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ORIGINAL ARTICLE

PI S and PI Z Alpha-1 antitrypsin deficiency worldwide. A review of existing genetic epidemiological data

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

ABSTRACT: ***Alpha-1 antitrypsin deficiency worldwide. A review of existing genetic data. F.J. de Serres, I. Blanco, E. Fernández-Bustillo.***

Background. **AAT deficiency is not a rare disease, but one of the most common congenital disorders increasing susceptibility of deficiency individuals to both lung and liver disease as well as other several adverse health effects. Therefore, information on accurate estimates of the magnitude of alpha-1 antitrypsin deficiency in any given country is critical for the development of screening programs for detection, diagnosis, and treatment of those individuals and/or families at risk.**

Method. **Genetic epidemiological studies for alpha-1 antitrypsin deficiency made by others have been used to determine the percentages and estimates of the numbers in each of the five phenotypic classes (PI MS, PI MZ, PI SS, PI SZ, and PI ZZ) of the most common deficiency alleles: PI S and PI Z in each of 69 countries worldwide and also when grouped into 13 major geographic regions.**

Results. **Our studies have demonstrated striking differences between these estimates when comparisons were made in numeric tables, maps and figures.**

Conclusions. **Our studies demonstrated striking differences in the prevalences of both the PIS and PIZ alleles among these 69 countries and the numbers at risk for AAT Deficiency in a given country in specific geographic regions. Data on the prevalence of the two major deficiency alleles as well as the numbers in those phenotypic classes known to be at risk for AAT Deficiency is considered critical for the identification of individuals at risk for adverse health effects associated with AAT Deficiency as well as the treatment and management of those individuals identified in a given country.**

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

[1] Center for the Evaluation of Risks to Human Reproduction, Environmental Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709-2233, U.S.A.
[2] Respiratory Diseases Branch, Hospital Valle del Nalon, 33920 Langreo, Principado de Asturias,
[3] Bio-statistics Unit, Hospital Central de Asturias, 33006 Oviedo, Principado de Asturias, Spain.

Correspondence: Dr. Frederick J. de Serres, Center for the Evaluation of Risks to Human Reproduction National Toxicology Program, National Institute of Environmental Health Sciences, PO Box 12233, Research Triangle Park, NC 27709-2233, U.S.A.

Correspondence during review: Dr. Frederick J. de Serres, 632 Rock Creek Road, Chapel Hill, NC 27514-6716, U.S.A.; e-mail: deserres@bellsouth.net

Introduction

Alpha1-antitrypsin (AAT) deficiency is a recessive heritable autosomal metabolic disease that results in the synthesis and secretion of defective AAT. Inherited AAT-deficiency is an example of so called conformational disorder. The genes are inherited as co-dominant alleles (products of both genes can be found in the circulation). Several point mutations in AAT cause a perturbation in protein structure resulting in increased intracellular polymerization. Polymerized AAT, may increase disease susceptibility not only by reducing the antiprotease activity of circulating AAT but also by depleting plasma levels of AAT as a result of impaired secretion. In very rare circumstances individuals may inherit AAT null alleles which are characterized by the total absence of serum AAT. About 100 genetic variants of AAT are recognizable. The alphabetic designation of these variants is based upon their electrophoretic mobility. PI M (medium mobility) is the normal allele, and the 2 most frequent deficient alleles are PI S and PI Z. PI ZZ phenotype results in very low serum concentration of AAT (10-15%). PI SS, PI MS, PI MZ, and PI SZ phenotypes result in intermediate serum AAT concentrations (35-70%). At least other 20 variants affect either the amount or the function of the AAT molecule in vivo, but in clinical practice, most (95%) AAT deficiency-related diseases are linked with the PI ZZ phenotype [1-3]. Individuals who are homozygous for the Z (Glu342Lys) alleles undergo significant intracellular polymerization of their AAT and demonstrate a profound suppression of their circulating plasma AAT levels. The retained AAT polymers in the endoplasmic reticulum of hepatocytes can cause liver damage with a variable clinical presentation, from neonatal hepatitis to liver cirrhosis and hepatocellular carcinoma in adults, whilst the lack of circulating protein may

promote development of COPD [4, 5]. The available level of evidence is high regarding to the relationship between AAT deficiency and a high risk for development and liver disease in children, adolescents, and adults, and pulmonary emphysema in adults. The available level of evidence is moderate or weak for the relationship between AAT deficiency and bronchial asthma, bronchiectasis, relapsing panniculitis, systemic vasculitis, fibromyalgia and several other diseases, such as rheumatoid arthritis, intracranial and abdominal aneurysms, arterial dissections, psoriasis, chronic urticaria, mesangiocapillary glomerulonephritis, pancreatitis and pancreatic tumors, multiple sclerosis, and other occasionally reported conditions [1-3].

Most important is the unique susceptibility of AAT-deficient individuals of the PI ZZ type to cigarette smoking [6, 7] as well as exposure to chemical and particulate environmental agents as well as viruses and bacteria [8-12] as important risk factors for the development of airways obstructive diseases [13].

We have used existing genetic epidemiological data on AAT Deficiency collected by others and published in the peer-reviewed medical literature on 69 countries worldwide both to develop estimates of the prevalences of these two deficiency alleles and to use them to obtain estimates of the percentages of the total population in each country in each of the five major deficiency phenotypic classes, namely: PI MS, PI MZ, PI SS, PI SZ and PI ZZ. This analysis has made use of the most recent estimates of the total population of each country and our estimates of the prevalences of PI S and PI Z for each of these 69 countries. Our analysis has used Hardy-Weinberg statistics, to determine the numbers of carriers (PI MS and PI MZ) and deficiency allele homozygotes and heterozygotes (PI SS, PI SZ, and PI ZZ) with 95% confidence intervals on all estimates. We have also grouped the data for individual countries into 13 geographic regions to facilitate comparisons both within a given geographic region as well as between these 13 geographic regions.

The present analysis has provided estimates of the numbers at risk for AAT Deficiency for each of these 69 countries out of a total estimated number of 193 countries worldwide. This unique database has resulted in estimates of the numbers at risk in a given country for a particular human genetic disease. We also have compared the numbers in each of these five phenotypic classes of the total populations from one country to another and demonstrated striking differences among countries in the same geographic region. Such information is critical for a better understanding of the spread of this disease into different counties worldwide. The new data suggest that AAT deficiency may be one of the most common serious single-locus human genetic diseases in the world.

Methods

Estimates of the total population in each country

Estimates of the total population of each country as of July 2006 were obtained from the CIA site (https://www.cia.gov/cia/publications/factbook/index.html).

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

The articles used in the present study were obtained through a variety of sources and have been discussed in earlier publications [13-27]. In the present study, the overall database has been increased from 58 countries, a total of 373 cohorts and 161,356 subjects [14], to 69 countries, a total of 514 cohorts, and 199,449 subjects. These 69 countries are only those out of a possible 193 countries worldwide (https://www.cia.gov/cia/publications/factbook/index.html) where there are genetic epidemiological studies on AAT Deficiency in the peer-reviewed medical literature. Notably absent are data from genetic epidemiological studies on AAT Deficiency in countries in the Caribbean, Central and South America.

Estimating gene frequencies of PI M, PI S, and PI Z

The formulas for developing estimates of the two deficiency allele frequencies and 95% confidence intervals were discussed in earlier articles [16, 24, 25, 28] and are summarized as follows. Basically, the gene frequency "y" was obtained by adding the total number of PI S and PI Z alleles, and expressing this number as a fraction of the total number of PI alleles in the population (the total number of alleles is twice the number of the subjects). PI S and PI Z 95% confidence intervals (95% CI) of outcomes for each selected survey, for "*p*" at a significance level of $\alpha < 0.05$, have been calculated using formulas of Documenta Geigy Scientific Tables for a binomial distribution [29]. When reported PI S or PI Z frequencies were zero: X = 0 (where X expresses the number of variant alleles), the lower calculated limit (p_l) was 0 ($p_l = 0$). The upper limit (p_u) was calculated according to this formula:

$$1\text{-antilog}\ \frac{\log \alpha}{N}$$

where *N* expresses the number of alleles studied. When reported frequencies of PI S or PI Z were different from 0 ($x \neq 0$), we have applied the following formula,

$$p_l,\ p_u = \frac{x\,\mu\,\frac{1}{2} + \frac{c^2}{2}\,\mu\,|c| \sqrt{\left(x\,\mu\,\frac{1}{2}\right)\left(1 - \frac{x\,\mu\,\frac{1}{2}}{N}\right) + \frac{c^2}{4}}}{N + c^2}$$

where *c* is the typified co-ordinate at a significance level of α. The prevalence of every phenotype has been calculated by applying the Hardy-Weinberg Equilibrium principle [30]. The Hardy-Weinberg equation is: $p^2 + 2pq + q^2 = 1$ (it is equal one because you are summing the frequency of all possi-

ble types); source: http://www.baa.duke.edu:16080/BAA93/H-WEQ.HTM. The data on the number of individuals in the total populations in different countries was obtained from: http://www.odci.gov/cia/publications/factbook/index.html.

Results

Comparison of the prevalences of PI S and PI Z in 13 geographic regions

The prevalences of PI S and PI Z are given in geographic maps of the world for PI S in fig. 1 and for PI Z in fig. 2. These maps make it possible to compare the prevalences of these two deficiency alleles in 13 major geographic regions worldwide, namely: Australia/New Zealand, Central and South Africa, Central Asia, Central Europe, Eastern and Southeastern Europe, Far East Asia, Middle East and North Africa, North America, Northern Europe, South Central Asia, Southeast Asia, Southern Europe, and Western Europe.

The distribution of the PI S allele in fig. 1 and PI Z allele in fig. 2 shows striking differences in prevalence within the same geographic region as well as from one geographic region to another. Of particular note are the differences in prevalences of each of these two deficiency alleles throughout Europe in general as well as among the countries in Sub-Sahara Africa.

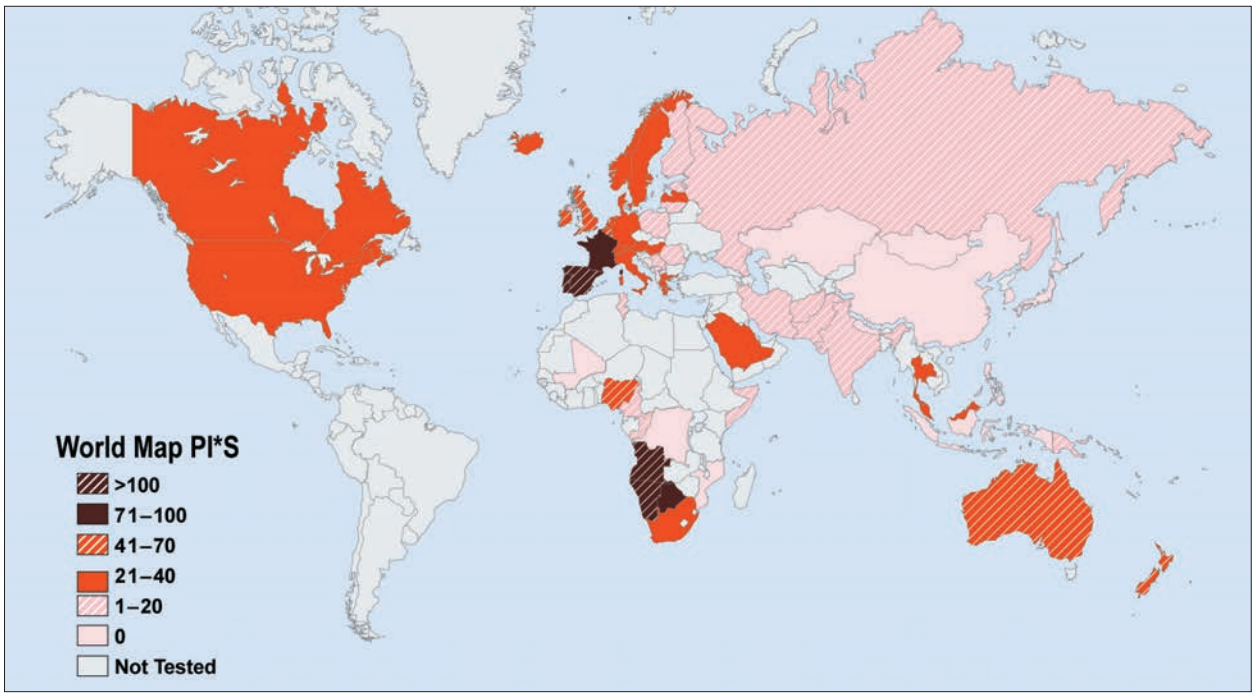

Fig. 1. - Map of the world with the PI S prevalences for each of 69 countries.

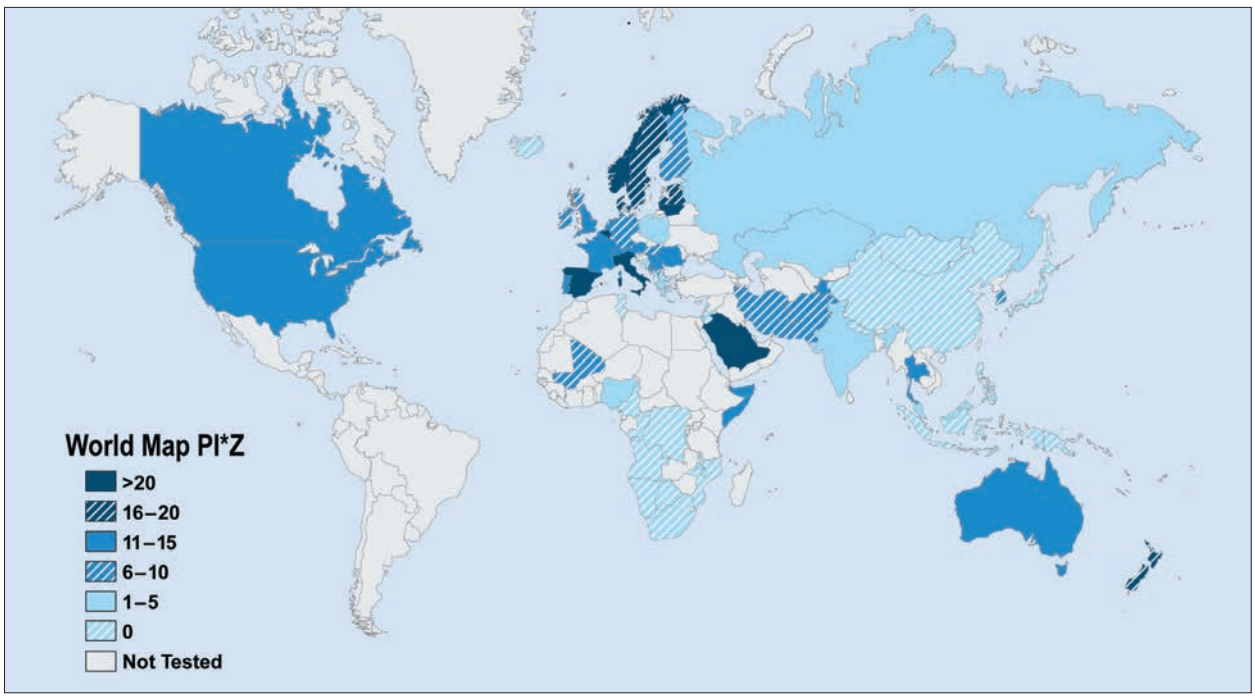

Fig. 2. - Map of the world with the PI Z prevalences for each of 69 countries.

Comparison of the percentages of the total populations in each of 69 countries for the five phenotypic classes of PI S and PI Z

The data plots in figs. 3-7 clearly demonstrate marked differences in the percentages of the total populations of each of these 69 countries in each of the five phenotypic classes.

Populations with >10% of the total population of phenotype PI MS include Afghanistan in Asia, Angola, Namibia and Nigeria in Africa, and Portugal, Spain, France and Belgium in Europe.

Populations with >3% of the total population of phenotype PI MZ include Latvia, Denmark, New Zealand, Estonia, Norway, Belgium and Spain.

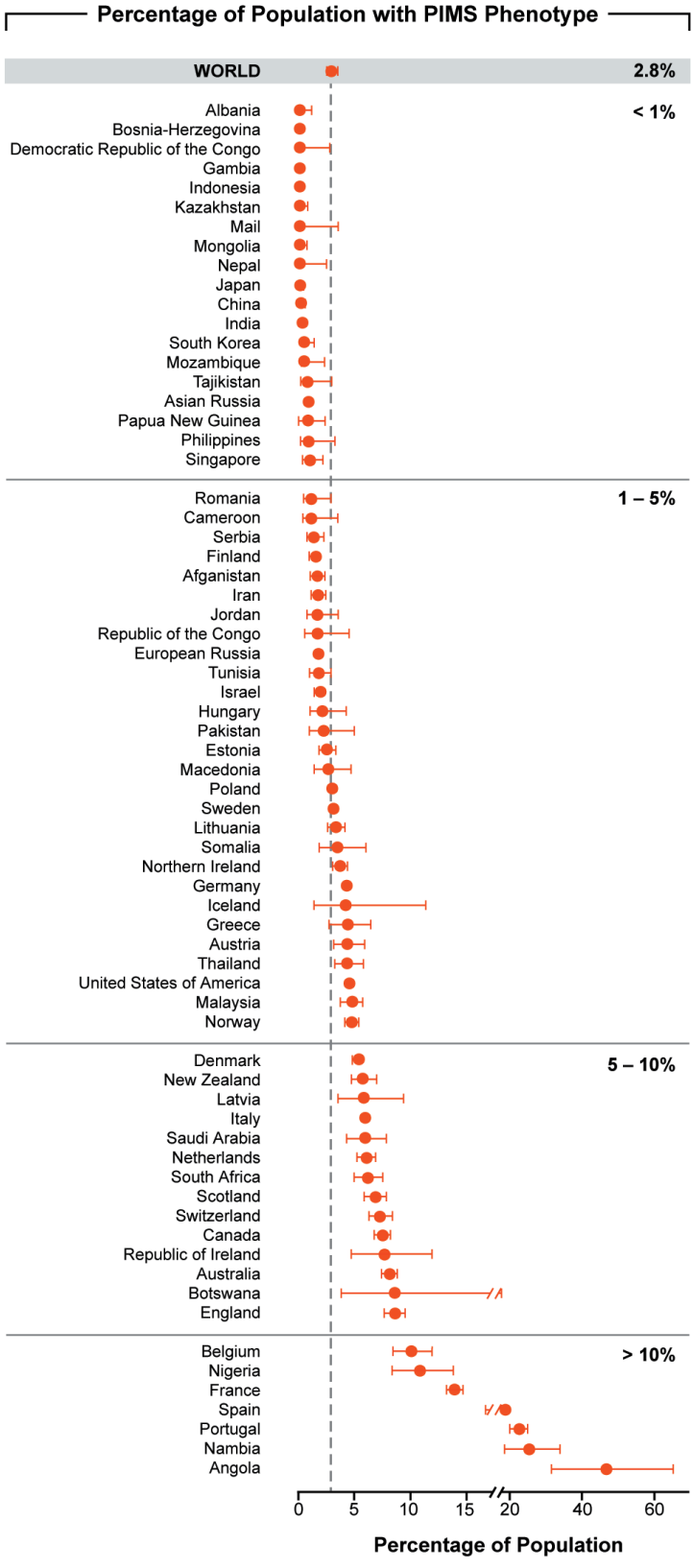

Fig. 3. - Percentages of the total population in each country with phenotype PI MS.

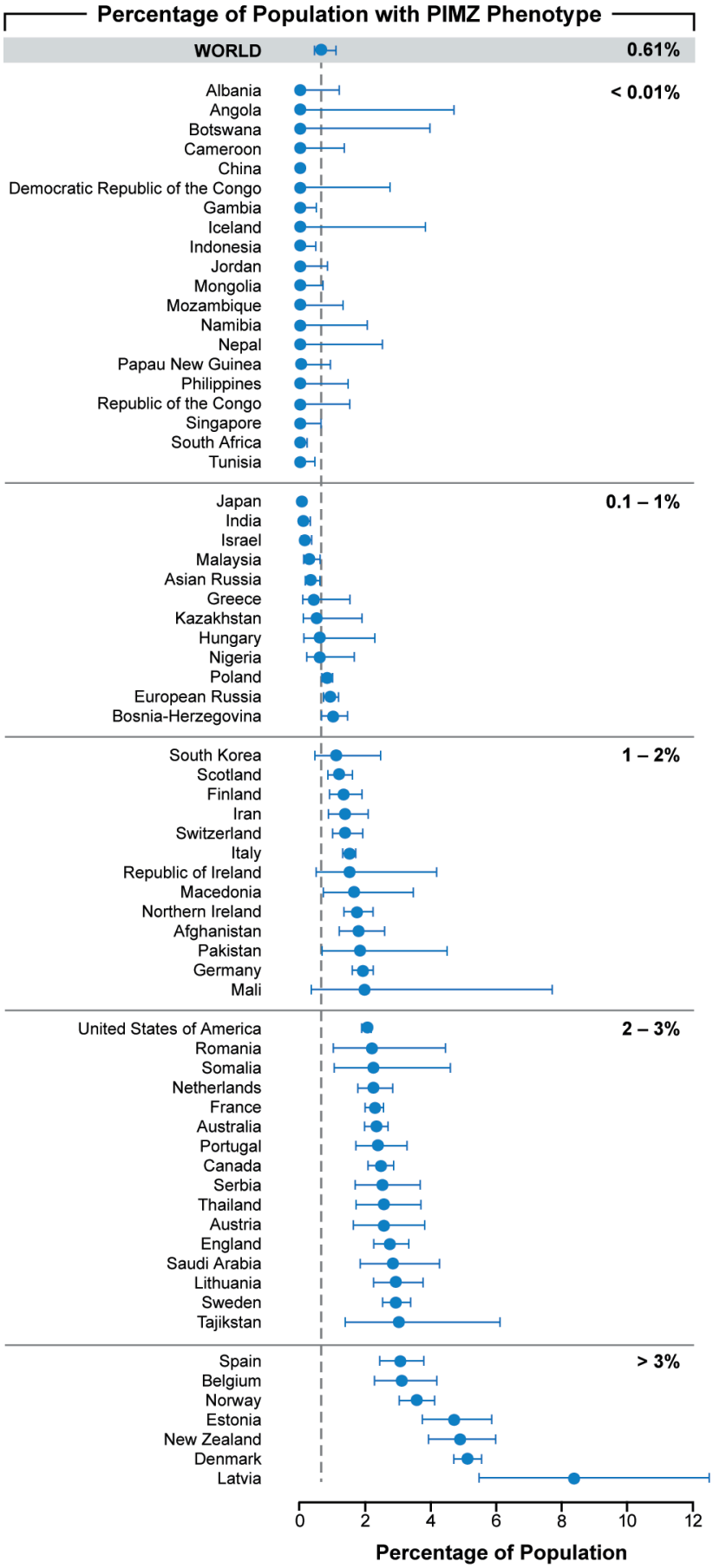

Fig. 4. - Percentages of the total population in each country with phenotype PI MZ.

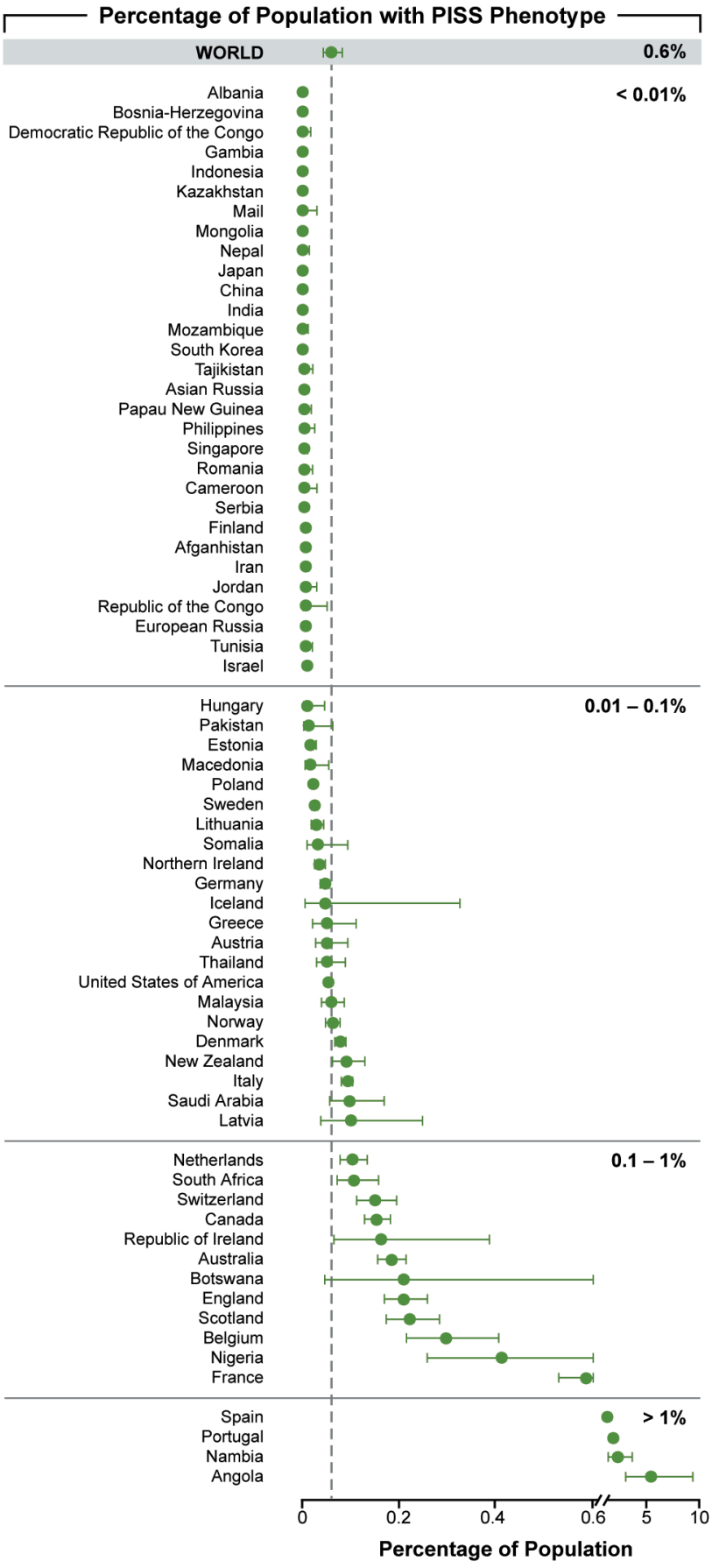

Fig. 5. - Percentages of the total population in each country with phenotype PI SS.

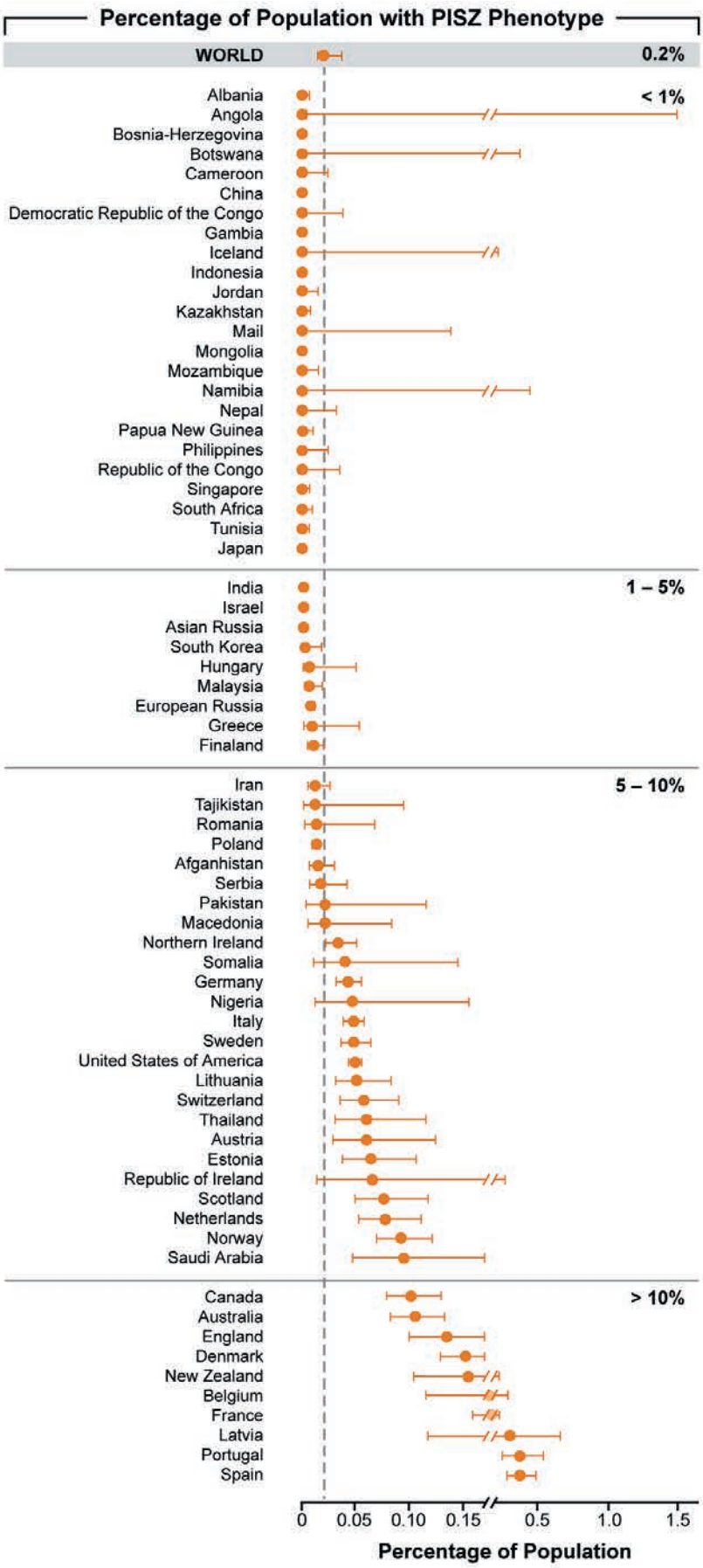

Fig. 6. - Percentages of the total population in each country with phenotype PI SZ.

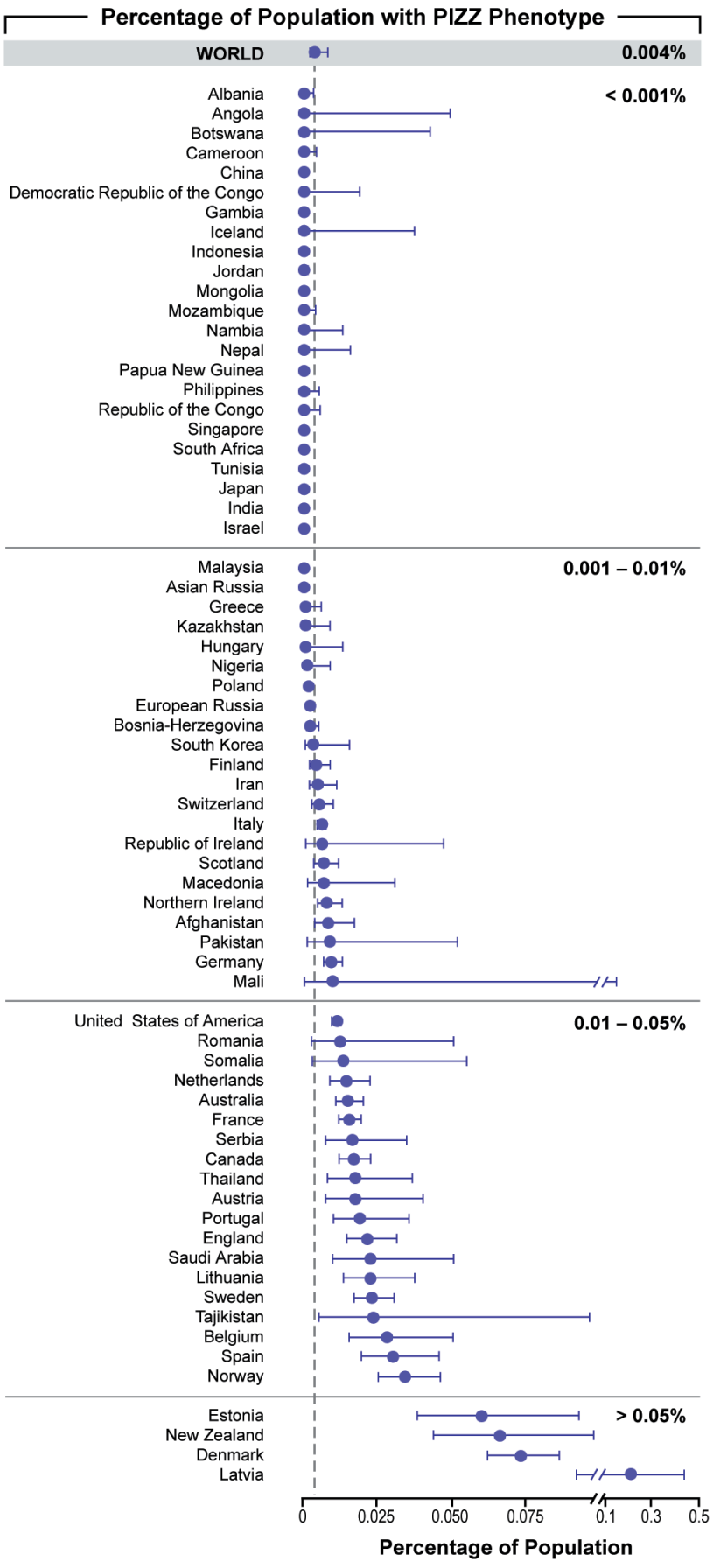

Fig. 7. - Percentages of the total population in each country with phenotype PI ZZ.

Populations with >1% of the total population of phenotype PI SS include Angola, Nambia, Portugal and Spain.
Populations with >10% of the total population of phenotype PI SZ include Spain, Portugal, Latvia, France, Belgium, New Zealand, Denmark, England, Australia and Canada.
Populations with >0.05% of the total population of phenotype PI ZZ include: Latvia, Denmark, New Zealand, and Estonia.

Calculation of the percentages and numbers of total World population for the five phenotypic classes of PI S and PI Z

The percentages in each phenotypic class of these two major deficiency alleles have been calculated for this portion of the total world population by combining the numbers for all of these 69 countries. Thus, using this approach, the percentages of the total world population for phenotypic class PI MS is 2.8%, for PI MZ is 0.6%, for PI SS is 0.6%, for PI SZ is 0.2% and for PI ZZ is 0.004%.

The calculated numbers of the total world population of 4,688,304,652 for all of these 69 countries for phenotypic class PI MS is 125,260,653 (105,917,993 - 160,351,348), for PI MZ is 28,596,350 (19,929,593 - 52,816,942), for PI SS is 2,702,584 (1,971,570 - 3,932,470), for PI SZ is 902,996 (651,675 - 1,756,218), and for PI ZZ is 163,673 (97,104 - 403,295).

Comparison of the numbers in each of the five phenotypic classes of PI S ad PI Z in each of 69 countries grouped into 13 geographic regions

A comparison of the estimated numbers in each of the five phenotypic classes of S and Z in each of the 69 countries grouped into 13 major geographic regions is given in table 1. Using Hardy-Weinberg statistical analysis [28] each estimate is given along with 95% confidence intervals. This tabulation makes it possible to compare the numbers in each of these five phenotypic classes both between countries in the same geographic region as well a between different geographic regions.

Table 1. - Data summaries of the numbers of each of the five PI phenotypes for carriers and deficiency allele combinations with 95% CI for 69 countries worldwide

Geographic Region		Number in each of five phenotypic classes with 95% confidence intervals (Hardy-Weinberg statistics)									
No.	Country and total population	PI MS	95% CI	PI MZ	95% CI	PI SS	95% CI	PI SZ	95% CI	PI ZZ	95% CI
1	Australia/ New Zealand 24,340,222										
	Australia 20,264,082	**1,634,682**	1,495,961-1,785,013	**467,052**	395,626-550,737	**36,906**	31,183-43,645	**21,089**	16,494-26,932	**3,013**	2,181-4,155
	New Zealand 4,076,140	**230,113**	188,281-280,374	**197,855**	159,337-244,871	**3,641**	2,480-5,324	**6,262**	4,198-9,300	**2,692**	1,776-4,061
2	Central Asia 121,424,207										
	Afghanistan 31,056,997	**29,930,910**	29,588,625-30,197,209	**547,702**	366,479-810,528	**1,818**	767-4,218	**4,269**	1,866-9,580	**2,506**	1,135-5,439
	Iran 68,017,860	**1,091,291**	717,428-1,642,316	**916,684**	578,913-1,432,592	**4,630**	2,029-10,371	**7,779**	3,274-18,093	**3,267**	1,321-7,891
	Kazakhstan 15,185,844	**0.0**	0-133,745	**72,397**	12,432-291,633	**0.0**	0-296	**0.0**	0-1,290	**87**	3-1,406
	Tajikistan 7,163,506	**53,431**	9,089-216,060	**213,724**	97,791-439,737	**104**	3-1,670	**835**	67-6,800	**1,670**	363-6,920
3	Central Europe 162,674,445										
	Austria 7,320,815	**313,773**	224,055-435,621	**185,045**	28,408-118,892	**3,695**	1,929-6,987	**4,358**	2,047-9,113	**1,285**	543-2,971
	Belgium 10,379,067	**8,871,669**	8,665,697- 9,056,130	**321,050**	234,560-436,695	**30,575**	22,115-42,101	**18,847**	11,849-29,775	**2,905**	1,587-5,264
	Germany 82,422,299	**3,397,686**	3,009,496-3,832,861	**1,558,795**	1,302,236-1,863,508	**37,306**	29,460-47,194	**34,231**	25,495-45,891	**7,852**	5,516-11,156
	Netherlands 16,491,461	**988,846**	851,273-1,146,717	**369,516**	288,999-471,057	**16,805**	12,627-22,319	**12,560**	8,574-18,337	**2,347**	1,455-3,766
	Poland 38,536,869	**1,115,552**	989,447-1,256,955	**312,513**	248,561-392,198	**8,420**	6,653-10,647	**4,718**	3,343-6,644	**661**	420-1,037
	Switzerland 7,523,934	**545,800**	469,703-632,981	**103,962**	73,416-146,299	**11,085**	8,329-14,718	**4,223**	2,604-6,803	**402**	203-786

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Table 1. - Data summaries of the numbers of each of the five PI phenotypes for carriers and deficiency allele combinations with 95% CI for 69 countries worldwide

Geographic Region		Number in each of five phenotypic classes with 95% confidence intervals (Hardy-Weinberg statistics)									
No.	Country and total population	PI MS	95% CI	PI MZ	95% CI	PI SS	95% CI	PI SZ	95% CI	PI ZZ	95% CI
4	Eastern Europe 62,500,540										
	Albania 3,581,655	0.0	0-43,899	0.0	0.0-43,899	0.0	0-135	0.0	0-269	0.0	0-135
	Bosnia-Herzegovina 4,498,976	0.0	0-6,774	44,017	28,790-66,612	0.0	0.0-2.6	0.0	0-50	109	47-248
	Greece 10,688,058	449,273	285,017-695,755	40,843	6,968-165,926	5,132	2,130-12,029	933	104-5,738	42	1-684
	Hungary 9,981,334	200,156	86,693-432,310	57,188	9,778-230,903	1,033	199-4,751	590	45-5,075	84	2-1,355
	Macedonia 2,050,554	51,954	27,039-96,174	33,062	14,325-71,549	342	95-1,153	435	101-1,716	138	27-638
	Romania 22,303,552	242,363	76,672-667,423	484,727	222,783-997,114	681	70-5,084	2,723	407-15,191	2,723	591-11,348
	Serbia 9,396,411	121,703	68,830-210,269	234,714	156,895-347,308	410	133-1,210	1,581	606-3,998	1,524	691-3,302
5	Far East 1,627,538,681										
	Asian Russia 45,000,000	346,223	216,650-546,213	138,489	64,170-285,307	685	270-1,694	548	160-1,769	110	24-462
	China 1,313,973,713	2,687,805	1,527,992-4,634,634	0.0	0-708,273	1,393	452-4,131	0.0	0-1.263	0.0	0-96
	Japan 127,417,244	63,412	16,358-202,180	42,275	7,314-170,599	8	0.5-81	11	0.5-136	4	0-57
	Mongolia 2,832,224	0.0	0-20,649	0.0	0-20,649	0.0	0-38	0.0	0-75	0.0	0-38
	Philippines 89,468,677	721,216	122,653-2,913,419	0.0	0-1,338,852	1,515	45-24,223	0.0	0-22,264	0.0	0-5,116
	South Korea 48,846,823	175,773	30,099-711,804	527,319	212,063-1,214,646	166	5-2,674	994	70-9,127	1,491	247-7,787
6	Middle East and North Africa 49,378,388										
	Israel 6,276,883	113,996	84,188-153,617	7,434	1,913-23,737	530	291-958	69	13-296	2	0-23
	Jordan 5,906,760	96,712	42,028-208,643	0.0	0-51,093	402	77-1,856	0.0	0-909	0.0	0-111
	Saudi Arabia 27,019,731	1,583,448	1,174,698-2,117,957	760,055	492,043-1,158,278	26,321	14,900-46,005	25,268	12,483-50,319	6,064	2614-13,759
	Tunisia 10,175,014	171,069	94,463-301,569	0.0	0-48,764	744	231-2,286	0.0	0-739	0.0	0-60
7	North America 331,543,147										
	Canada 33,098,932	2,450,659	2,224,570-2,697,612	807,728	682,276-955,063	50,466	41,961-60,641	33,267	25,739-42,939	5,482	3,947-7,601
	United States of America 298,444,215	13,322,416	12,596,165-14,088,284	6,054,649	5,571,675-6,578,116	160,197	143,685-178,575	145,610	127,113-166,760	33,088	28,113-38,932
8	Northern Europe 134,793,811										
	Denmark 5,450,661	287,260	263,618-312,880	278,586	255,320-303,833	4,237	3,593-4,994	8,219	6,961-9,700	3,985	3,371-4,710
	Estonia 1,324,333	32,586	23,625-44,672	62,068	49,245-77,934	218	117-405	831	486-1,412	792	506-1,232
	European Russia 103,000,000	1,727,305	1,415,656-2,104,231	946,696	722,088-1,237,482	7,478	5,047-11,050	8,197	5,149-12,996	2,246	1,313-3,822
	Finland 5,231,372	75,714	52,160-109,058	68,387	46,162-100,434	282	135-581	509	239-1,070	230	106-493

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Table 1. - Data summaries of the numbers of each of the five PI phenotypes for carriers and deficiency allele combinations with 95% CI for 69 countries worldwide

Geographic Region		Number in each of five phenotypic classes with 95% confidence intervals (Hardy-Weinberg statistics)									
No.	Country and total population	PI MS	95% CI	PI MZ	95% CI	PI SS	95% CI	PI SZ	95% CI	PI ZZ	95% CI
	Iceland 299,388	12,469	3,860-33,960	0.0	0-11,555	136	14-976	0.0	0-664	0.0	0-113
	Latavia 2,274,735	131,311	78,363-214,160	189,671	123,700-284,675	2,221	837-5,664	6,417	2,642-15,058	4,635	2,085-10,008
	Lithuania 3,585,906	116,596	90,627-149,438	104,414	79,980-135,752	1,011	619-1,644	1,811	1,092-2,986	811	482-1,356
	Norway 4,610,820	218,031	190,098-249,777	163,032	139,109-190,815	2,815	2,160-3,664	4,210	3,162-5,598	1,574	1,157-2,138
	Sweden 9,016,596	275,766	237,177-320,287	263,644	225,968-307,261	2,258	1,683-3,026	4,318	3,206-5,807	2,064	1,527-2,785
9	South Central Asia 1,285,448,488										
	India 1,095,351,995	3,215,504	1,403,599-6,961,215	918,715	158,487-3,714,172	2,432	467-11,324	1,390	105-12,084	199	6-3,224
	Nepal 27,676,547	0.0	0-704,252	0.0	0-704,252	0.0	0-4,483	0.0	0-8,966	0.0	0-4,483
	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
10	Southeast Asia 334,632,886										
	Indonesia 245,452,739	0.0	0-1238849	0.0	0-1,238,849	0.0	0-1,589	0.0	0-3,178	0.0	0-1,589
	Malaysia 24,385,858	1,140,439	919,328-1,410,172	62,662	22,927-156,064	14,193	9,341-21,471	1,560	466-4,752	43	6-263
	Paupa New Guinea 5,670,544	44,193	11,301- 140,645	0.0	0-54,542	87	6-878	0.0	0-680	0.0	0-132
	Singapore 4,492,150	40,532	14,781-100,752	0.0	0-30,047	95	13-577	0.0	0-344	0.0	0-51
	Thailand 64,631,595	2,796,507	2,068,571-3,755,288	1,631,296	1,095,704-2,403,262	32,884	18,356-58,341	38,365	19,446-74,673	11,190	5,150-23,894
11	Southern Europe 170,013,357										
	France 60,876,136	8,459,305	8,011,518-8,928,347	1,372,093	1,200,482-1,567,171	353,788	320,228-390,693	114,768	95,969-137,155	9,308	7,190-12,037
	Italy 58,133,509	3,380,553	3,137,504-3,641,090	865,864	746,896-1,003,073	53,101	45,979-61,302	27,202	21,891-33,776	3,484	2,606-4,652
	Portugal 10,605,870	2,341,072	2,092,043-2,612,373	251,053	179,163-349,447	175,698	144,790-212,577	37,683	24,800-56,871	2,021	1,062-3,804
	Spain 40,397,842	7,391,275	6,726,264-8,108,543	1,227,523	977,131-1,537,673	437,979	370,713-516,551	145,477	107,708-195,913	12,080	7,823-18,576
12	Sub-Sahara Africa 313,336,723										
	Angola 7,993,572	3,704,338	2,510,453-5,233,355	0.0	0.0-378,305	429,161	231,182-759,977	0.0	0.0-109,873	0.0	0.0-3,971
	Botswana 1,639,833	138,911	61,522-286,456	0.0	0.0-65,485	3,388	743-13,499	0.0	0.0-6,172	0.0	0.0-705
	Cameroon 17,340,702	194,469	49,646-617,177	0.0	0.0-239,299	551	37-5,508	0.0	0.0-4,271	0.0	0.0-828
	Democratic Republic of the Congo 62,660,551	0.0	0.0-1,738,339	0.0	0.0-1,738,339	0.0	0.0-12,065	0.0	0.0-24,129	0.0	0.0-12,065
	Gambia 1,641,564	0.0	0.0-8,627	0.0	0.0-8,627	0.0	0.0-11	0.0	0.0-23	0.0	0.0-11
	Mali 11,716,829	0.0	0.0-419,223	227,489	38,292-906,149	0.0	0.0 -3,763	0.0	0.0-16,266	1,126	34-17,579
	Mozambique 19,686,505	71,717	3,707-463,194	0.0	0.0-264,125	66	0.2-2,725	0.0	0.0-3,108	0.0	0.0-886

→

Table 1. - Data summaries of the numbers of each of the five PI phenotypes for carriers and deficiency allele combinations with 95% CI for 69 countries worldwide

Geographic Region		Number in each of five phenotypic classes with 95% confidence intervals (Hardy-Weinberg statistics)									
No.	Country and total population	PI MS	95% CI	PI MZ	95% CI	PI SS	95% CI	PI SZ	95% CI	PI ZZ	95% CI
	Namibia 2,044,147	511,182	364,397-697,030	0.0	0.0-42,484	43,870	24,851-75,059	0.0	0.0-9,150	0.0	0.0-279
	Nigeria 131,859,731	14,221,630	10,969,381-18,280,620	790,091	246,406-2,216,234	537,228	337,556-846,344	59,692	15,165-205,212	1,658	170-12,439
	Republic of the Congo 3,702,314	61,959	19,581-169,730	0.0	0.0-57,247	264	27-1,956	0.0	0.0-1,319	0.0	0.0-222
	Somalia 8,863,338	297,680	159,032-537,507	198,453	90,907-409,429	2,650	782-8,453	3,533	894-12,878	1,178	256-4,905
	South Africa 44,187,637	2,710,557	2,188,911-3,343,929	0.0	0.0-106,086	46,836	31,152-70,076	0.0	0.0-4,446	0.0	0.0-71
13	Western Europe 60,679,757										
	England 50,093,800	4,276,331	3,810,693-4,792,742	1,372,156	1,119,436-1,678,462	104,563	84,128-129,773	67,103	49,427-90,895	10,766	7,260-15,916
	Northern Ireland 1,710,300	61,808	51,421-74,151	29,648	22,686-38,614	590	412-843	566	364-878	136	80-229
	Republic of Ireland 3,797,257	287,376	176,684-454,852	57,475	17,954-159,510	6,076	2421-14,674	2,430	492-10,292	243	25-1,805
	Scotland 5,078,400	345,718	299,429-398,447	59,307	42,398-82,516	11,214	8,711-14,406	3,848	2,467-5,967	330	175-618
	World 4,688,304,652	133,090,705	113,708,163-168,172,533	28,596,350	19,929,594-52,816,941	2,702,584	1,971,573-3,932,472	902,996	613,837-1,794,055	163,673	97,103-403,297

In table 2, the data for each of the 13 geographic regions are given along with a summary for all of the 69 countries collated as a summary for this portion of the 193 countries in the World. Of particular interest are the estimates of 28,596,350 for phenotype PI MZ, 902,996 for phenotype PI SZ, and 163,673 for phenotype PI ZZ out of an estimated 4,688,304,652 inhabitants for these 69 countries.

Table 2. - Comparison of the numbers in each phenotypic class in each of 13 geographic regions and the 95% confidence intervals (Hardy-Weinberg statistics) on each estimate

Geographic Region			Numbers in each phenotypic class with 95% confidence intervals (Hardy-Weinberg statistics)								
No.	Region	Total population	PI MS	95% CI	PI MZ	95% CI	PI SS	95% CI	PI SZ	95% CI	PI ZZ	95% CI
1	Australia/ New Zealand	24,340,222	1,864,796	1,684,243-2,065,387	664,907	554,962-795,608	40,547	33,663-48,969	27,351	20,691-36,232	5,705	3,957-8,216
2	Central Asia	121,424,207	31,075,632	30,315,142-32,189,329	1,750,507	1,055,614-2,974,489	6,553	2,799-16,556	12,883	5,208-35,763	7,530	2,821-21,656
3	Central Europe	162,674,445	15,233,326	14,209,671-16,361,265	2,850,881	2,176,180-3,428,649	107,886	81,113-143,966	78,936	53,912-116,563	15,451	9,724-24,981
4	Eastern Europe	62,500,540	1,065,450	544,251-2,152,603	894,549	439,538-1,923,312	7,598	2,626-24,365	6,262	1,262-32,038	4,621	1,358-17,710
5	Far East	1,627,538,681	3,994,428	1,913,750-9,028,899	708,083	283,546-3,738,326	3,766	772-32,840	1,552	230-34,633	1,604	271-13,556
6	Middle East and North Africa	49,378,388	1,965,225	1,395,376-2,781,786	767,490	493,955-1,281,871	27,998	15,500-51,105	25,337	12,495-52,263	6,067	2,614-13,953
7	North America	331,543,147	15,773,075	14,820,734-16,785,895	6,862,378	6,253,951-7,533,180	210,663	185,646-239,216	178,877	152,851-209,700	38,570	32,060-46,533
8	North Europe	134,793,811	2,877,037	2,355,184-3,38,463	2,076,498	1,641,571-2,649,740	20,657	14,204-32,004	34,513	22,936-55,291	16,337	10,547-26,656
9	South Central Asia	1,285,448,488	6,764,183	2,823,644-15,817,467	3,875,948	1,229,888-11,760,818	22,633	3,816-120,339	35,058	5,160-209,351	14,227	1,912-92,507
10	Southeast Asia	344,632,886	4,021,661	3,013,980-6,645,706	1,693,957	1,118,631-3,882,674	47,259	27,715-82,856	39,924	19,911-83,627	11,233	5,156-25,929
11	Southern Europe	170,013,357	21,572,205	19,967,328-23,90,353	3,716,534	3,103,672-4,457,364	1,020,567	881,710-1,181,123	325,130	250,367-423,715	26,892	18,681-39,069
12	Sub-Sahara Africa	313,336,723	21,912,444	16,326,629-31,795,187	1,216,033	375,605-6,431,809	1,064,014	26,331-1,799,436	63,225	16,059-396,87	3,962	460-3,962
13	Western Europe	60,679,757	4,971,233	4,338,225-5,720,192	1,518,586	1,202,474-1,959,101	122,443	95,672-59,697	73,947	52,750-108,033	11,475	7,540-18,567
	World	4,688,304,652	133,090,705	113,708,163-168,172,533	28,596,350	19,929,594-52,816,941	2,702,584	1,971,573-3,932,472	902,996	613,837-1,794,055	163,673	97,103-403,297

Comparison of the prevalences of PI S and PI Z in 13 geographic regions worldwide

The maps shown in figs. 8-20 make it possible to compare the prevalences of the most common deficiency alleles PI S and PI Z in each of these 69 countries grouped into13 major geographic regions.

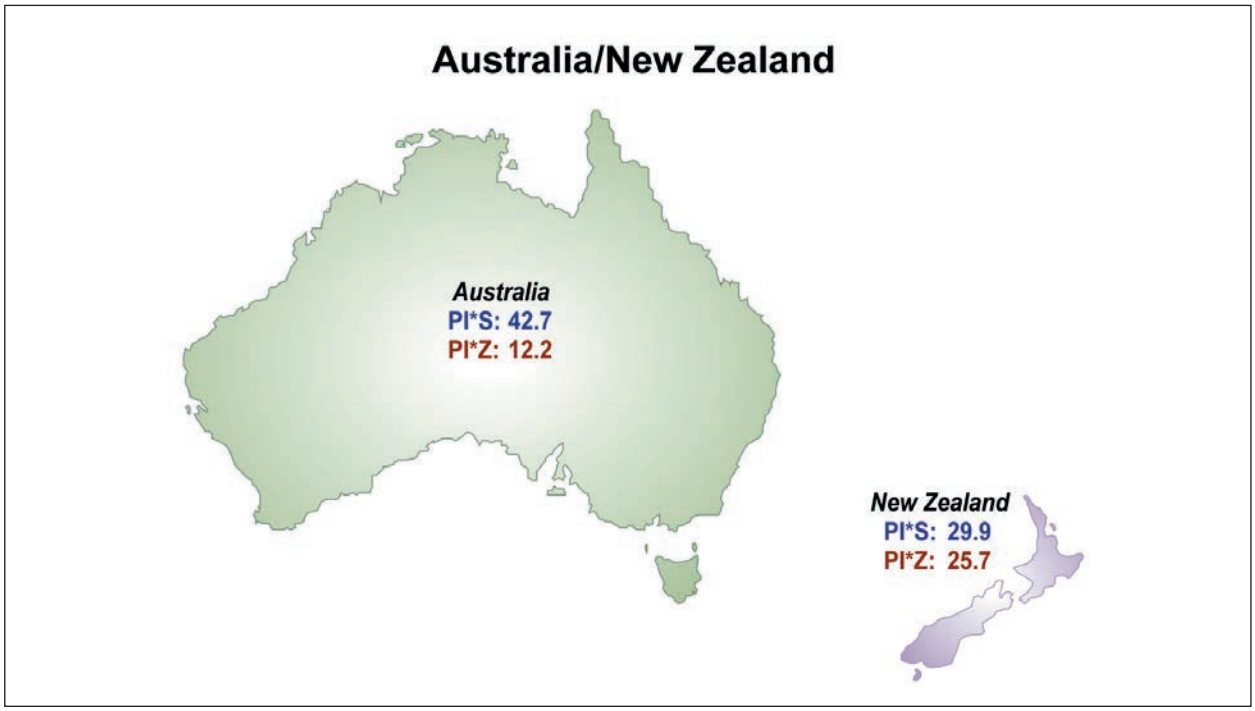

Fig. 8. - Prevalence of the PI S and PI Z deficiency alleles in Australia/New Zealand.

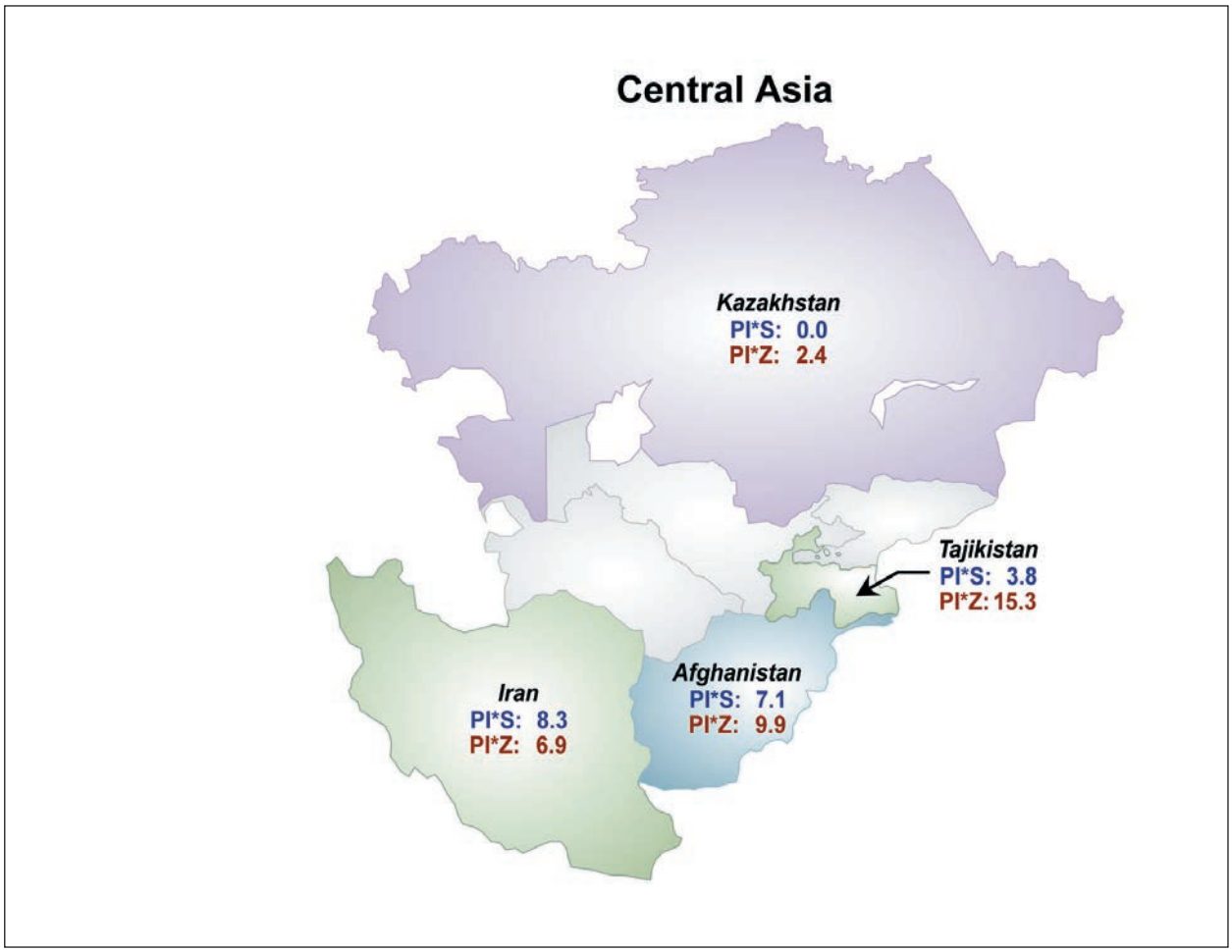

Fig. 9. - Prevalence of the PI S and PI Z deficiency alleles in Central Asia.

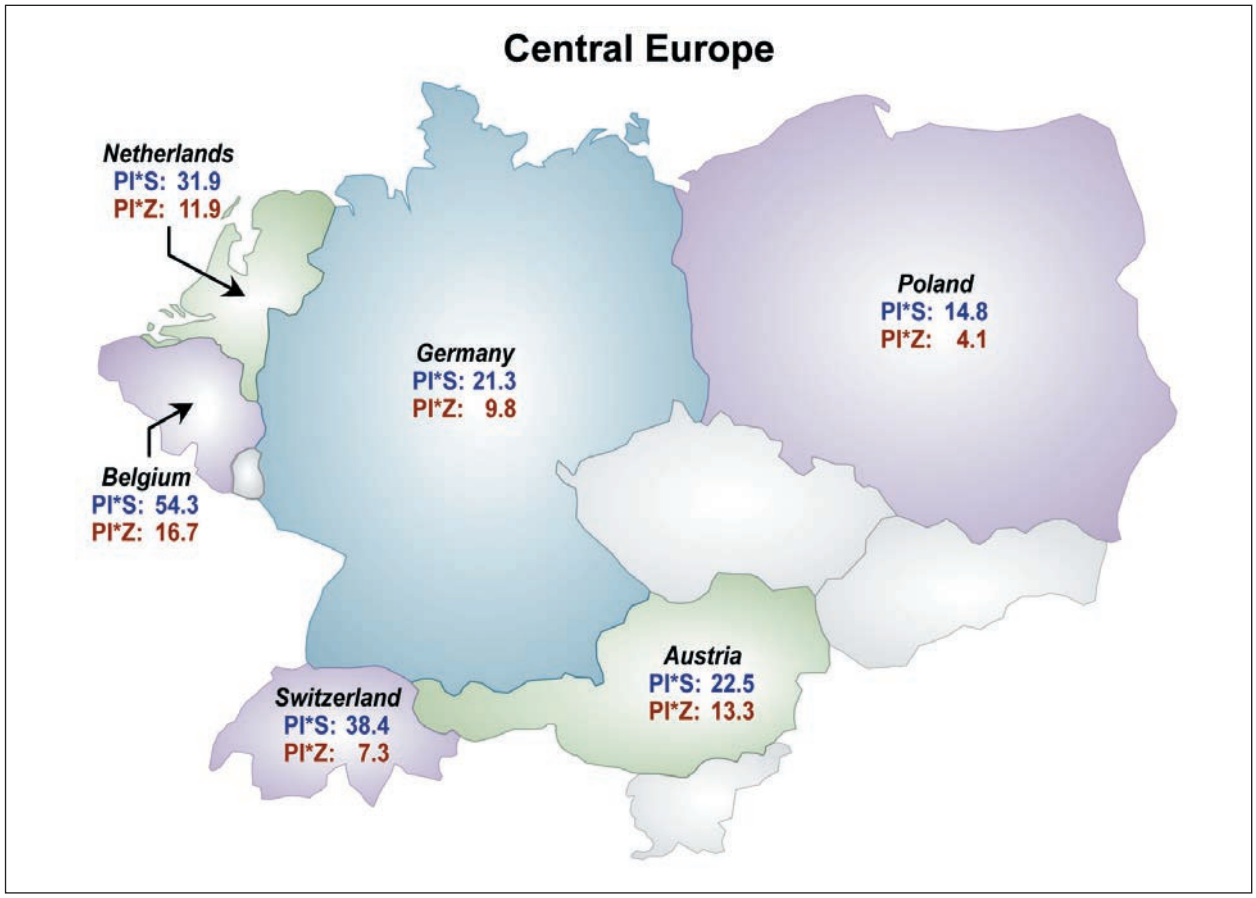

Fig. 10. - Prevalence of the PI S and PI Z deficiency alleles in Central Europe.

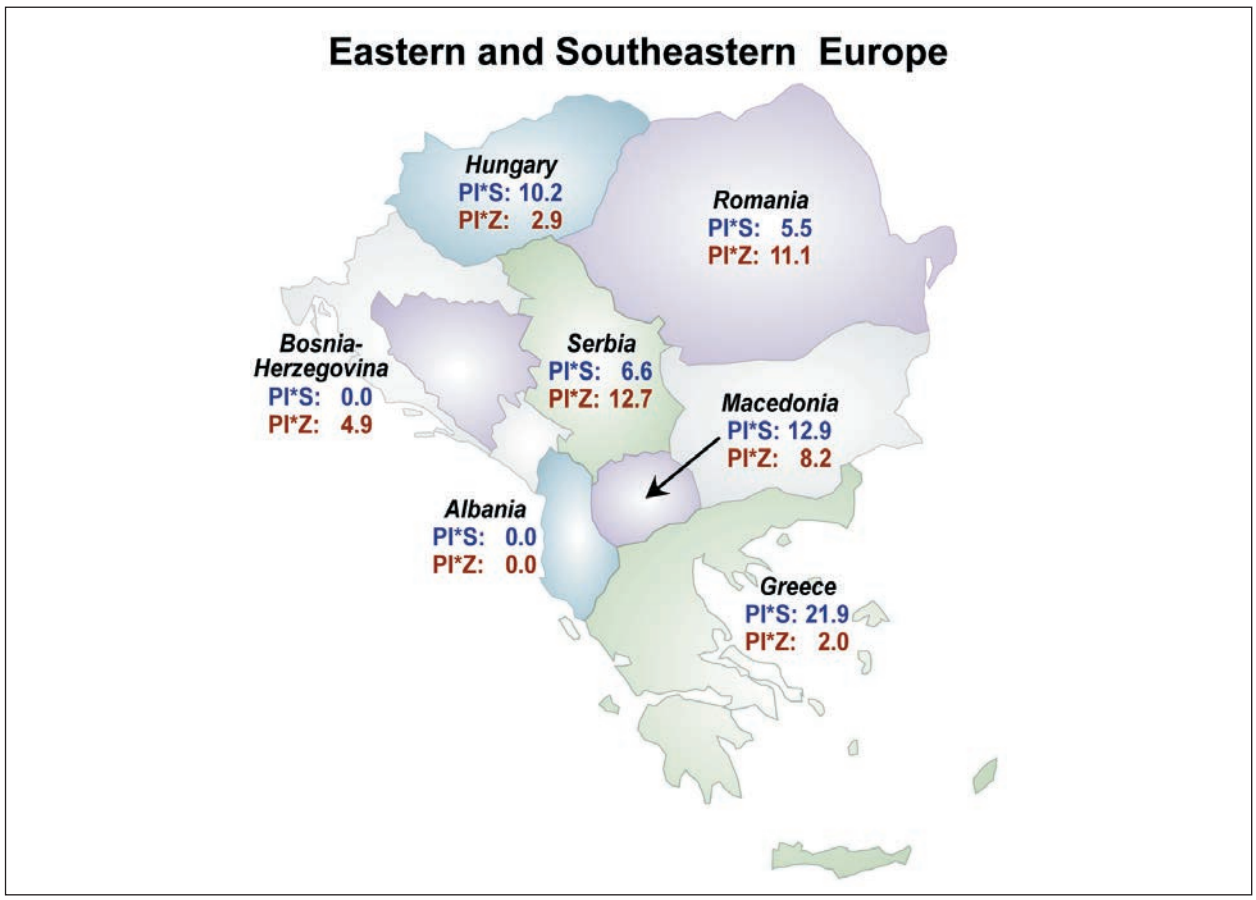

Fig. 11. - Prevalence of the PI S and PI Z deficiency alleles in Eastern and Southeastern Europe.

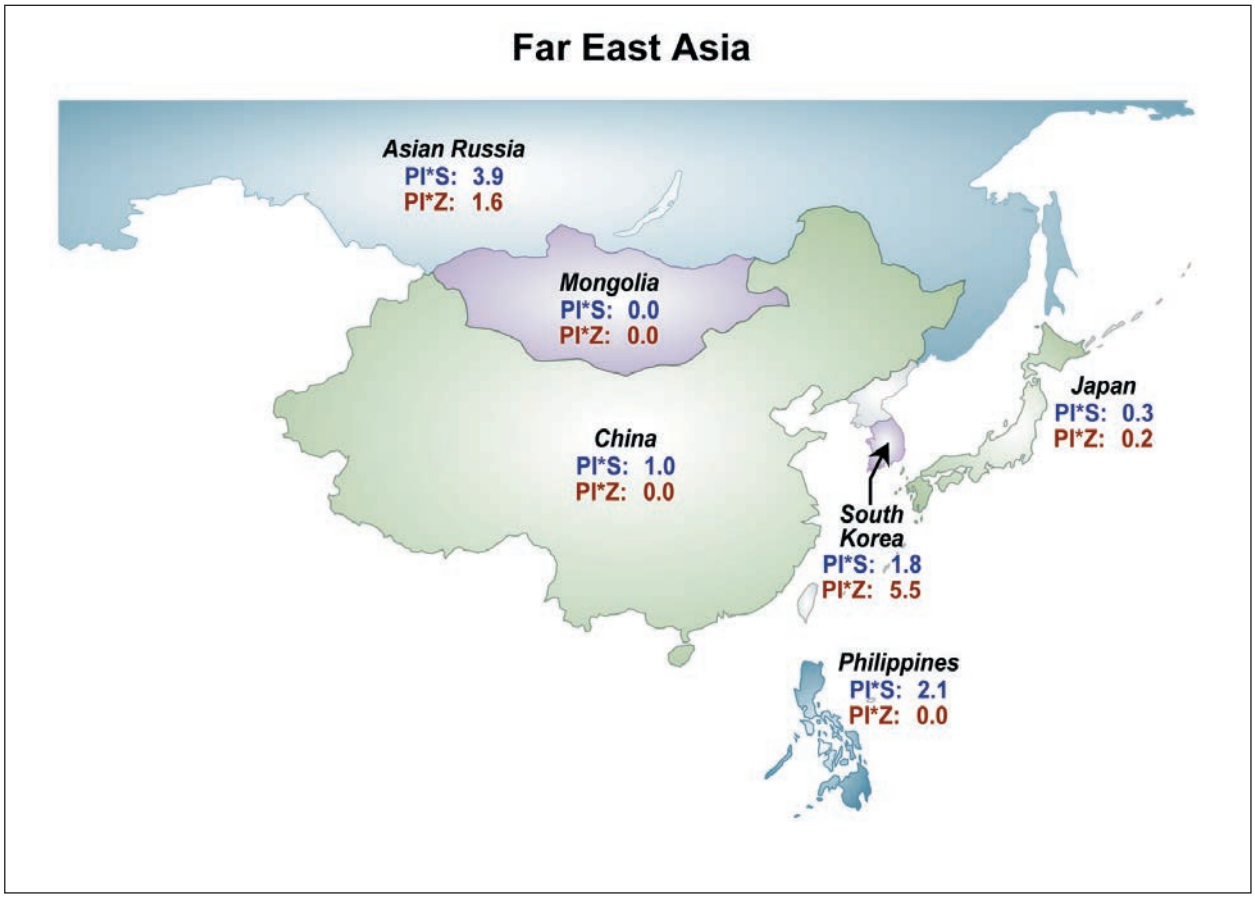

Fig. 12. - Prevalence of the PI S and PI Z deficiency alleles in Far East Asia.

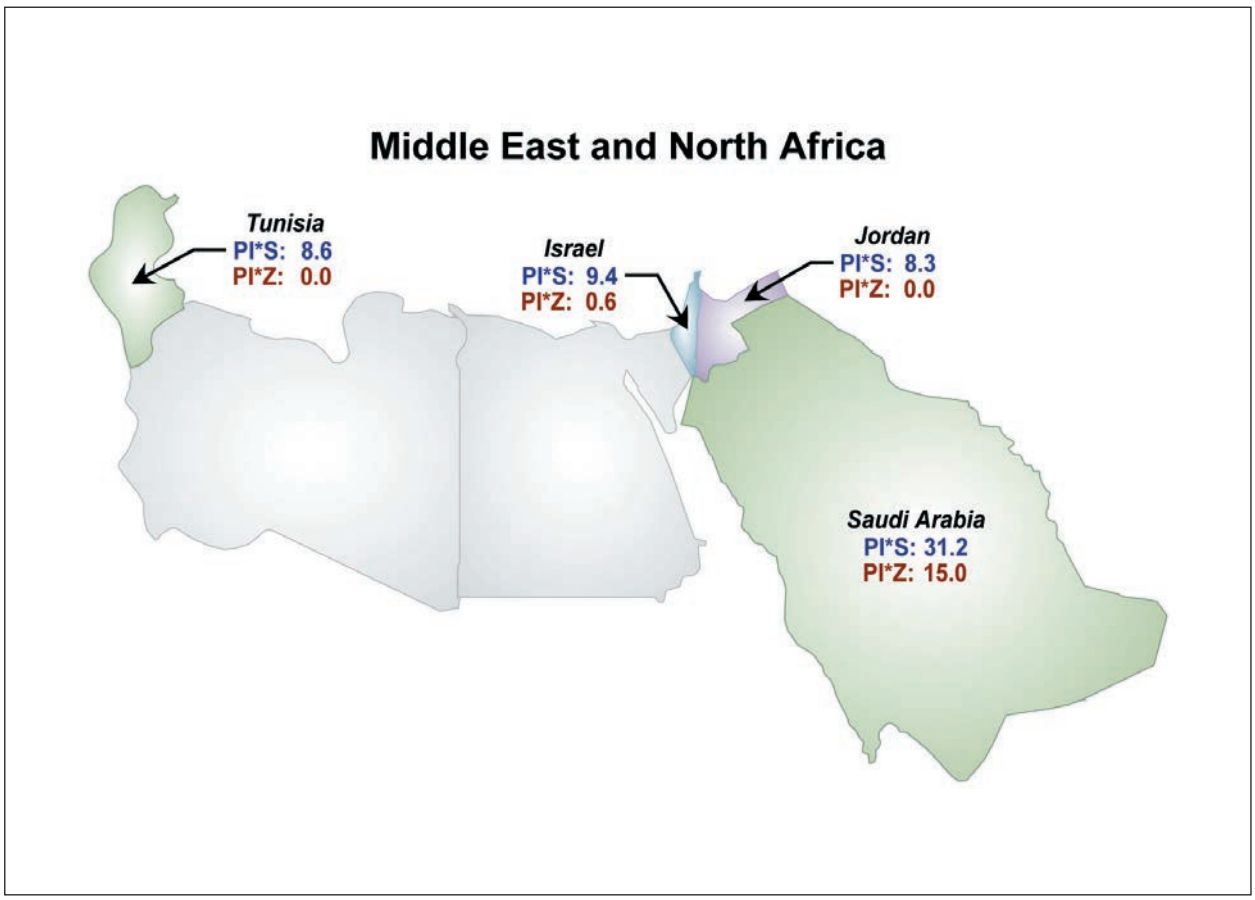

Fig. 13. - Prevalence of the PI S and PI Z deficiency alleles in Middle East and North Africa.

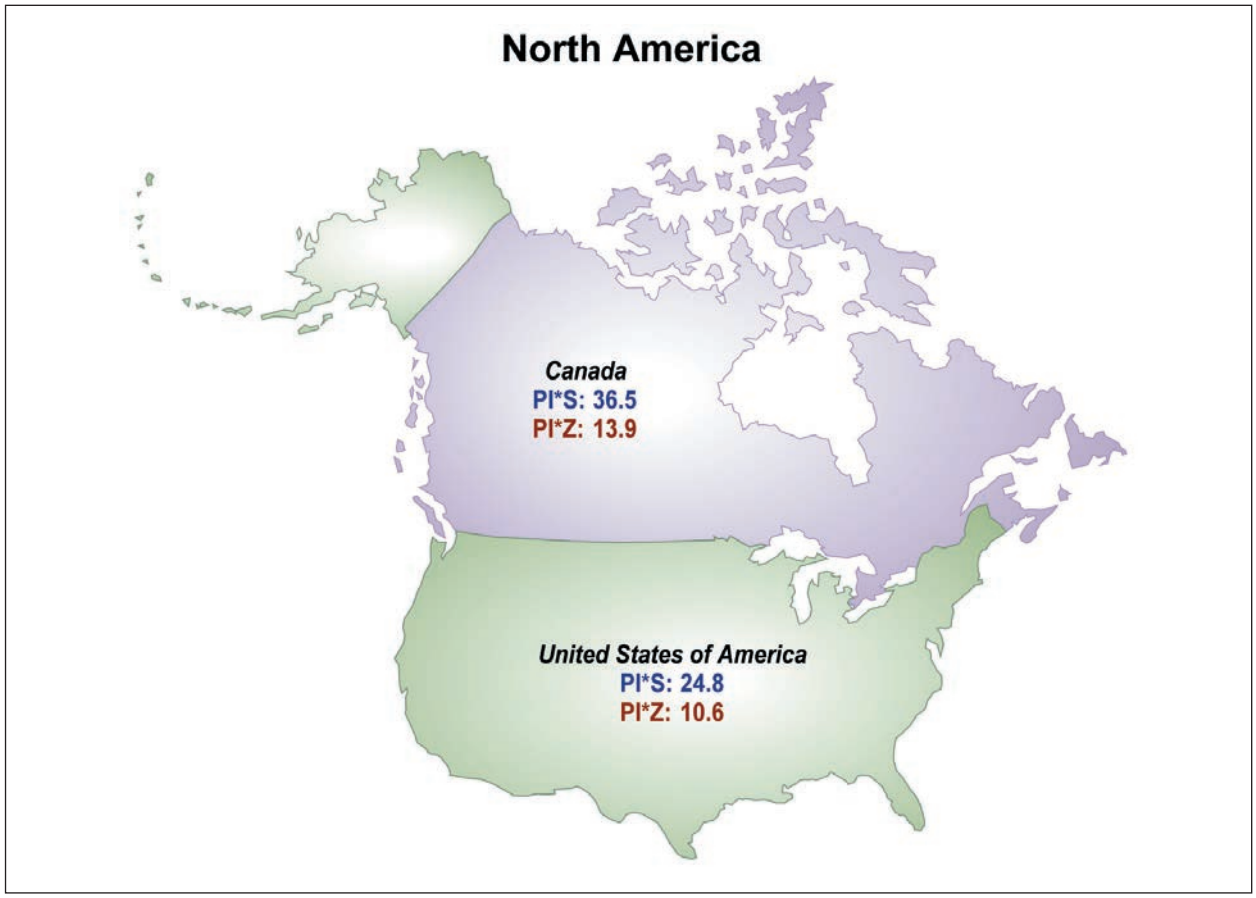

Fig. 14. - Prevalence of the PI S and PI Z deficiency alleles in North America.

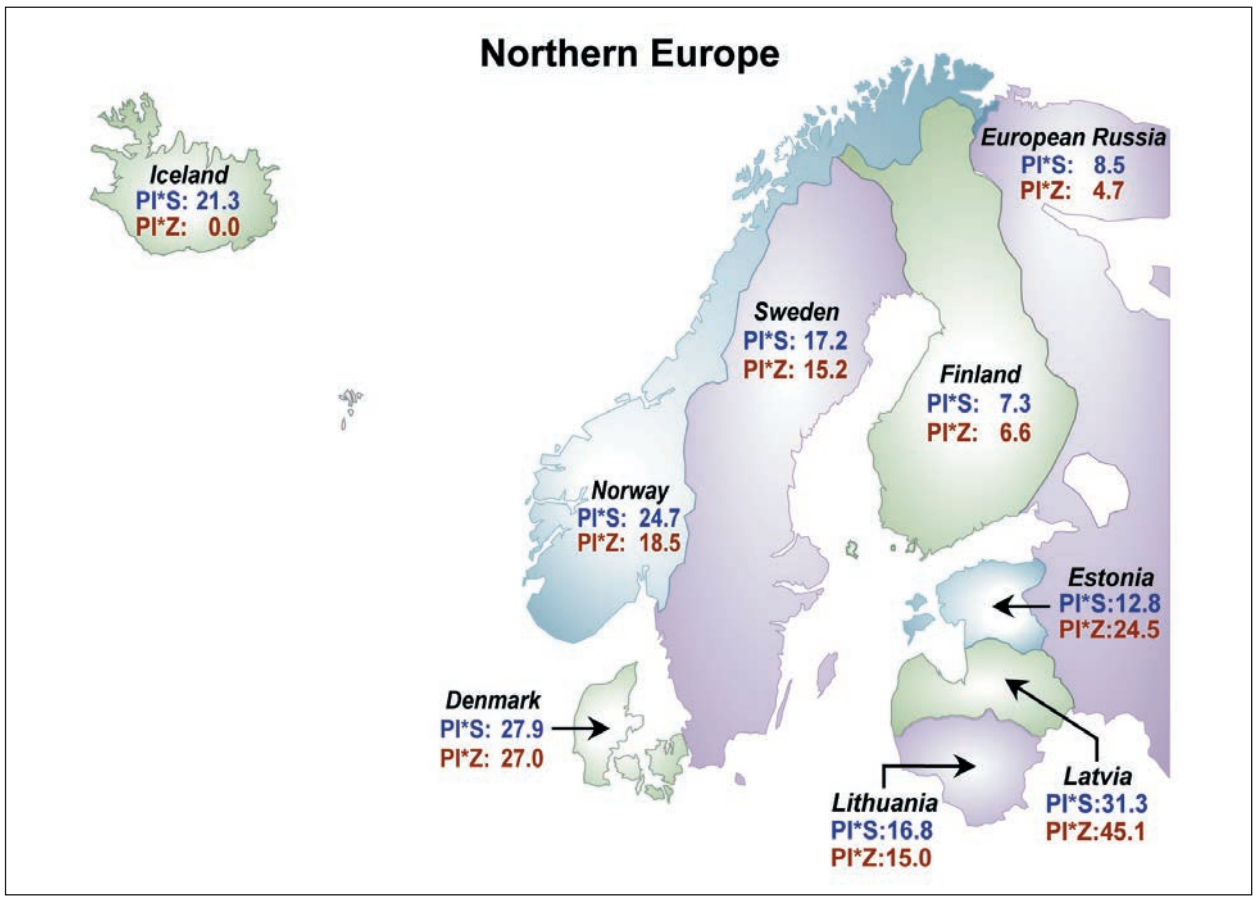

Fig. 15. - Prevalence of the PI S and PI Z deficiency alleles in Northern Europe.

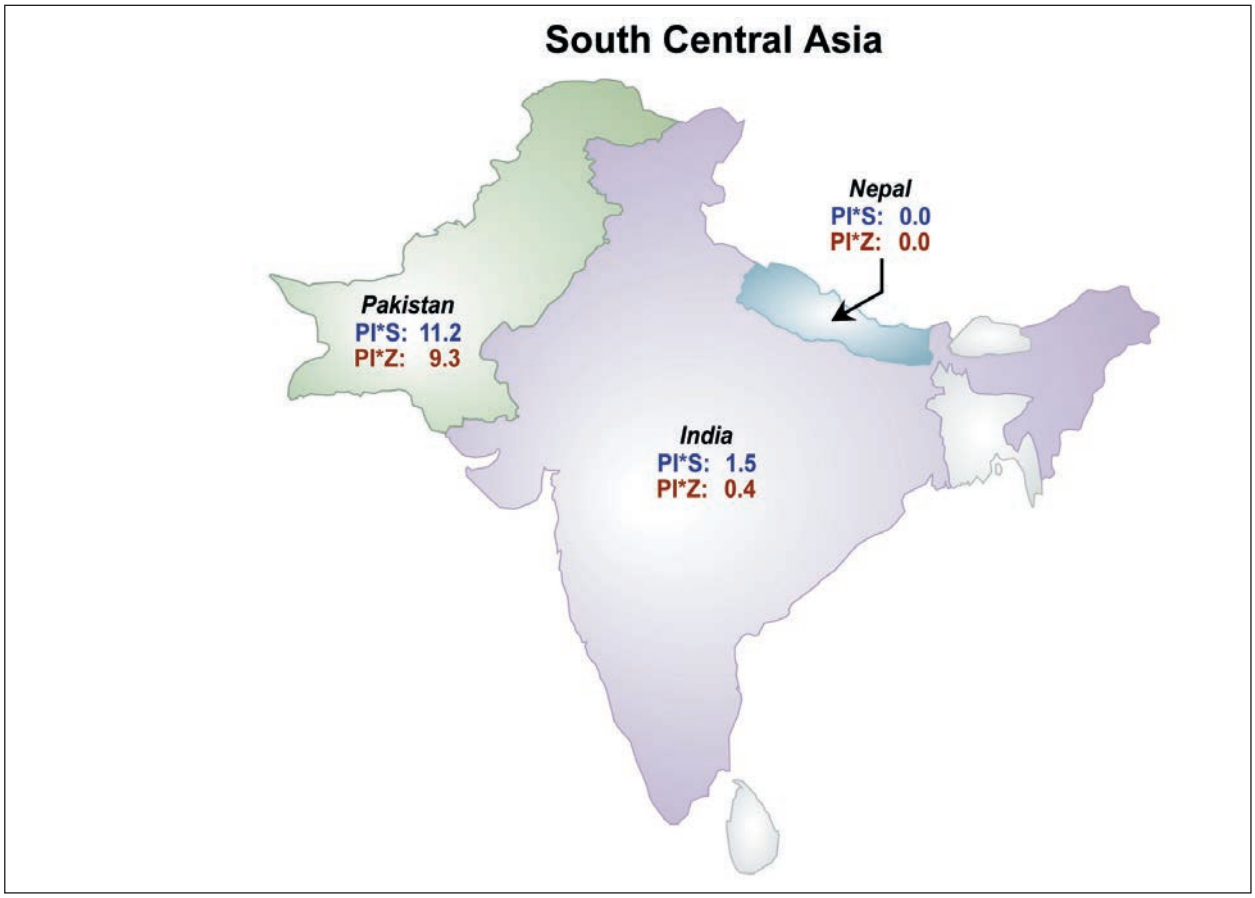

Fig. 16. - Prevalence of the PI S and PI Z deficiency alleles in South Central Asia.

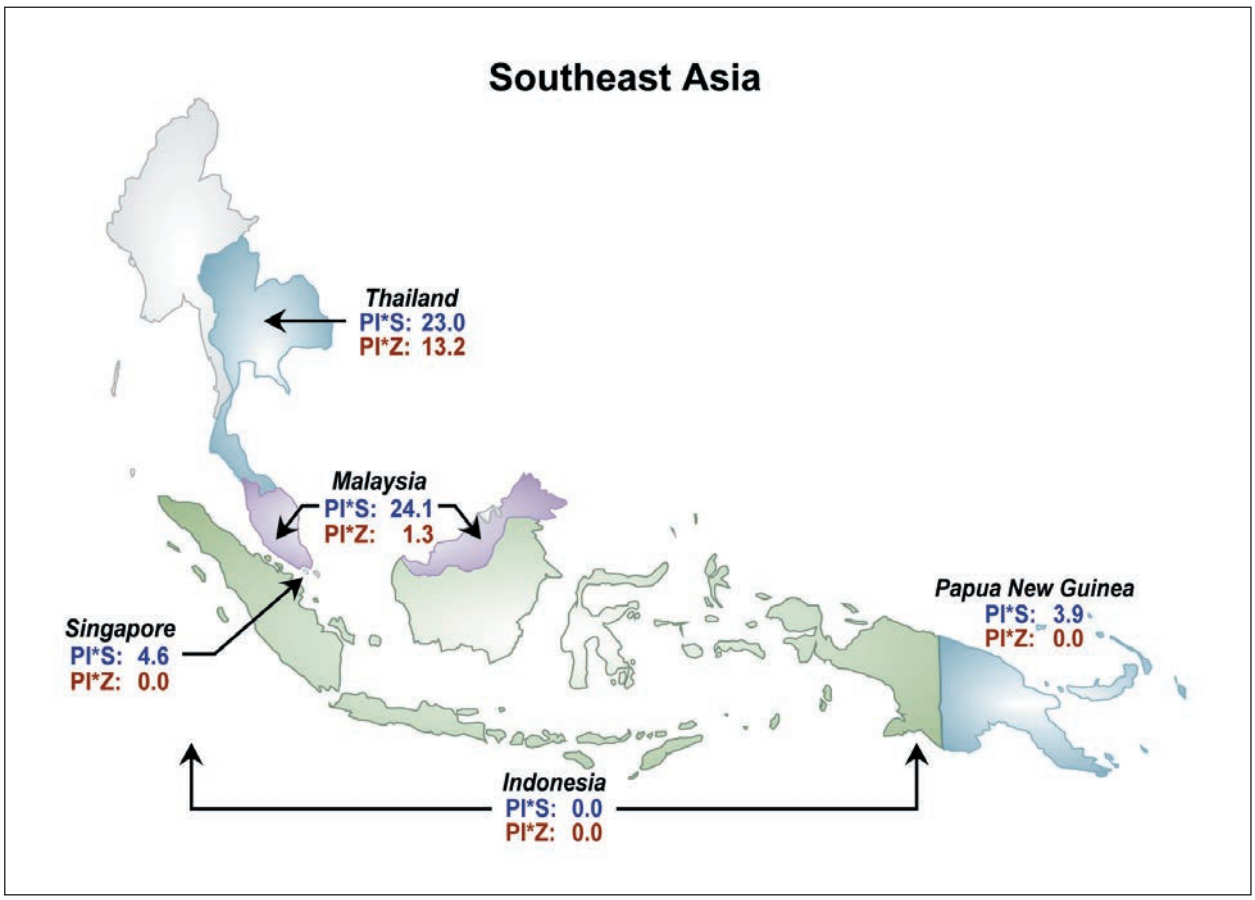

Fig. 17. - Prevalence of the PI S and PI Z deficiency alleles in Southeast Asia.

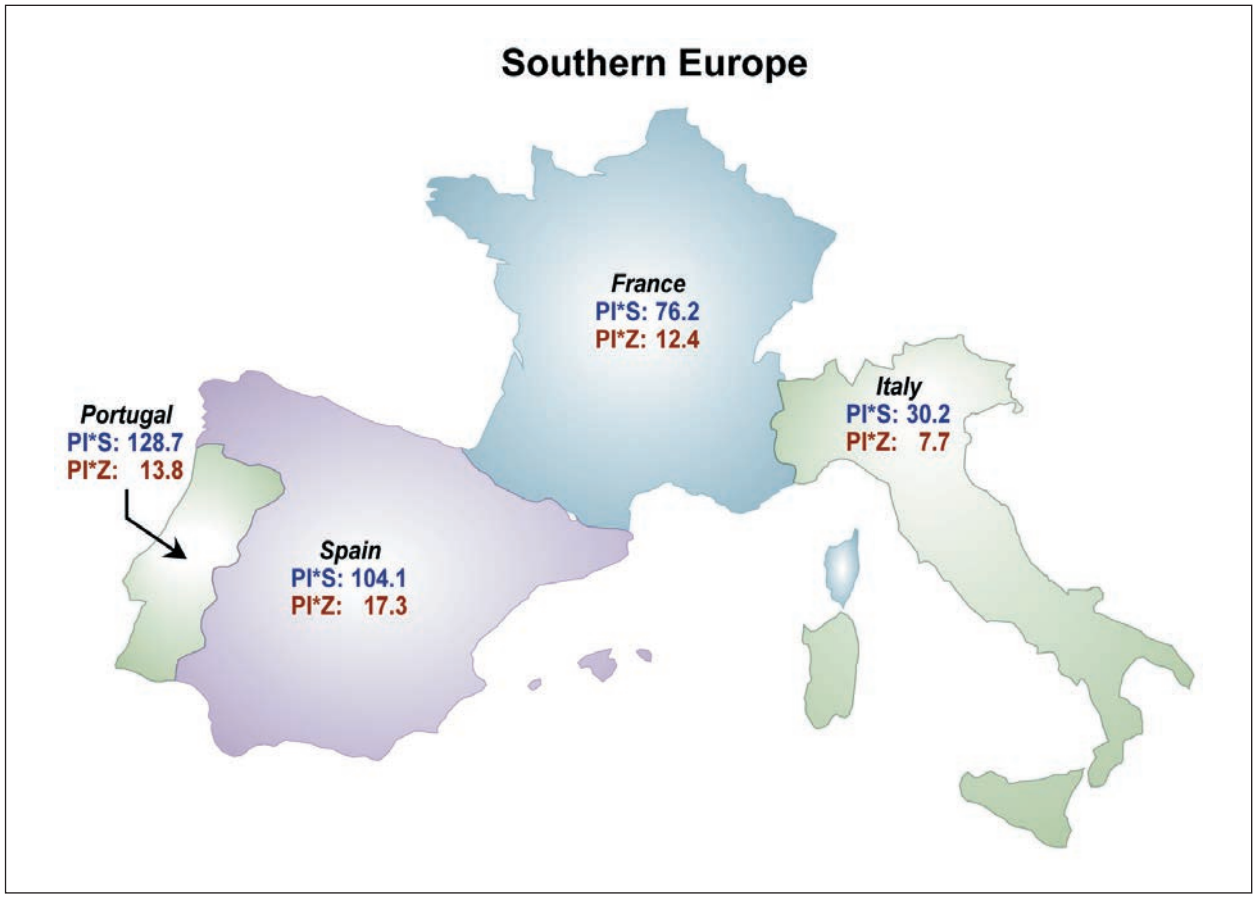

Fig. 18. - Prevalence of the PI S and PI Z deficiency alleles in Southern Europe.

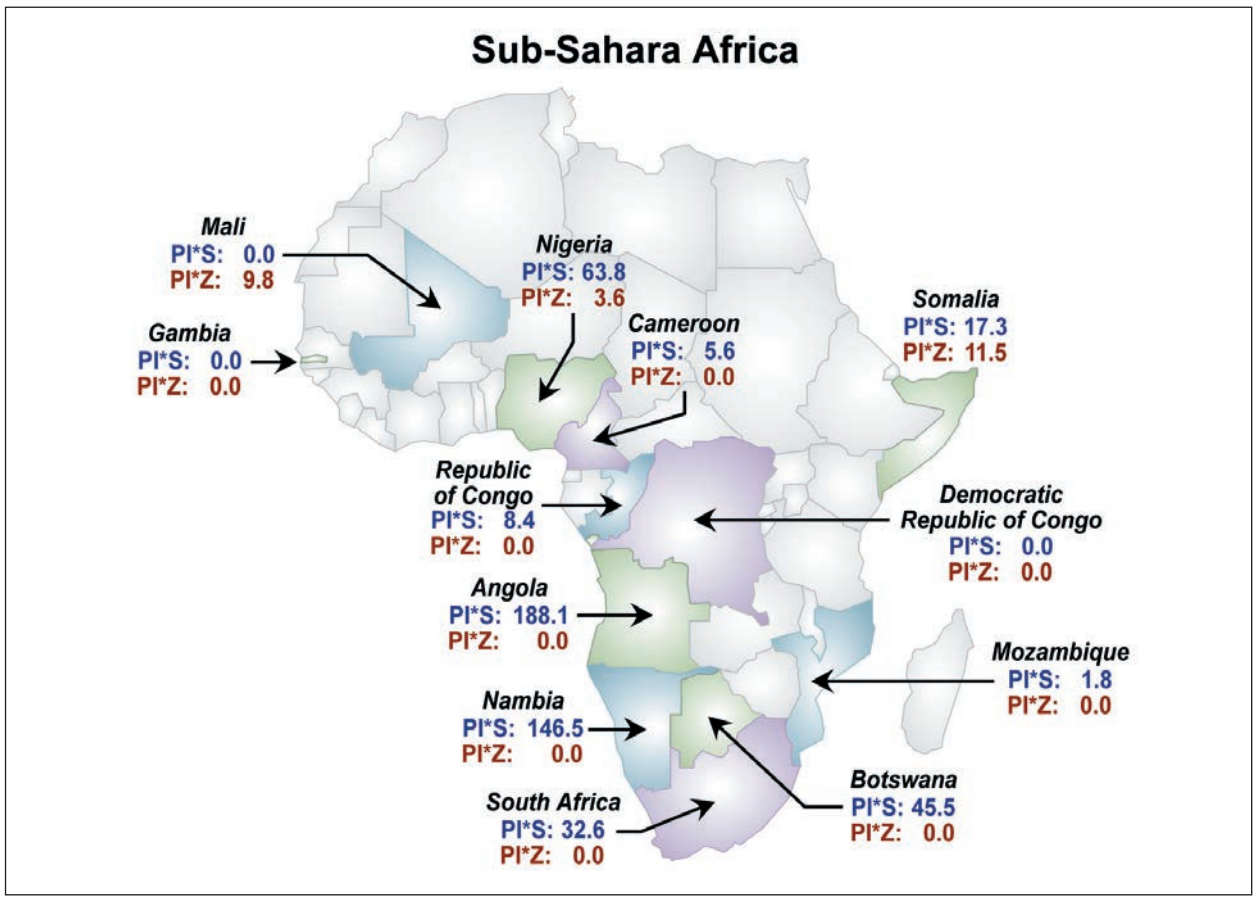

Fig. 19. - Prevalence of the PI S and PI Z deficiency alleles in Sub-Sahara Africa.

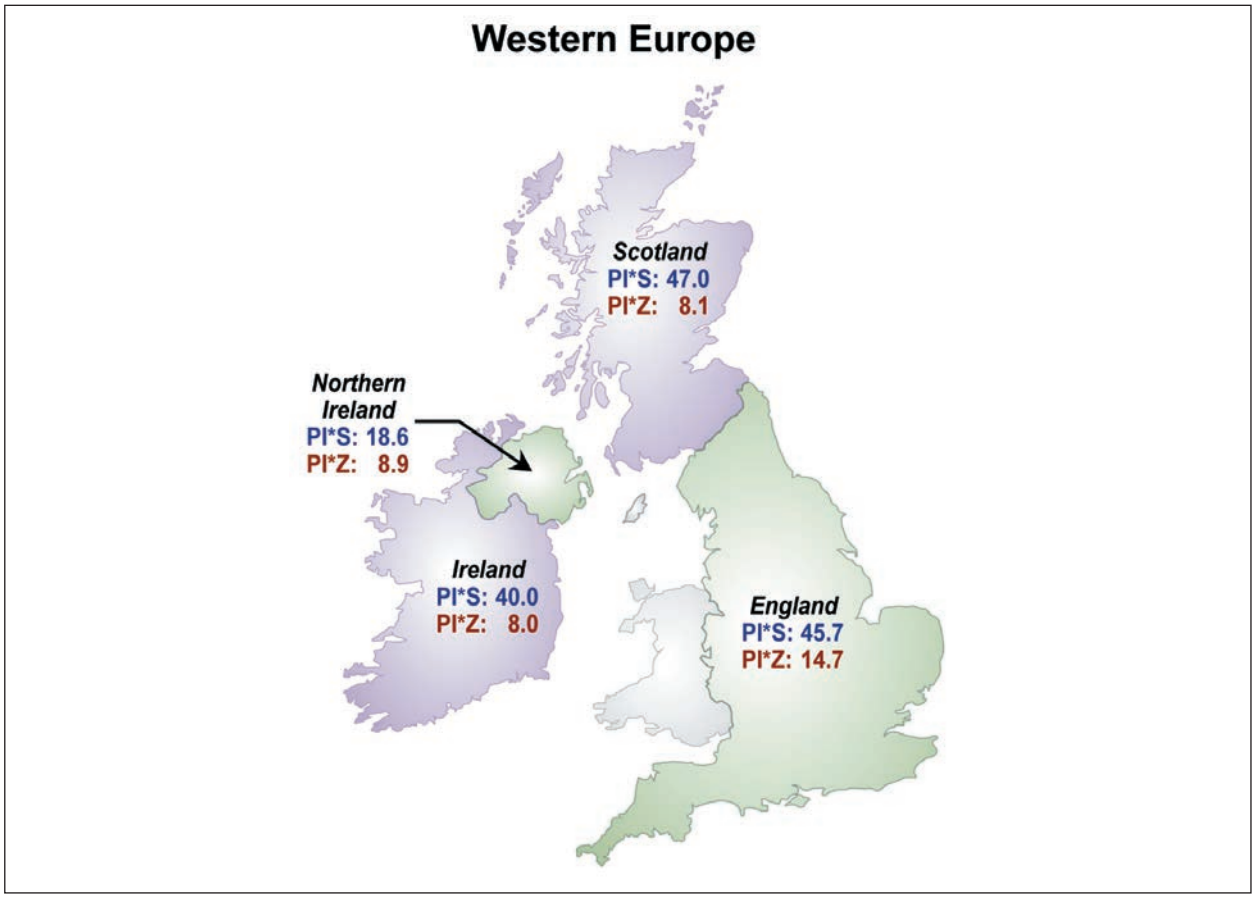

Fig. 20. - Prevalence of the PI S and PI Z deficiency alleles in Western Europe.

Comparison of the numbers of subjects in each of the five phenotypic classes of PI S and PI Z in each country in each of the 13 geographic regions

The entire database of 199,449 subjects has been tabulated into 13 geographic regions in table 3. These regions are: Australia/New Zealand, Central Asia, Central Europe, Eastern and Southeastern Europe, Far East Asia, Middle East and North Africa, North America, Northern Europe, South Central Asia, Southeast Asia, Southern Europe, Sub-Sahara Africa, and Western Europe. These groupings permit comparison of the number of subjects in each cohort in countries in the same geographic region as well as between geographic regions.

Table 3. - Inventory of countries, number of control cohorts and subjects in 13 geographic regions worldwide

No.	Geographic Region	Countries	Cohorts	
		Count	No.	Size
1	**Southern Europe**			
	France	1	20	11,978
	Italy	1	42	19,042
	Portugal	1	4	1,488
	Spain	1	28	7,763
2	**Central Europe**			
	Austria	1	1	678
	Belgium	1	1	1,345
	Germany	1	17	8,736
	Switzerland	1	3	2,462
	The Netherlands	1	5	2,670
3	**Western Europe**			
	England	1	6	3513
	Northern Ireland	1	2	3,310
	Republic of Ireland	1	1	250
	Scotland	1	3	2,543
4	**North America**			
	Canada	1	8	5,711
	United States	1	38	27,809

→

Table 3. - Inventory of countries, number of control cohorts and subjects in 13 geographic regions worldwide

No.	Geographic Region	Countries	Cohorts	
		Count	No.	Size
5	**Australia and New Zealand**			
	Australia	1	12	6,233
	New Zealand	1	5	1,750
6	**Northern Europe**			
	European Russia			
	Denmark	1	2	10,096
	Estonia	1	2	1,850
	Finland	1	12	3,498
	Iceland	1	1	94
	Latvia	1	2	488
	Lithuania	1	5	2,799
	Norway	1	6	5,036
	Sweden	1	12	6,164
7	**Eastern and Southeastern Europe**			
	Albania	1	3	300
	Bosnia-Herzegovina	1	2	2,441
	European Russia	1	18	8286
	Greece	1	9	502
	Hungary	1	33	3,711
	Macedonia	1	3	331
	Poland	1	11	9,539
	Romania	1	3	362
	Serbia	1	2	1,549
	Slovakia	1	1	102
8	**Central and South Africa**			
	Angola	1	1	101
	Botswana	1	1	88
	Gambia	1	1	701
	Cameroon	1	1	266
	Democratic Republic of the Congo	1	1	132
	Mali	1	1	102
	Mozambique	1	1	274
	Namibia	1	2	157
	Nigeria	1	3	564
	Republic of the Congo	1	4	237
	Republic of South Africa	1	9	1,254
	Somalia	1	1	347
9	**Middle East and North Africa**			
	Israel	1	12	2,442
	Jordan	1	1	424
	Saudi Arabia	1	4	801
	Tunisia	1	5	883
10	**South Central Asia**			
	India	1	25	2,295
	Nepal	1	1	144
	Pakistan	1	1	269
11	**Central Asia**			
	Afghanistan	1	11	1,765
	Iran	1	5	987
	Kazakhstan	1	7	616
	Tajikistan	1	6	524
12	**Far East Asia**			
	Asian Russia	1	14	2,564
	Japan	1	6	4,203
	Mongolia	1	17	505
	PR China	1	20	6,806
	South Korea	1	7	543
13	**Southeast Asia**			
	Indonesia	1	8	1,105
	Malaysia	1	6	1,886
	Papua New Guinea	1	2	183
	Singapore	1	2	545
	Thailand	1	4	1,064
	The Philippines	1	1	243
	World Summary	69	514	199,449

Discussion

The primary objective of the present analysis is to demonstrate that the two major deficiency alleles of AAT Deficiency are in widespread distribution worldwide and to expand our original analysis [14] from 58 to 69 countries and from 11 to 13 geographic regions.

Our analysis demonstrates that there are substantial populations at risk for AAT Deficiency worldwide. The summation of the data on the 69 countries grouped into 13 major geographic regions indicates that AAT Deficiency may constitute the largest documented number of individuals at risk for any human genetic disease. In countries colonized by Europeans in the New world (i.e. North-America, Australia and New Zealand) PI S and PI Z frequencies are a reflection of the European Caucasian population frequency, with intermediate and high values of both genes. High PI Z frequencies are found in Afghanistan, where the Pashtuns, an ethnic group which constitutes up to 42% of the Afghan population, have an Indo-European ethnical origin. Both of the PI S and PI Z alleles are rare in Orientals and Australian Aboriginals.

However, even though the current database on 69 countries consists of 514 cohorts and 199,449 subjects, such genetic epidemiological studies have only "scratched the surface" due to the lack of any significant genetic epidemiological studies on the general populations of countries in Central and South America as well as in the smaller countries on islands in the Caribbean. Also absent from the peer-reviewed medical literature are detailed studies on different parts of most of the countries in the 69 country database as well as precise information on the populations studied as well as their location within a given country. This paucity of the genetic epidemiological studies in many regions of a given country makes it impossible, for example, to perform the type of analysis that we reported earlier [19] on 14/20 regions in Italy to investigate the possibility of regional differences within a given country due to the differences in the genetic make-up of the original settlers.

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

By combining the data on the percentages of the total population for each of these 69 countries in each of the five phenotypic classes of PI S and PI Z, it makes it possible to compare their prevalences among countries in close proximity. It is evident from comparison of these prevalences in the countries of Eastern and Southeastern Europe, Middle East and North Africa, Northern Europe, Southern Europe, and Sub-Sahara Africa that there can be marked differences in these prevalences between counties in the same geographic region.

The prevalences of the PI S allele are high for countries in Southern Europe and Sub-Sahara Africa. There are nine countries in the Northern Europe geographic region where the prevalences of both deficiency alleles are exceptionally higher than in most other countries in the present study. The highest prevalence o the PI S allele is found in Latvia, followed by Denmark, Norway, Iceland, Sweden, Lithuania, Estonia, European Russia and Finland. The highest prevalence of the PI Z allele was found in Latvia, followed by Denmark, Estonia, Norway, Lithuania, and Sweden.

The four countries in the Southern Europe geographic region are characterized by very high prevalences of both deficiency alleles with the highest prevalence of PI S found in Portugal, followed by Spain, France and Italy. Five to ten-fold lower prevalences of he PI Z deficiency allele are found in these four countries with the highest prevalence in Spain, followed by Portugal, France and Italy. This analysis shows that Italy has the lowest prevalence of both deficiency alleles in this geographic region. The four countries in the Western Europe geographic region exhibit high prevalences of both deficiency alleles. With regard to PI S, with the highest prevalence in Scotland followed by England, Northern Ireland and Ireland. The PI Z deficiency allele was found in all four countries with the highest prevalence in England followed by Scotland, Northern Ireland and Ireland.

There are seven countries in the Eastern and Southeastern Europe geographic region with striking differences with Albania having no prevalences of either deficiency allele, Greece having the highest parlance of the PI S allele and Serbia the highest prevalence of the PI Z deficiency allele followed closely by Romania.

When we compare the PI S and PI Z prevalences in Australia/New Zealand (fig. 8) with North America (fig. 14), we can see that these four New World countries, settled with immigrants primarily from many of the same countries in Europe, have comparable prevalence frequencies for both deficiency alleles.

The five countries in the Far East Asia geographic region all have very low or no prevalences of the PI S deficiency allele with South Korea having the highest prevalence of the PI Z deficiency allele. Three of the four countries in Central Asia, namely Afghanistan, Iran, and Tajikistan have much higher prevalences of both deficiency alleles than the neighboring country of Kazakhstan. All four of these countries have significantly high prevalences of the PI Z deficiency allele with Tajikistan having the highest prevalence of all four countries.

There are four countries in the Middle East and North Africa geographic region with Saudi Arabia having the highest prevalence of both the PI S and the PI Z deficiency allele. The PI Z allele is either absent (Jordan and Tunisia) or with a very low prevalence (Israel) in the other three countries.

Of the three countries in the South Central Asia geographic region, Pakistan has a high prevalence of the PI S deficiency allele followed by India and Nepal. Pakistan also has the highest prevalence of the PI Z deficiency allele followed by India and Nepal.

There are five countries in the Southeast Asia geographic region with Thailand having the highest prevalence of the PI S deficiency allele followed by Malaysia, Singapore, Indonesia and Papua new Guinea. The highest prevalence of the PI Z deficiency allele is found in Thailand, followed by Malaysia with none in Singapore or Papua New Guinea.

The twelve countries in the Sub-Sahara Africa geographic region show very striking differences in the prevalences of the PI S and PI Z deficiency alleles with the highest prevalence o the PI S deficiency allele in Angola, Namibia, followed by Nigeria, Botswana and South Africa. Much lower prevalences were found in Somalia, Republic of South Africa and Mozambique. This allele was not found in Mali, Gambia and Democratic Republic of Congo. The PI Z deficiency allele was found in only three of the twelve countries in this region, namely: Somalia, Mali and Nigeria.

Differences in the prevalences of the PI S and PIZ deficiency alleles with a given country

It is well know that Celtic tribes emigrated from Ireland to Brittany on the West coast of France and also to the Asturias and Galicia Provinces in northern Spain [31, 32]. It is reasonable to assume that the current populations derived from these Celtic emigrants in both France and Spain might have very different prevalences of the PI S and PI Z alleles than inhabitants in other part of these two countries. In an earlier manuscript on AAT Deficiency in Europe [22], the data on individual cohorts were collated to provide estimates of the prevalences of these two alleles for each of these countries. This made it possible to compare prevalences between countries but not within a given country.

However, in another publication where we compared the prevalences of these two deficiency alleles in 14 out of 20 regions of Italy, we found [19] that there were striking differences between their prevalences among these 14 regions. It is well known that the country of Italy was settled in its early history by very diverse ethnic subgroups [33] many of which gave rise to the present names of the 20 individual regions. It also is well known that in more recent times that Italy now includes small clusters of German-, French-, and Slovene-Italians in the north, and Albanian-Italians and Greek-Italians in the south. We have no information on the PIS and PIZ deficiency allele frequencies in the pre-Roman ethnic subgroups. However, since the deficiency allele frequencies for PI S and PI Z were demonstrated to be quite different in the various European countries [22, 24] from which this latter group of immigrants were derived [33], it is not unexpected that these deficiency allele frequencies would be different in the various regions where these immigrants settled. Thus, it is also not totally unexpected that there would be differences between the prevalences found in the countries in the same geographic region. These are interesting and valuable studies for the identification of individuals that may be at high risk for AAT Deficiency, but the genetic epidemiological data for most countries in our current database [14, 16-18, 22, 24, 25] is totally inadequate for such an analysis.

We have used Hardy-Weinberg statistical analyses which assume random mating within given populations. It is clear that the model is inadequate for statistical analysis of the population of the whole country of Italy and raises the question as to whether it is suitable model for each of the 14 regions within Italy. This analysis has demonstrated striking differences of the prevalence of this disease in these 14 different regions in Italy. These differences, in turn, raise the issue of how to use such control cohort data to get a best estimate of the prevalence of AAT Deficiency in the whole county of Italy. This analysis also impacts the development of such estimates for the other countries in the overall country database worldwide [14].

Targeted screening to detect individuals with AAT Deficiency

AAT Deficiency was not a well-known genetic disease in the medical community [13]. The main reason given is that there was too little information on the incidence of patients with either the PI MZ or PI ZZ phenotypes nor the risk that such phenotypes might give to carriers for adverse health effects. Thus, laboratory tests for identification were not generally performed to determine whether patients presenting with asthma, or COPD were positive for AAT Deficiency. Criteria of the identification and management of patients with AAT Deficiency has recently been reviewed [2, 34, 35] and worldwide attention has been brought to the attention of members of the medical community worldwide as a result of the work of these expert committees in Europe and the United States.

The value of such studies on regional differences in the frequency of different genetic diseases also was demonstrated in a study of the idiopathic hemochromatosis gene frequency by Lindmark and Eriksson in Sweden [36]. In this study, striking differences also were found that were attributed to a difference in the population structure and composition of the local population in the county of Jämtland that were not representative of the entire country of Sweden. These findings in Sweden provide an important clue that can be extended to targeted screening studies in any country to identify, in this case, individuals at high risk for AAT Deficiency. For countries in the new world (for example, Australia, Canada, New Zealand, and the United States of America,) targeted screening to identify individuals at high risk for AAT Deficiency could use census data to identify those cities and other locales where there are high numbers of immigrants from those countries in Europe with high prevalences of AAT deficiency alleles.

Identification of individuals with AAT Deficiency can be improved, for example, by targeted screening of particular population subgroups. Highly significant increases in the detection of those PI S and PIZ phenotypes that are at risk for AAT Deficiency can be made by targeted screen-

ing [15] of white COPD patients. The odds ratios (OR) for each of the phenotypic classes among white COPD patients demonstrate highly significant decreases in the normal phenotype PIMM (OR 0.527), no significant change in the PI MS (OR 1.063) and PI SS (OR 1.227) deficiency phenotypes, but highly significant increases in the prevalences of the PI MZ (OR 3.559), PI SZ (OR 3.869), and PI ZZ (OR 12.168) deficiency phenotypes [15]. The result of our COPD-AAT Deficiency study supports the concept of targeted screening for alpha-1 antitrypsin deficiency in countries with large populations of white (Caucasian) COPD patients [15].

Deleterious environmental exposures of susceptible subgroups

The major environmental factor affecting the health of AAT Deficient individuals is cigarette smoking and the data in the literature predominantly on individuals of phenotype PI ZZ is extensive. Less well known is the risk to various environmental chemicals and particulates nor the populations at risk. For example, questions exist as to whether there is an increased risk for adverse health effects when individuals in each of the five phenotypic classes of PI S and PI Z of AAT deficiency are exposed to toxic environmental agents [9-12].

Origin of the two major deficiency alleles PI S and PI Z

It is generally thought that humans emigrated out of Africa between 50 and 70,00 years ago [32] carrying only a handful of the genetic markers that existed there at least 150 to 200,00 years ago on that continent. Both of the PI S and PI Z deficiency alleles are found in some existing African populations [18], but whether these were the original variants or introduced by European settlers later in the 16th to 19th century [18] is unknown. It is generally accepted that the PI Z allele arose in Northern Europe and more specifically in Scandinavia between 66-216 generations ago [37]), and that the PI S allele arose 300-450 generations ago on the Iberian Peninsula [38]. At this time, there is a wide variation in the prevalence of PI S and PI Z in different countries in Europe [21], Africa [18], North America, Australia/New Zealand [16], and Asia [20]. In our study on the prevalences of these two alleles in 14/20 regions of Italy, significant differences in prevalence were found [19] that can be attributed to differences in the ethnic composition of the indigenous populations in many of these regions in Italy.

It is evident from the present analysis that the two most common deficiency alleles are in widespread distribution throughout the portion of the world where genetic epidemiological studies have been made by others. Notably absent from the present database are genetic epidemiological studies on countries on islands in the Caribbean, Central America, and most notably missing are such studies on any of the countries in South America. Information on the CIA site on the ethnic composition of the South American countries in particular indicates the presence of high concentrations of European settlers, predominantly from Spain and Portugal, but also from other countries as France, Germany, and Italy (https://www.cia.gov/cia/publications/factbook/index.html). Thus, our estimates of the numbers at risk for AAT Deficiency worldwide must be considered as underestimates since we have not been able to include data from any of these countries.

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 PI Z 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 Nambia, 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[18]. 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).

The origin of PI S and PI Z deficiency alleles in Asian countries 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 [20]. 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. 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.

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 as well as various different cultures in Asian countries. It is 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 ethnic populations are the result of independent spontaneous mutations during the course of their ancient and independent histories.

In conclusion, the genetic epidemiological database on the prevalence of the two most common deficiency alleles PI S and PI Z has shown that they both exist in many of the 69 countries worldwide where there are genetic epidemiological studies in the peer-reviewed medical literature. In most countries individuals with phenotypes that put them at risk for various environmental exposures have not been identified. There are cost effective targeted screening approaches that could be used, for example, on white COPD patients, and it is also possible that there is a high prevalence of AAT Deficiency in patients with asthma. Identifi-

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

In summary, AAT Deficiency is widespread throughout the world, with significantly high prevalence in countries throughout many of the 13 geographic regions studied. It also is clear that AAT Deficiency is not just a disease of Caucasians (or whites) from Northern Europe, but is prevalent in many different races in numerous countries throughout the world. Unfortunately, it also is clear that most individuals who are carriers of this disease have not as yet been identified.

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