Estimation of the numbers and prevalences of the PI*S and PI*Z deficiency alleles of AAT Deficiency in Asia

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Abstract

The present paper focuses on updating estimates of the numbers of individuals carrying the two most common deficiency alleles PI*S and PI*Z for alpha-1-antitrypsin deficiency (AAT Deficiency) in 20 countries located in Asia. A total of 170 cohorts with 31,177 individuals were selected from 20 Asian countries. The total AAT Deficiency 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 these Asian countries and regions also were found for the prevalence of the deficiency alleles PI*S and PI*Z. These numbers demonstrate that AAT Deficiency is not just a genetic disease that affects smaller numbers than various countries, for example, in Europe.

There were marked differences between the prevalences 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 less than 1,700 in each of the remaining countries.

Introduction

Although Alpha-1-antitrypsin deficiency (AAT Deficiency) is as a whole one of the most common hereditary disorders worldwide, AAT Deficiency prevalence varies markedly from one country to another [1-4] and affects many different racial subgroups. AAT Deficiency also can vary markedly within a given country as illustrated by the differences in the prevalences of PI*S and PI*Z within 14 of the 20 regiones in Italy [5]. Alpha-1-antitrypsin (AAT) is the human serum most prevalent proteases inhibitor, mainly

secreted by hepatocytes. The AAT gene is highly pleomorphic, with about 100 alleles having identified to date. Variants are classified according to the protease inhibitor (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 AT plasma concentrations below 60%. The majority of a given population has the PIMM phenotype, which expresses normal serum AAT levels. The two commonest allelic variants that produce AAT deficiency are PI*Z and PI*S. The range of serum levels of AAT according to phenotype (measured by using the purified standard used in the U.S. 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 less than 11 μM is associated with an increased risk for pulmonary emphysema [6-8].

Most pathology related to AAT Deficiency is linked to Z allele, and in clinical practice 96% of patients have a ZZ phenotype [1, 9, 10]. The remaining 4% mostly belongs to SZ, MZ, and in a lesser amount, to 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 AAT Deficiency associated diseases has been established to date [3, 5, 11].

AAT Deficiency 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].

Knowledge of the AAT Deficiency prevalence in every community is essential from a public health perspective [14]. The specific issue that was investigated in the present paper is: "What are the estimates of the prevalence and number of subjects for the most common

defective alleles PI*S and PI*Z in Asian countries?" The present study focuses on to estimate the total number of ZZ, SZ and MZ individuals in 20 Asian countries with available studies, and goes beyond of others published, 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 utilizes available data from epidemiological studies performed by others to determine the frequencies of deficiency allele combinations for PI*S and PI*Z, in the healthy control cohorts of individual case studies from different Asian countries: Russia in North Asia, Israel, Jordan and Saudi Arabia in Middle East Asia, Afghanistan, India, Iran, Kazakhstan, Nepal, Pakistan, and Tajikistan in Central Asia, Indonesia, Malaysia, Singapore , and Thailand in Southeast Asia, and China, Japan, Mongolia, Philippines, and South Korea in Far East Asia.

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 Drs. Elena V. Balanovska, and Oleg 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 cohort data consists of 14 new cohorts with a total number of 2,564 subjects for Asian Russia, 4 additional cohorts with a total number of 2,650 additional subjects for China, and 1 cohort with a total number of 1,807 additional subjects for Japan. In addition, there are 17 new cohorts with a total number of 505 subjects for Mongolia, and 3 new cohorts with a total number of 217 additional subjects for South Korea.

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

The data from the individual cohorts for a given country were combined to get 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, PIMS, PIMZ, PISS, PISZ, and PIZZ) in the total population of each of these countries as well as in all of Asia.

The formulas for developing estimates of the allele frequencies gene prevalence, the numbers of deficiency allele combinations and 95% confidence intervals (95% 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 updated in November 2005 (http://www.odci.gov/cia/publications/factbook/index.html)

To assess the statistical reliability of each survey, we have calculated the coefficient of variation (cv) for PI*S and PI*Z frequencies in each control cohort. This cv provides an estimate of the precision (or better, the imprecision) of results from each survey. The formulas developed by Dr. Fernández-Bustillo for getting estimates of Numerical Precision Factor Scores (PFS) on a value scale from 0 to 12 to assess the statistical quality in terms of precision (or imprecision) of each selected survey were discussed in earlier papers [4]. The PFS values assigned to the individual countries are the mean of the PFS given to individual cohorts for each country. They also can be considered an indication of the quality of the cohort database in terms of the total size of the cohort for each of these 20 countries.

Criteria for selection of studies

Reliable selected studies for the present analysis should fulfil the following criteria: (1) AT phenotyping performed by isoelectrofocusing (IEF) or antigen-antibody crossed electrophoresis (AACE); (2) statistical precision factor score of $\geq$ 2, 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 characterization was carried out by means of the IEF method. Starch gel electrophoresis method (SG) is a less reliable method. The crossed antigen-antibody electrophoresis method (CAAE) technique is an expensive and time consuming method, and although it does give reliable results, since 1976 CAEE was gradually 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 moderately deficiency phenotypes, such as MS, SS and MZ could express AT serum concentrations over a given cut off value.

Criterion 3: Numerical Precision Factor Score (PFS) scale for assessing the statistical quality in terms of precision (or imprecision) of each selected survey.

The *cv* depends on the sample size and the PI*S and PI*Z allelic frequencies. Cohorts from countries having 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, to adjust the PFS rise by PI*S frequencies. For East Asian countries where both PI*S and PI*Z frequencies are very low, we have accepted a PFS value of ≥ 2 for selection.

Criterion 3. 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.

Results

A total of 170 cohorts, having a total of 31,177 subjects were selected from 20 countries in Asia. The mean PFS of these 170 selected cohorts exhibited a value of 10.3 in a scale of 0-12 points when the individual cohorts from each of these 20 countries were combined into a single cohort for each country to develop a total cohort population of 170 for all of Asia.

Overview

These 170 control cohorts are distributed as follows:

14 from North Asia (Russia [16]), 17 from Middle East Asia (12 from Israel [17-21], 1 from Jordan [22], 4 from Saudi Arabia [23-25, 26]. , 27 from South Central Asia (26 from India [27-30], 1 from Nepal [31]), 26 from Central Asia (7 from Afghanistan [32-34], 5 from Iran [35, 36], 7 from Kazakhstan [37], 1 from Pakistan [38], 3 from

Tajikistan [32]), and 49 from Far East Asia (23 from China [16, 30, 39-42], 7 from Japan [31, 43-46], 17 from Mongolia [16], and 2 from South Korea [16, 30, 47].)

In Table 1, calculated statistical values of the allele frequencies for PI*S and PI*Z, and the prevalences of the five phenotypic classes of deficiency allele (PIMZ, PISZ and PIZZ) and (PIMS and PISS) also are given, each with 95% confidence intervals. The countries are listed according to the 5 different geographic regions: North Asia, Middle East Asia, Central Asia, Southeast Asia, and Far East Asia. The final column gives the total prevalence of all 5 phenotypic classes of the two deficiency alleles PI*S and PI*Z in each of these 20 countries.

Table 1- Estimates of the P*IS and PI*Z gene frequency and phenotype prevalence of each of the 5 phenotypic classes in 21 countries in Asia

Country	Total population	No. of subjects and ☼ = mean PF score	PI*S and PI*Z calculated frequency x 1000 (95% CI)		PIMZ, PISZ and PIZZ calculated prevalence 1/x (Hardy-Weinberg)			PIMS and PISS calculated prevalence 1/x (Hardy-Weinberg)		Total PIS and PIZ calculated prevalence 1/x (Hardy-Weinberg)
			PI*S	PI*Z	PI MZ	PI SZ	PI ZZ	PI MS	PI SS	
North Asia										
Asian Russia	43,000,000*	2,564 ☼ 2.4	3.9 (2.5-6.1)	1.6 (0.7-3.2)	325 (158-701)	82,176 (25,434-281,313)	410,881 (97,384-1,899,529)	130 (82-208)	65,741 (26,570-166,646)	92.6 (92.4-92.7)
Middle East Asia										
Israel	6,276,883	2,442 ☼ 2.6	9.4 (7.0-12.7)	0.6 (0.2-2.0)	824 (258-3,2040)	86,426 (20,201-451,453)	2,650,384 (261,458-39,739,458)	54 (40-730)	11,273 (6,243-20,519)	50.2 (49.9-50.5)
Jordan	5,759,732	424 ☼ 6.8	8.3 (3.6-17.7)	6.8 (0.0-4.3)	0 (0.0-116)	0.0 (0-6,499)	0 (0-53,075)	61 (28-141)	14,676 (3,183-76,2340)	60.8 (60.4-61.2)
Saudi Arabia	26,417,599	801 ☼ 3.1	31.2 (23.5-41.3)	15.0 (9.8-22.6)	36 (23-560)	4,456 (1,964-10,335)	4,456 (1,964-10,335)	17 (13-23)	1,027 (587-1,813)	11.3 (11.2-11.3)
Central Asia										
Afghanistan	29,928,987	1,785 ☼ 2.0	7.1 (4.7-10.6)	9.9 (7.0-13.9)	51 (36-73)	7,121 (3,387-15,197)	10,172 (5,159-20,296)	72 (48-109)	19,937 (8,896-45,516)	29.7 (29.7-29.8)

Country	Total population	No. of subjects and ☼ = mean PF score	PI*S and PI*Z calculated frequency x 1000 (95% CI)		PIMZ, PISZ and PIZZ calculated prevalence 1/x (Hardy-Weinberg)			PIMS and PISS calculated prevalence 1/x (Hardy-Weinberg)		Total PIS and PIZ calculated prevalence 1/x (Hardy-Weinberg)
			PI*S	PI*Z	PI MZ	PI SZ	PI ZZ	PI MS	PI SS	
India	1,080,264,388	**2,295** ☼ 2.0	1.5 (0.6-3.3)	0.4 (0.08-1.8)	1,164 (288-6,749)	752,432 (86,531-9,911,117)	5,267,025 324,358-175,550,903)	333 (154-762)	429,961 (92,338-2,238,217)	258 (258-259)
Iran	68,017,860	**1,087** ☼ 3.1	4.1 (2.0-8.2)	2.8 (1.1-6.3)	182 (79-451)	43,7624 (9,706-220,353)	131,2852 (25,024-793,811)	122 (62-250)	58,349 (15,059-244,669)	72.7 (72.5-72.8)
Kazakhstan	15,185,844	417 ☼ 2.0	0.0 (0.0-4.4)	2.4 (0.4-9.60)	210 (52-1,222)	0 (0-11,773)	173,889 (10,798-5,793,290)	0 (0-114)	0 (0-51,3410	209.5 (208.0-211.0)
Nepal	27,676,547	144 ☼ 2.3	0.0 (0.0-12.7)	0.0 (0.0-12.7)	0 (0-39)	0 (0-3,087)	0 (0-6,174)	0 (0-39)	0 (0-6,1740	0.0 (0-7,502,698)
Pakistan	162,419,946	269 ☼ 2.5	11.2 (4.5-25.4)	9.3 (3.4-22.9)	55 (22-152)	4,824 (863-32,132)	11,578 (1,915-85,176)	46 (20-1140	8,040 (1,554-48,486)	24.7 (24.7-24.7)
Tajikistan	7,163,506	262 ☼ 2.0	3.8 (0.7-15.3)	15.3 (7.1-31.1)	34 (16-73)	8,581 (1,053-106,243)	4,290 (1,035-19,749)	134 (33-788)	68,644 (4,288-2,286,242)	26.6 (26.5-26.7)
Southeast Asia										
Indonesia	241,973,879	**1,105** ☼ 2.2	1.4 (0.3-4.3)	0.0 (0.0-1.7)	0 (0-302)	0 (0-69,442)	0 (0-359,518)	372 (117-1,447)	542,678 (53,652-8,133,340)	372 (370-373)
Malaysia	23,953,136	1,886 ☼ 5.1	24.1 (19.6-30.0)	1.3 (0.5-3.3)	389 (156-1,0640	15,635 (5,131-52,339)	569,119 (92,730-4,197,265)	21 (17-27)	1,718 (1,136-2,611)	20.0 (20.0-20.0)

Country	Total population	No. of subjects and ☼= mean PF score	PI*S and PI*Z calculated frequency x 1000 (95% CI)		PIMZ, PISZ and PIZZ calculated prevalence 1/x (Hardy-Weinberg)			PIMS and PISS calculated prevalence 1/x (Hardy-Weinberg)		Total PIS and PIZ calculated prevalence 1/x (Hardy-Weinberg)
			PI*S	PI*Z	PI MZ	PI SZ	PI ZZ	PI MS	PI SS	
Philippines	87,857,473	243 ☼ 3.9	2.1 (0.1-13.30)	0.0 (0.0-7.6)	0 (0-660)	0 (0-4,898)	0 (0-17,490)	245 (38-4,762)	236,196 (5,693-86,672,103)	244.8 (244.0-245.6)
Singapore	4,425,720	545 ☼ 4.4	4.6 (1.7-11.3)	0.0 (0.0-3.4)	0 (0-149)	0 (0-13,063)	0 (0-87,606)	111 (44-303)	47,524 (7,792-350,137)	110.2 (109.2-111.3)
Thailand	65,44,371	1,064 ☼ 3.1	22.6 (16.9-30.0)	13.2 (8.9-19.2)	40 (27-59)	1,685 (866-3,324)	5,776 (2,705-12,550)	23 (17-31)	1,965 (1,108-3,521)	14.3 (14.3-14.3)
Far East Asia										
China	1,306,313,812	**6,806** ☼ 5.4	1.0 (0.6-1.8)	0.0 (0.0-0.3)	0 (0-1,855)	0 (0-1,040,706)	0 (0-13,619,860)	489 (283-860)	943,357 (318,085-2,909,878)	489 (488-489)
Japan	127,417,244	6,010 ☼ 12.5	0.3 (0.06-0.8)	0.2 (0.03-0.7)	3,014 (747-17,442)	12,040,033 (937,391-269,146,123)	36,120,100 (2,221,831-1,203,959,705)	2,009 (630-7,789)	16,053,378 (1,581,942-240,671,296)	1205 (1198-1213)
Mongolia	2,791,272	505 ☼ 8.1	0.0 (0.0-3.7)	0.0 (0.0-3.7)	0.0 (0-137)	0.0 (0-37,619)	0 (0-75,238)	0 (0-137)	0 (0-75,238)	0.0 (0.0-756,673)
South Korea	48,422,644	**543** ☼ 2.9	1.8 (0.3-7.4)	5.5 (2.3-12.6)	93 (40-2310	49,142 (5,352-697,209)	32,761 (6,273-197,916)	278 (69-1,627)	294,849 (18,266-9,824,380)	69.3 (69.1-69.5)
Asia										

Country	Total population	No. of subjects and ☼ = mean PF score	PI*S and PI*Z calculated frequency x 1000 (95% CI)		PIMZ, PISZ and PIZZ calculated prevalence 1/x (Hardy-Weinberg)			PIMS and PISS calculated prevalence 1/x (Hardy-Weinberg)		Total PIS and PIZ calculated prevalence 1/x (Hardy-Weinberg)
			PI*S	PI*Z	PI MZ	PI SZ	PI ZZ	PI MS	PI SS	
Asia	1,572,802,445	31,177 ☼ 3.4	5.4 (4.9-6.1)	2.2 (1.8-2.6)	236 (236-236)	42,793 (32,349-56,661)	216,530 (153,409-306,056)	93 (93-93)	33,829 (27,286-41,960)	66.5 (66.5-66.5)

☼ Precision Factor Score, * Population estimate Wikipedia (2002 estimate)

Using the data given 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 and these calculations are given in Table 2 along with 95% confidence intervals on each estimate. In addition, in the final column of Table 2, the total number of individuals in each of these 5 phenotypic classes is given for each country.

Table 2. Summaries of the estimates of the numbers of carriers and deficiency allele combinations of PiS and PiZ in 20 countries in Asia

Region/Country	Total population	Calculated numbers of carriers and deficiency allele combinations (Hardy-Weinberg Equilibrium statistics) with 95% CI					
		PIMS (95% CI)	PIMZ (95% CI)	PISS (95% CI)	PISZ (95% CI)	PIZZ (95% CI)	Total (95% CI)
North Asia							
Asian Russia	43,000,000*	346,223 (216,650 – 546,213)	138,489 (64,170 – 285,307)	685 (270 – 1,694)	548 (160 – 1,769)	110 (24 -462)	486,053 (484,695 – 487,415)
Middle East Asia							
Israel	6,276,883	116,737 (86,205-157,319)	7,613 (1,959-24,310)	557 (306-1,005)	73 (14-311)	2 (0-240)	124,982 (124,297-125,670)
Jordan	5,759,732	94,305 (40,982-203,450)	0 (0-49,821)	392 (76-1,810)	0 (0-886)	0 (0-109)	94,697 (94,101-95,298)
Saudi Arabia	26,417,599	1,548,161 (1,148,520-2,070,758)	743,117 (481,077-1,132,466)	25,734 (14,568-44,980)	24,705 (12,204-49,197)	5,929 (2,556-13,453)	2,347,646 (2,344,781-2,350,515)
Central Asia							
Afghanistan	29,928,987	415,997 (273,872-615,384)	582,396 (410,127-821,169)	1,501 (658-3,364)	4,203 (1,969-8,835)	2,942 (1,475-5,801)	1,007,040 (1,005,108-1,008,976)
India	1,080,264,388	3,247,546 (1,417,605-7,030,198)	927,870 (160,068-3,750,994)	2,512 (483-11,699)	1,436 (109-12,484)	205 (6-3,330)	4,179,570 (4,175,572-4,183,571)
Iran	68,017,860	559,280 (271,819-1,104,114)	372,853 (150,907-856,505)	1,166 (278-4,517)	1,554 (309-7,008)	518 (86-2,718)	935,371 (933,490-937,256)
Kazakhstan	15,185,844	0 (0-133,745)	72,397 (12,432-291,633)	0 (0-296)	0 (0-1,290)	87 (3-1,406)	72,484 (71,959-73,013)
Nepal	27,676,547	0 (0-704,252)	0 (0-704,252)	0 (0-4,483)	0 (0-8,966)	0 (0-4,483)	0 (0-4)
Pakistan	162,419,946	3,548,679 (1,420,045-8,152,000)	2,957,232 (1,071,401-7,342,393)	20,201 (3,350-104,532)	33,669 (5,055-188,301)	14,029 (1,907-84,800)	6,573,809 (6,568,888-6,578,734)

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	Population						
Tajikistan	7,163,506	53,431 (9,089-216,060)	213,724 (87,791-439,737)	104 (3-1,670)	835 (67-6,800)	1,670 (363-6,920)	269,764 (268,766-270,765)
Southeast Asia							
Indonesia	241,973,879	650,700 (167,189-2,076,689)	0 (0-802,242)	448 (30-4,510)	0 (0-3,485)	0 (0-673)	651,146 (649,568-652,728)
Malaysia	23,953,136	1,120,203 (903,015-1,385,149)	61,550 (22,521-153,295)	13,941 (9,175-21,090)	1,532 (458-4,668)	42 (6-258)	1,197,268 (1,195,178-1,199,360)
Singapore	4,425,720	40,044 (14,612-99,473)	0 (0-29,666)	93 (13-568)	0 (0-339)	0 (0-51)	40,137 (39,748-40,531)
Thailand	65,44,371	2,831,674 (2,094,584-3,802,513)	1,651,810 (1,109,483-2,433,484)	33,297 (18,586-59,075)	38,847 (19,690-75,612)	11,330 (5,215-24,195)	4,566,959 (4,562,920-4,571,001)
Far East Asia							
China	1,306,313,812	2,672,334 (1,519,208-4,607,922)	0 (0-704,191)	1,385 (449-4,107)	0 (0-1,255)	0 (0-96)	2,673,718 (2,670,518-2,676,922)
Japan	127,417,244	63,412 (16,358-202,180)	42,275 (7,314-170,599)	8 (1-81)	11 (0-136)	4 (0-57)	105,709-(105,073-106,348)
Mongolia	2,791,272	0 (0-20,350)	0 (0-20,350)	0 (0-37)	0 (0-74)	0 (0-37)	0 (0-4)
Philippines	87,857,473	358,578 (18,451-2,322,755)	0 (0-1,325,171)	372 (1-15,433)	0 (0-17,610)	0 (0-5,023)	358,950 (357,779-360,124)
South Korea	48,422,644	173,918 (29,771-704,549)	521,754 (209,750-1,202,266)	164 (5-2,651)	985 (69-9,047)	1,478 (245-7,719)	698,300 (696,675-699,928)
Asia							
Asia Totals	1,572,802,445	16,881,108 (16,865,273-16,895,909)	6,672,479 (6,666,220-6,678,329)	46,492 (37,484-57,641)	36,754 (27,758-48,619)	7,264 (5,139-10,252)	23,644,097 (23,634,640-23,653,558)

* Population estimate Wikipedia (2002 estimate)

A comparison of the geographic distribution of the deficiency allele frequencies for PIS and PIZ for each of these 20 countries is shown in Fig. 1 for the PI*S allele and Fig. 2 for the PI*Z allele. The prevalences of these two deficiency alleles in each of these 20 Asian countries are compared in Fig. 3

The geographical distribution and calculated numbers for PIMS and PIMZ phenotypic classes are shown in Fig. 4. The geographical distribution and calculated numbers for PIZZ and PISZ phenotypic classes are shown in Fig. 5. The geographical distribution and calculated numbers for PISS and PISZ phenotypic classes are shown in Fig. 6.

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

Discussion

Our tabulation demonstrates that both the PI*S and PI*Z alleles are found in 18 of the 20 countries, and it also demonstrates very striking differences for the distribution of the PI*S and PI*Z AAT Deficiency alleles among these Asian countries as shown for the PI*S allele in Fig. 1 and the PI*Z allele in Fig. 2. 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 to South and West to East change in PI*S and PI*Z prevalences found in Europe [15], no such East to West trend was found for these 20 countries in Asia. In fact, there are striking differences in both prevalences 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 above mentioned 20 Asian countries, the estimated number of ZZ consists of 7,264 individuals. These calculated numbers for each of these 20 Asian countries are 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, and South Korea (1,478). In contrast, ZZ individuals were not found in Jordan (0), Nepal (0), Indonesia (0), Singapore,(0), China (0), and Philippines (0), with low numbers in Israel (2), Japan ((4), Malaysia (42), and Kazakhstan (87), and higher numbers in Asian Russia (110), India (205), and Iran (518)

We are aware that these data should be considered an approximation, since our calculations might have bias related to the sample composition and to 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 also there are marked differences in the contribution of AAT Deficiency data in the 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 in geographic location. This is true for Jordan, Saudi Arabia, Kazakhstan, Nepal, Pakistan, Tajikistan, Philippines, Singapore, Mongolia and South Korea. Inclusion of the 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 should be confirmed as well as extended to other geographic regions in each country.

In addition to the ZZ individuals, we have calculated that there are in Asia 46,492 SZ phenotype individuals and 6,672,479 MZ phenotype individuals, and an impressive number of almost 37 million individuals with MS and SS phenotypes. Although both the PIMS and PISS phenotypes are currently not considered as being at increased risk for development of diseases, and that penetrance (number of subjects who develop clinical disease) of PIMZ and PISZ phenotypes is clearly lower if compared to PIZZ, it is our intention to provide these numbers to illustrate (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 prevalences of PIS and PIZ 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 (95% CI: 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 our earlier publication [15].

*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 PIMS, 6,672,479 (6,666,220 - 6,678,329) for PIMZ, 46,492 (37,484 - 57,641) for PISS, 36,754 (27,758 - 48,619) for PISZ and 7,264 (5,139 - 10,252) for PIZZ. These estimates are in contrast with 40,940,921 (39,913,011 - 41,993,343) for PIMS, 15,440,983 (14,817,481 - 16,089,864) for PIMZ, 797,199 (759,427 - 836,809) for PISS, 601,331 (563,866 - 641,251) for PISZ, and 113,397 (104,666 - 122,849) for PIZZ. Comparison of the phenotypic data obtained from our earlier analysis of AAT Deficiency in Europe with the current database on 20 countries in Asia demonstrates that there are significantly higher numbers in each of the 5 phenotypic classes of AAT Deficiency in these 20 countries in Asia than the 21 countries in Europe!

-The origin of PIS and PIZ deficiency alleles in Asian countries

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

Conclusions

We can conclude that AAT Deficiency is widespread throughout the world. In addition, it is clear that there are significantly high prevalences in countries throughout the continent of Asia. It also is clear that AAT Deficiency is not just a disease of Caucasians (or whites), but that this disease is prevalent in many different races throughout the world.

Acknowledgment

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Figure legends:

Fig.1 Comparison of the geographic distribution of the prevalence of the deficiency allele PIS for each of 20 Asian countries.

Fig. 2. Comparison of the geographic distribution of the prevalence of the deficiency allele PIZ for each of 20 Asian countries.

Fig. 3. Prevalence of the deficiency alleles PIS and PIZ for each of 20 Asian countries in selected geographic regions.

Fig. 4. Geographic distribution and calculated numbers for phenotypes PIMS and PIMZ for each of 20 Asian countries.

Fig. 5. Geographical distribution and calculated numbers for PISS and PISZ for each of 20 Asian countries.

Fig. 6. Geographical distribution and calculated numbers for PISZ and PIZZ for each of 20 Asian countries.

Fig. 1. Comparison of the geographic distribution of the prevalence of the deficiency allele PIS for each of 20 Asian countries.
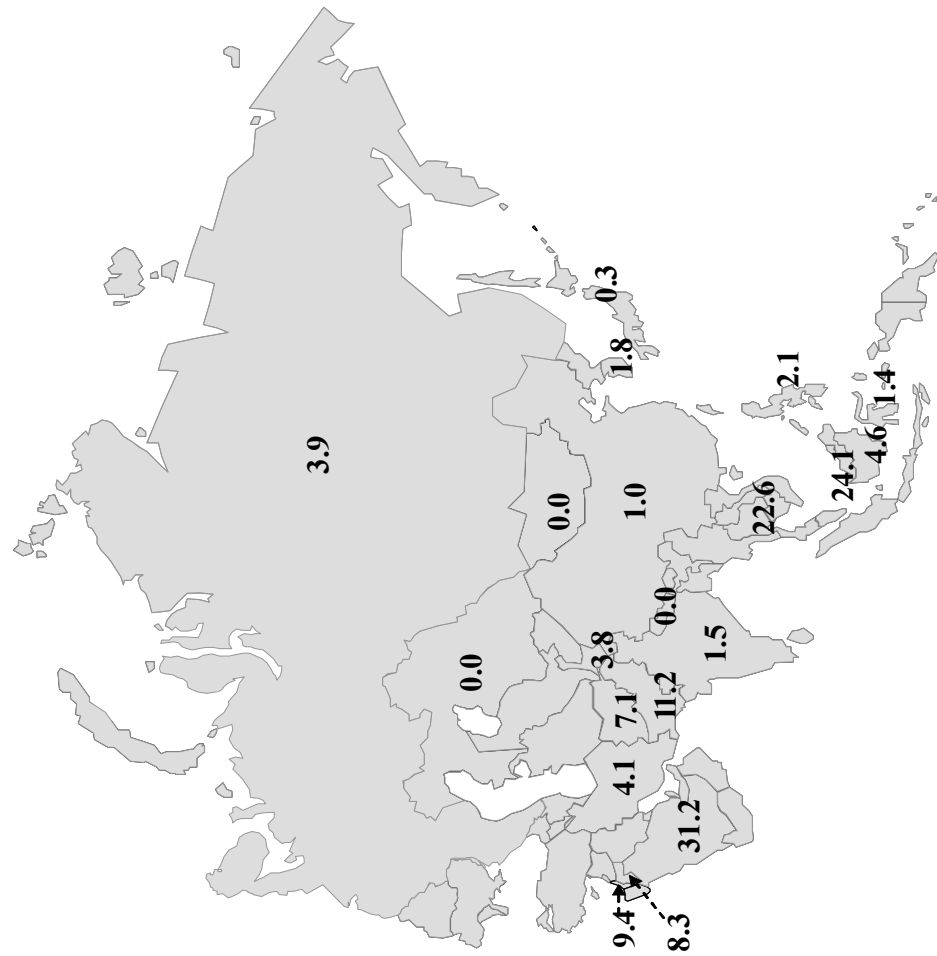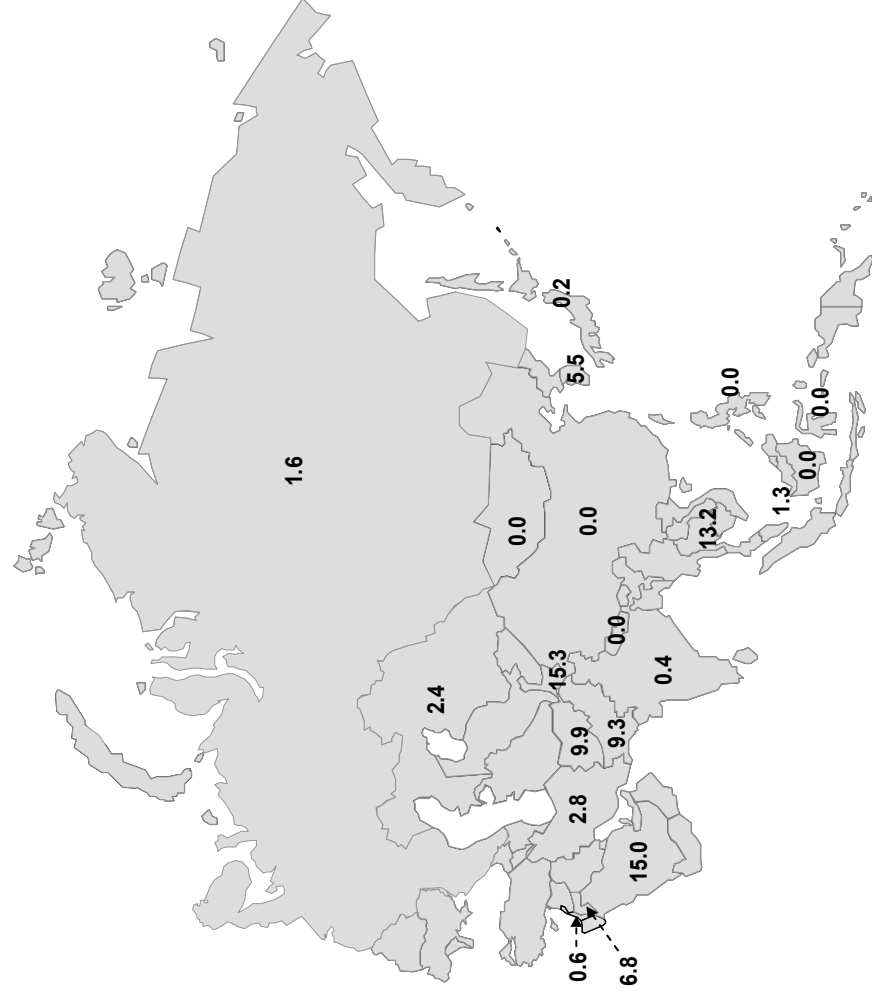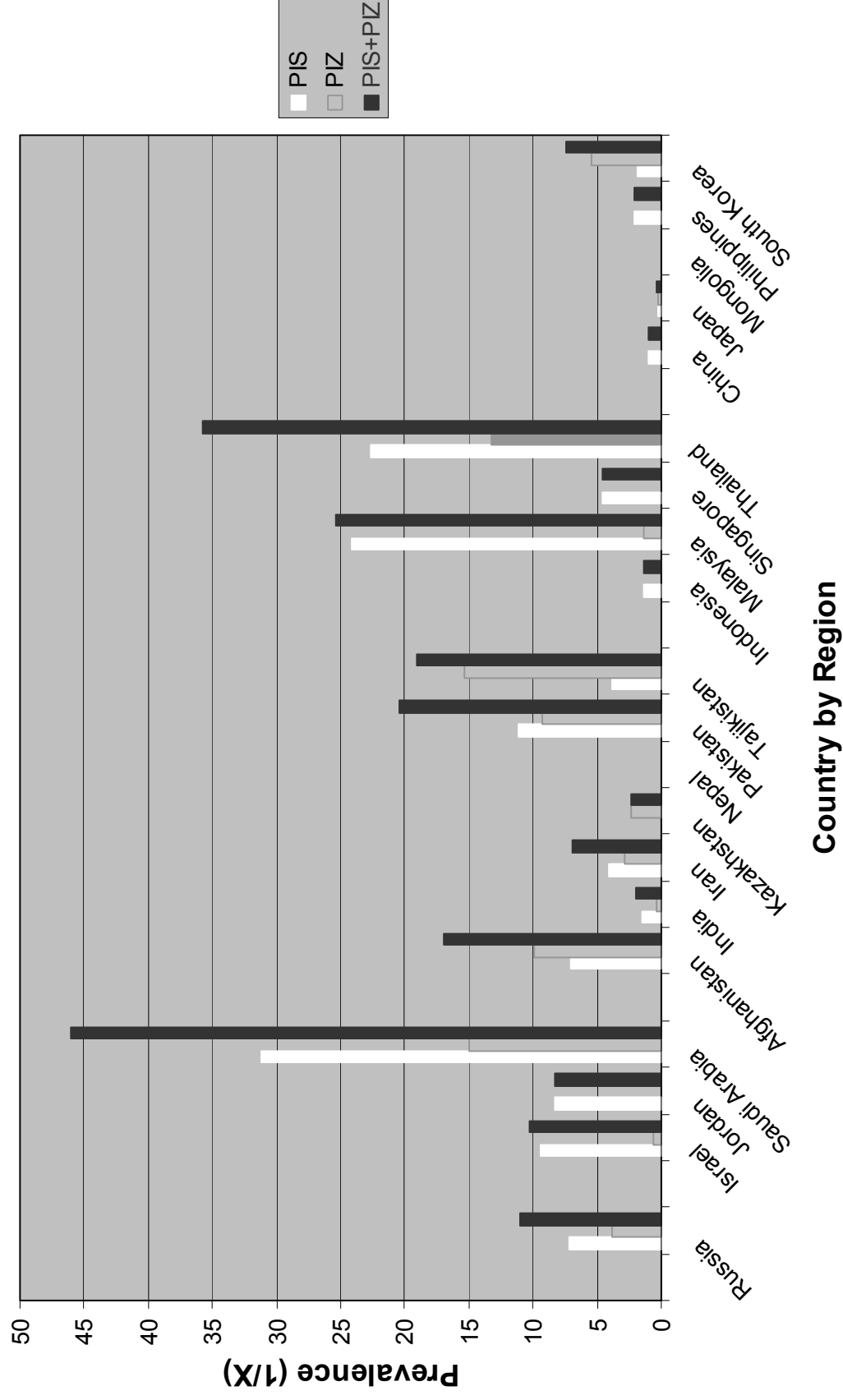
Fig. 2. Comparison of the geographic distribution of the prevalence of the deficiency allele PIZ for each of 20 Asian countries.

Prevalence of the Deficiency Alleles PIS and PIZ in 20 Countries in Asia

Prevalence (1/X)

Country by Region

Legend: PIS, PIZ, PIS+PIZ

Countries: Russia, Israel, Jordan, Saudi Arabia, Afghanistan, India, Kazakhstan, Iran, Nepal, Pakistan, Tajikistan, Indonesia, Malaysia, Singapore, Thailand, China, Japan, Mongolia, Philippines, South Korea

Number of PIMS and PIMZ Phenotypes in 20 Countries in Asia

Countries by Region

Number

Legend: PIMZ Numbers, PIMS Numbers
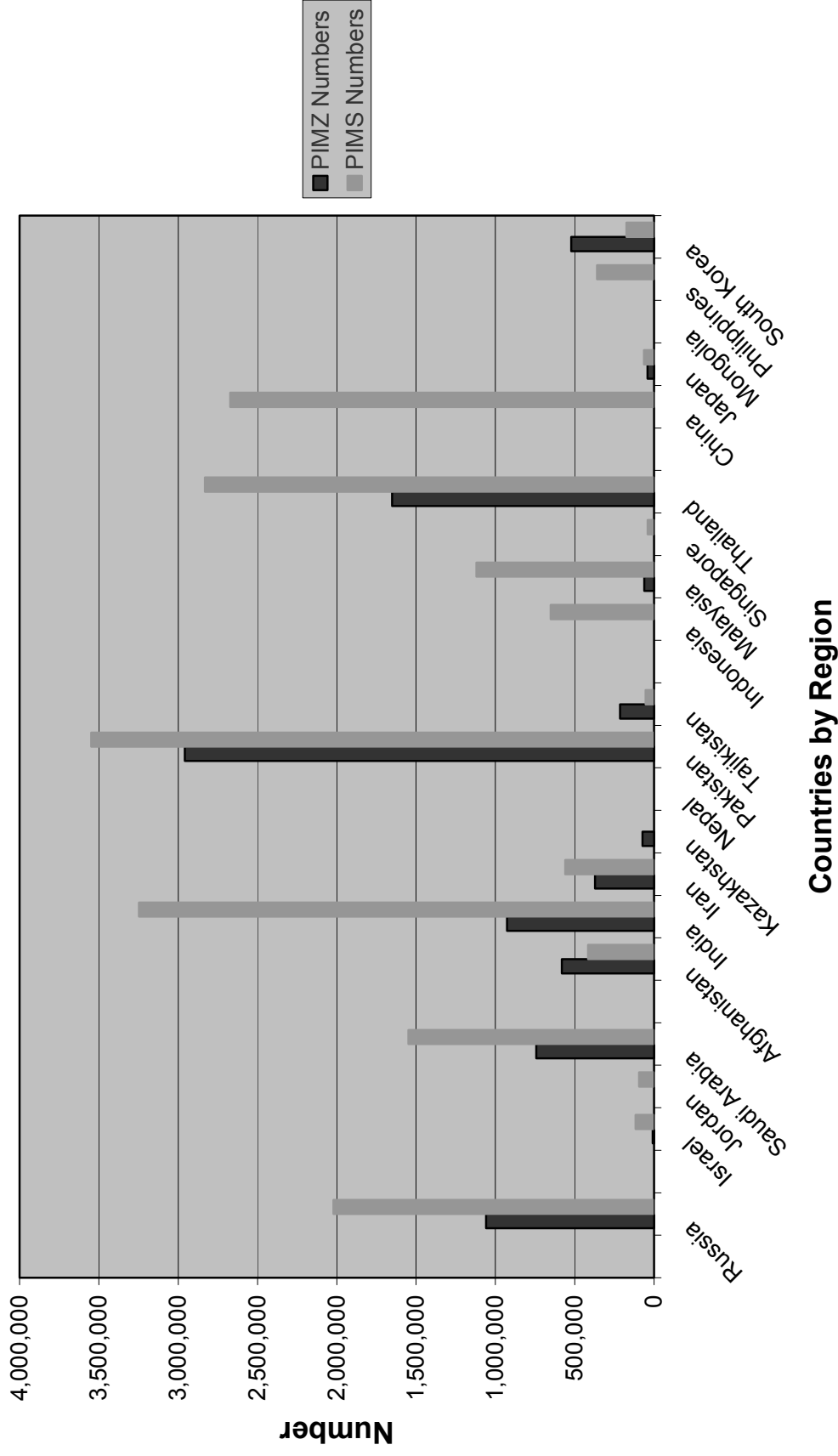
Number of PISS and PISZ Phenotypes in 20 Countries in Asia

Countries by Region

Number

Legend: PISS Numbers, PISZ Numbers

Countries: Russia, Israel, Jordan, Saudi Arabia, Afghanistan, India, Iran, Kazakhstan, Nepal, Pakistan, Tajikistan, Indonesia, Malaysia, Singapore, Thailand, China, Japan, Mongolia, Philippines, South Korea
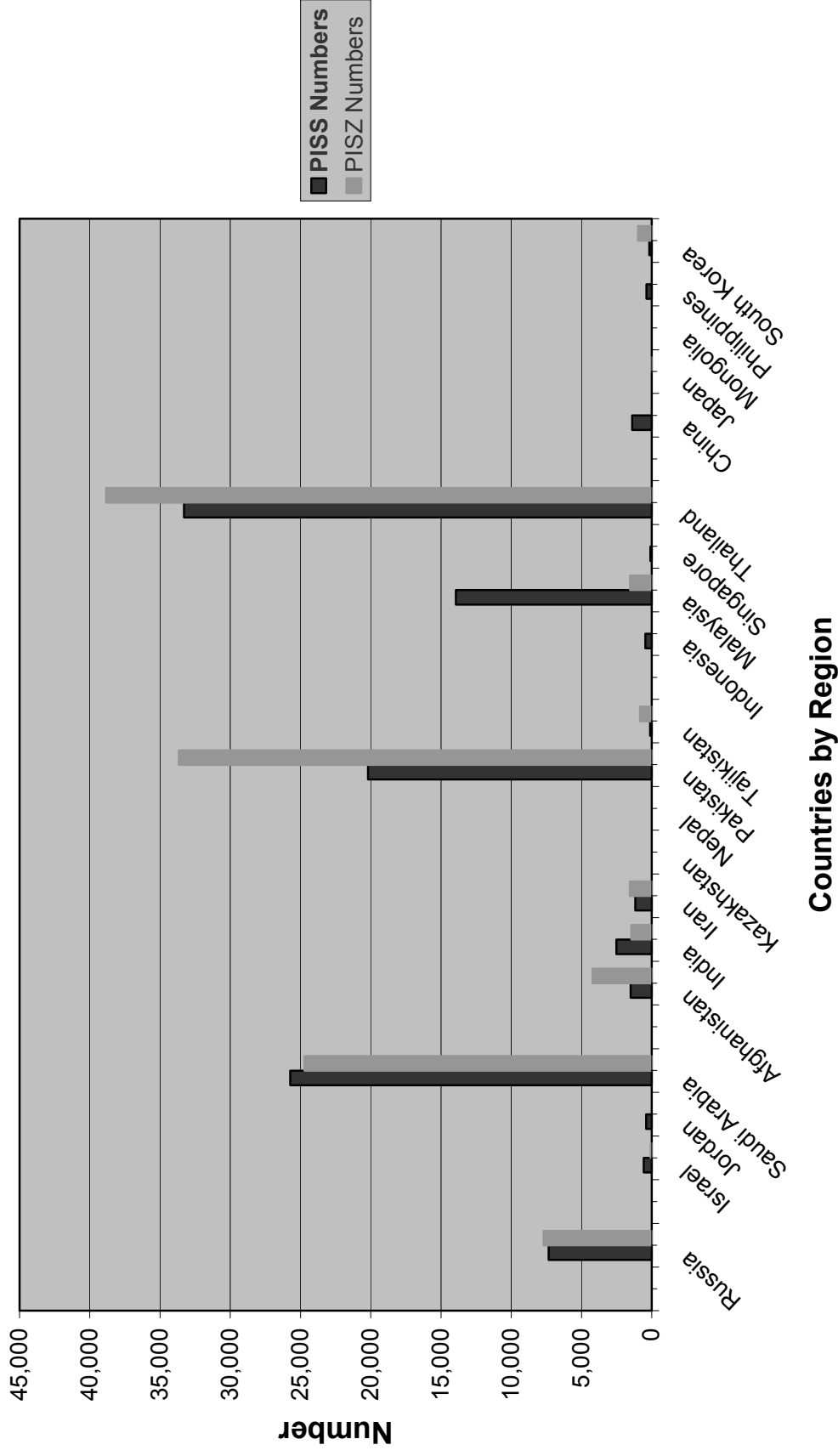
Numbers of PIZZ and PISZ Phenotypes in 20 Countries in Asia

Legend: PIZZ Numbers, PISZ Numbers

Y-axis (Numbers): 0, 5,000, 10,000, 15,000, 20,000, 25,000, 30,000, 35,000, 40,000, 45,000

X-axis (Countries by Region): Russia, Israel, Jordan, Saudi Arabia, Afghanistan, India, Iran, Kazakhstan, Nepal, Pakistan, Tajikistan, Indonesia, Malaysia, Singapore, Thailand, China, Japan, Mongolia, Philippines, South Korea