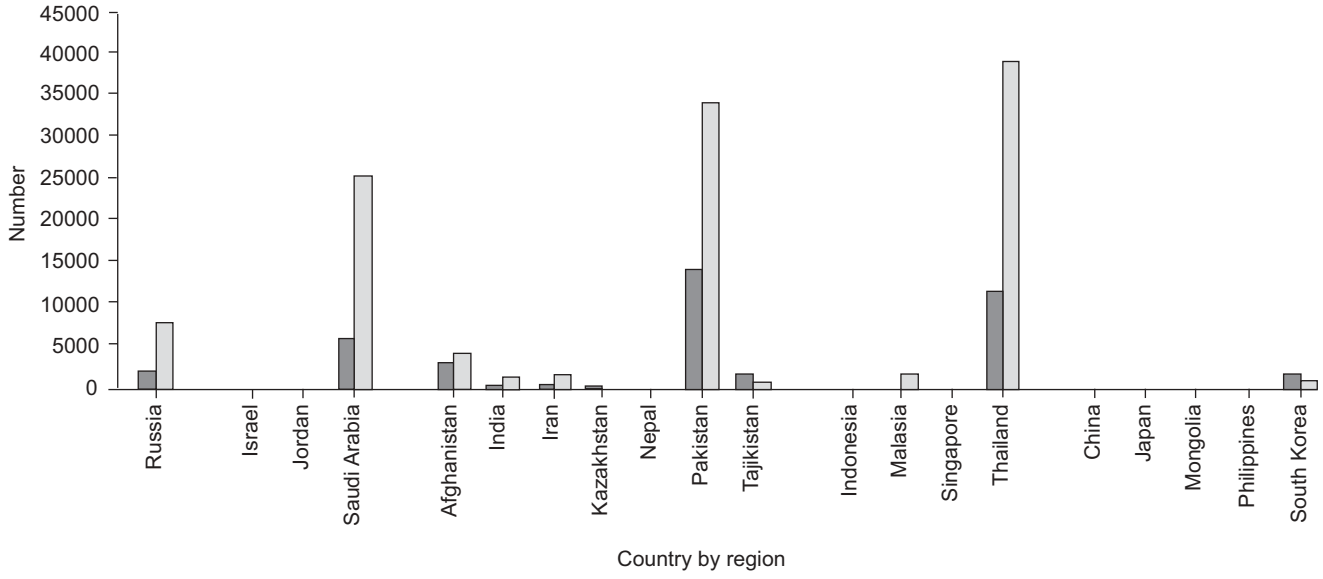

FIGURE 6. Geographical distribution and calculated numbers for protease inhibitor (PI) phenotypes PI*ZZ (■) and PI*SZ (■) for 20 Asian countries.

With an estimated total population of 1,572,802,445 individuals in these 20 countries, the AT-D total population consisted of 7,264 (95% CI 5,139–10,252) PI*ZZ; 36,754 (27,758–48,619) PI*SZ; 6,672,479 (6,666,220–6,678,329) PI*MZ; 16,881,108 (16,865,273–16,895,909) PI*MS, and 46,492 (37,484–57,641) PI*SS phenotypes.

DISCUSSION

The current study demonstrates that both the PI*S and PI*Z alleles are found in 18 out of the 20 Asian countries examined, and also demonstrates very striking differences for the distribution of the PI*S and PI*Z AT-D alleles among these Asian countries, as shown for the PI*S and PI*Z alleles in figures 1 and 2, respectively. Neither of these deficiency alleles was found in Nepal and only the PI*Z deficiency allele was found in Kazakhstan. In contrast to the North–South and East–West change in PI*S and PI*Z prevalence found in Europe [53], no such East–West trend was found for these 20 Asian countries. In fact, there are striking differences in both prevalence and number for both of these two deficiency alleles within a given geographic region.

With an estimated total population of 1,572,802,445 individuals for the 20 previously mentioned Asian countries, the estimated number of ZZ individuals is 7,264 with calculated numbers for each of the 20 countries as follows: The largest number of ZZ individuals was found in Pakistan (14,029), followed by Thailand (11,330), Saudi Arabia (5,929), Afghanistan (2,942), Tajikistan (1,670) and South Korea (1,478). In contrast, no ZZ individuals were found in Jordan, Nepal, Indonesia, Singapore, China or the Philippines, with only low numbers in Israel (two), Japan (four), Malaysia (42) and Kazakhstan (87), and higher numbers in Russia (110), India (205), and Iran (518).

The present authors are aware that these data should be considered an approximation, since calculations may have bias related to the sample composition and the sources of the subjects recruited. Is important to note that in several countries there is a remarkable lack of epidemiological studies in extensive geographic regions, and there are also marked differences in the contribution of AT-D data in different regions of the same country. It also is important to note that for some of the countries listed the cohort sample sizes are small and need to be expanded both in size as well as geographial location. This is true for Jordan, Saudi Arabia, Kazakhstan, Nepal, Pakistan, Tajikistan, Philippines, Singapore, Mongolia and South Korea. Inclusion of cohort data from these countries has demonstrated, with the exception of Nepal and Mongolia, the presence of the PI*S and PI*Z deficiency alleles in these populations. However, these preliminary results need to be confirmed as well as extended to other geographic regions in each country.

In addition to the ZZ individuals, the current calculations indicate that in Asia there are 46,492 SZ and 6,672,479 MZ phenotype individuals, and an impressive number of almost 37 million individuals with MS and SS phenotypes. Although both the PI*MS and PI*SS phenotypes are not currently considered as being at increased risk for development of diseases, and that penetrance (number of subjects who develop clinical disease) of PI*MZ and PI*SZ phenotypes is clearly lower if compared with PI*ZZ, it is the current authors' intention to provide these numbers to illustrate the following: 1) the very large numbers of individuals with the PI*S and PI*Z deficiency alleles in these 20 countries; and 2) the need for follow-up epidemiological studies to confirm and extend these original observations.

*Comparison of the prevalence of PI*S and PI*Z in Asian countries with those found in Europe*

The data in table 1 give mean deficiency allele frequencies of 5.4 (95% CI 4.9–6.1) for PI*S and 2.2 (1.8–2.6) for PI*Z in contrast with 37 (36–38) for PI*S and 14 (13–14) for PI*Z for 21 countries in Europe in an earlier publication [53].

*Comparison of the numbers in each of the five phenotypic classes of PI*S and PI*Z found in Asian countries with those found in Europe*

The data in table 1 give a total of 16,881,108 (16,865,273–16,895,909) for PI*MS, 6,672,479 (6,666,220–6,678,329) for PI*MZ, 46,492 (37,484–57,641) for PI*SS, 36,754 (27,758–48,619) for PI*SZ and 7,264 (5,139–10,252) for PI*ZZ. These estimates are in contrast with 40,940,921 (39,913,011–41,993,343) for PI*MS, 15,440,983 (14,817,481–16,089,864) for PI*MZ, 797,199 (759,427–836,809) for PI*SS, 601,331 (563,866–641,251) for PI*SZ, and 113,397 (104,666–122,849) for PI*ZZ. Comparison of the phenotypic data obtained from the authors earlier analysis of AT-D in Europe with the current database on 20 countries in Asia demonstrates that there are significantly higher numbers in each of the five phenotypic classes of AT-D in these 20 Asian countries than the 21 countries examined in Europe.

*The origin of PI*S and PI*Z deficiency alleles in Asian countries*

The origin of these deficiency alleles is probably best accounted for on the basis of movement of people over time to major cities in Pakistan, for example, as well as in Saudi Arabia. The high incidence in Thailand most probably arose due to its location on a major trade route from Europe to the Far East. The prevalence in Japan could well be attributed to the settlement in selected cities by the Portuguese in the 16th century; however, the prevalence in South Korea is without explanation on the basis of available historical data. Thus, the movement of people in the past appears to be the most reasonable explanation for transport of both deficiency alleles from various countries in Europe to selected countries in Asia.

In summary, α_1-antitrypsin deficiency is widespread throughout the world, with significantly high prevalence in countries throughout the continent of Asia. It also is clear that α_1-antitrypsin deficiency is not just a disease of Caucasians (or whites), but is prevalent in many different races throughout the world.

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REFERENCES

1 de Serres FJ. Worldwide racial and ethnic distribution of alpha1-antitrypsin deficiency: details of an analysis of published genetic epidemiological surveys. *Chest* 2002; 122: 1818–1829.
2 de Serres FJ, Blanco I, Fernandez-Bustillo E. Health implications of alpha1-antitrypsin deficiency in Sub-Sahara African countries and their emigrants in Europe and the New World. *Genet Med* 2005; 7: 175–184.
3 de Serres FJ, Blanco I, Fernandez-Bustillo E. Genetic epidemiology of alpha-1 antitrypsin deficiency in North America and Australia/New Zealand: Australia, Canada, New Zealand and the United States of America. *Clinical Genetics* 2003; 64: 382–397.
4 de Serres F, Blanco I, Bustillo EF. Genetic epidemiology of alpha-1 antitrypsin deficiency: France, Italy, Portugal, and Spain. *Clin Genet* 2003; 63: 490–509.
5 de Serres FJ, Luisetti M, Ferrarotti I, Blanco I, Bustillo E. Alpha-1 antitrypsin deficiency in Italy: regional differences of the PIS and PIZ deficiency alleles of alpha-1 antitrypsin deficiency in Italy. *Monaldi Arch Chest Dis* 2005; 63: 133–141.
6 Wilson-Cox D. Alpha-1 antitrypsin deficiency, *In*: Scriver CR, Beaudet AL, Sly WS, *et al.*, eds. The Metabolic and Molecular Bases of Inherited Disease. New York, The McGraw-Hill, Companies, 1995; pp. 4125–4158.
7 Crystal RG, Brantly ML, Hubbard RC, Curiel DT, States DJ, Holmes MD. The alpha 1-antitrypsin gene and its mutations. Clinical consequences and strategies for therapy. *Chest* 1989; 95: 196–208.
8 Crystal R. The alpha-1 antitrypsin gene and its deficiency states. *Trends Genet* 1989; 5: 411–417.
9 Blanco I, Fernandez E, Bustillo E. Alpha-1-antitrypsin PI phenotypes S and Z in Europe: an analysis of the published surveys. *Clin Genet* 2001; 60: 31–41.
10 Blanco I, Bustillo EF, Rodriguez MC. Distribution of alpha1-antitrypsin PI S and PI Z frequencies in countries outside Europe: a meta-analysis. *Clin Genet* 2001; 60: 431–441.
11 de Serres FJ. Alpha-1 antitrypsin deficiency is not a rare disease but a disease that is rarely diagnosed. *Environ Health Perspect* 2003; 111: 1851–1854.
12 Blanco I, Canto H, de Serres FJ, Fernandez-Bustillo E, Rodriguez MC. Alpha(1)-antitrypsin replacement therapy controls fibromyalgia symptoms in 2 patients with PI ZZ alpha(1)-antitrypsin deficiency. *J Rheumatol* 2004; 31: 2082–2085.
13 Blanco LE, de Serres FJ, Fernandez-Bustillo E, *et al.* Alpha 1-antitrypsin and fibromyalgia: new data in favour of the inflammatory hypothesis of fibromyalgia. *Med Hypotheses* 2005; 64: 759–769.
14 Stoller JK, Snider GL, Brantly ML. American Thoracic Society/European Respiratory Society Statement: Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Resp Crit Care Med* 2003; 168: 818–855.
15 World Factbook database. www.odci.gov/cia/publications/factbook/index.html. Last updated November 2005.
16 Nevo S, Kanaaneh H, Cleve H. A genetic study of alpha 1-antitrypsin in an Israeli Arab population, with a new allele: Piv-s. *Isr J Med Sci* 1982; 18: 891–893.
17 Nevo S. Protease inhibitor subtypes in some population groups from Israel. *Hum Hered* 1987; 37: 170–181.
18 Nevo S, Cleve H, Bar-Shani, Joel A., Liron M. Bulgarian Jews in Israel: genetic blood markers. Red-cell antigens, serum proteins and red-cell isozymes. *Hum Hered* 1989; 39: 333–344.
19 Nevo S, Cleve H. PI polymorphism in Israel: report on six Jewish population groups. *Am J Med Genet* 1991; 39: 399–403.
20 Nevo S, Cleve H, Koller A, *et al.* Serum protein polymorphisms in Arab Moslems and Druze of Israel: BF, F13B, AHSG, GC, PLG, PI, and TF. *Hum Biol* 1992; 64: 587–603.

21 Saleh H, Davrinche C, Charlionet R, Rivat C. Alpha-1-antitrypsin phenotypes in a population of Jordan. *Hum Hered* 1986; 36: 192–194.

22 Goedde HW, Benkmann HG, Agarwal DP, *et al.* Genetic studies in Saudi Arabia: red cell enzyme, haemoglobin and serum protein polymorphisms. *Am J Phys Anthropol* 1979; 50: 271–277.

23 Al-Balla SRS, El-Hazmi MAF, Al-Dalaan AN, Warsy AS. Alpha-1-antitrypsin phenotypes in rheumatoid-arthritis. *Saudi Med J* 1992; 13: 555–559.

24 Warsy AS, Elhazmi MAF, Sedrani SH. Alpha-1-antitrypsin phenotypes in saudi-arabia - a study in the Central Province. *Ann Saudi Med* 1991; 11: 159–162.

25 Warsy AS, el-Hazim MAF, Hamooda H, Kilic N. Alpha-1-antitrypsin: frequencies of Pim subtypes in a Saudi Population. *Saudi Med J* 1991; 12: 376–379.

26 Reddy PH, Mastana SS. Genetic variation of serum proteins (GC, TF and PI subtypes) in the Baigas of Madhya Pradesh, India. *Anthropol Anz* 1995; 53: 53–56.

27 Kamboh MI, Board PG, Kirwood C. Re-evaluation of the proposed interrelationship between thyroxine-binding globulin (TBG) and alpha1-antitrypsin (PI). *Clin Chim Acta* 1984; 139: 65–73.

28 Walter H, Naidu JM, Danke-Hopfe H, *et al.* Genetic serum protein markers in eight south Indian caste and tribal populations. *Z Morphol Anthropol* 1993; 79: 355–365.

29 Saha N. Alpha 1-protease inhibitor (PI) subtypes in seven populations of east Asia. *Ann Hum Biol* 1990; 17: 229–234.

30 Yuasa I, Suenaga K, Gotoh Y, Ito K, Yokoyama N, Okada K. PI(alpha 1-antitrypsin) polymorphism in the Japanese: confirmation of PI*M4 and description of new PI variants. *Hum Genet* 1984; 67: 209–212.

31 Spitsyn VA, Novoradovskii AG, Spitsyna NKh, Parik IuIa. [Polymorphism of alpha1-antitrypsin in Pamir populations. Reproductive compensation--possible mechanism for maintaining genetic diversity gor PI genes in human populations]. *Genetika* 1989; 25: 2218–2224.

32 Rahimi AG, Goedde HW, Flatz G, Kaifie S, Benkmann HG, Delbruck H. Serum protein polymorphisms in four populations of Afghanistan. *Am J Hum Genet* 1977; 29: 356–360.

33 Goedde HW, Benkmann HG, Flatz G, Bienzle U, Kroeger A. alpha 1-antitrypsin subtypes in the populations of Germany, Ecuador, Afghanistan, Cameroon, and Saudi-Arabia. *Z Morphol Anthropol* 1980; 70: 341–346.

34 Hashemi M, Alavian SM, Ghavami S, *et al.* High prevalence of alpha 1 antitrypsin deficient phenotypes in viral hepatitis B infected patients in Iran. *Hepatol Res* 2005; 33: 292–297.

35 Walter H, Mohammadzadeh Z, Schuler I, Farhud DD. Serum protein polymorphisms (HP, TF, GC and PI) in four Iranian population samples. *Ann Hum Biol* 1992; 19: 35–39.

36 Petrishev VN, Lebedeva IA, Shneider Iu V. [Genetic polymorphism of the alpha 1-antitrypsin system in the native population of the Kazakh SSR]. *Genetika* 1987; 23: 2257–2264.

37 Shahid A, Siddiqui AA, Zuberi SJ, Waqar M. Phenotypes of alpha 1 antitrypsin in Karachi, Pakistan. *J Pak Med Assoc* 2000; 50: 374–376.

38 Chongsrisawat V, Jantaradsamee P, Vivatvakin B, Pongpaew P, Poovorawan Y. Alpha 1-antitrypsin phenotype of children with liver diseases in Thailand. *Asian Pac J Allergy Immunol* 1998; 16: 27–30.

39 Pongaew P, Schelp FP. Alpha-1-protease inhibitor phenotypes and serum concentrations in Thailand. *Hum Genet* 1980; 54: 119–124.

40 Saha N. Alpha 1-protease inhibitor (PI) subtypes in seven populations of east Asia. *Ann Hum Biol* 1990; 17: 229–234.

41 Constans J, Gouaillard C, Brequet G. Serum protein polymorphism in Bali (Indonesia). *Ann Hum Biol* 1986; 13: 537–545.

42 Kirk RL, McDermid EM, Blake NM, Wight RL, Yap EH, Simons MJ. The distribution of red cell enzyme and serum protein groups in a population of Dani (Pit River, West Irian). *Humangenetik* 1973; 17: 345–350.

43 Malcolm LA, Woodfield DG, Blake NM, Kirk RL, McDermid EM. The distribution of blood, serum protein and enzyme groups on Manus Island (Admiralty Islands, New Guinea). *Hum Hered* 1972; 22: 305–322.

44 Ying QL, Liang ZQ. Allelic frequencies of plasma alpha-1-antitrypsin in Chinese. *Sci Sin [B]* 1984; 27: 161–168.

45 Ying QL, Zhang ML, Liang CC, *et al.* Alpha-1-antitrypsin types in five Chinese national minorities. *Hum Genet* 1985; 71: 225–226.

46 Xu JJ, Cui MY, Chen LZ, *et al.* Polymorphisms of Pi, Hp, ADA and AK in Mongolian, Korean and Zhuang populations of China. *Ann Hum Biol* 1986; 13: 245–251.

47 Schievink WI, Katzmann JA, Piepgras DG. Alpha-1-antitrypsin deficiency in spontaneous intracranial arterial dissections. *Cerebrovasc Dis* 1998; 8: 42–44.

48 Harada S, Miyake K, Suzuki H, Oda T. New phenotypes of serum alpha1-antitrypsin in Japanese detected by gel slab isoelectric focusing. *Hum Genet* 1977; 38: 333–336.

49 Miyake K, Suzuki H, Oka H, Oda T, Harada S. Distribution of alpha 1-antitrypsin phenotypes in Japanese: description of Pi M subtypes by isoelectric focusing. *Jinrui Idengaku Zasshi* 1979; 24: 55–62.

50 Ohtani H, Saito M. Alpha-1-antitrypsin: frequencies of PiM subtypes and serum concentration in the Japanese population. *Hum Hered* 1985; 35: 62–64.

51 Sebetan IM, Akaishi S. Alpha-1-antitrypsin (PiM) subtypes in Japanese. *Forensic Sci Int* 1981; 18: 155–159.

52 Lee SS, Lawton JW, Ko KH. Alpha1 antitrypsin phenotypic variability is not associated with ANCA in southern Chinese. *Ann Rheum Dis* 2001; 60: 725–726.

53 Blanco I, de Serres FJ, Fernandez-Bustillo E, Lara B, Miravitlles M. Estimated numbers and prevalence of PI*S and PI*Z alleles of alpha-1-antitrypsin deficiency in European countries. *Eur Respir J* 2006; 27: 77–84.