Monaldi Arch Chest Dis
2005; 63: 3, 133-141

ORIGINAL ARTICLE

Alpha-1 antitrypsin deficiency in Italy: regional differences of the PIS and PIZ deficiency alleles

F.J. de Serres[1], M Luisetti[2], I. Ferrarotti[2], I. Blanco[3], E. Fernández-Bustillo[4]

ABSTRACT: ***Alpha-1 antitrypsin deficiency in Italy: regional differences in the distribution of the PIS and PIZ deficiency alleles. F.J. de Serres, M Luisetti, I. Ferrarotti, I. Blanco, E. Fernández-Bustillo.***

Background. **Critical to the effective diagnosis and management of disease is information on its prevalence in a particular geographic area such as Italy. Alpha-1-antitrypsin deficiency (AAT Deficiency) is one of the most common serious hereditary diseases in the world, but its prevalence varies markedly from one country to another. AAT Deficiency affects at least 120.5 million carriers and deficient subjects worldwide for the two most prevalent deficiency alleles PIS and PIZ. This genetic disease is known to exist in Italy and is related to a high risk for development of jaundice in infants, liver disease in children and adults, and pulmonary emphysema in adults.**

Methods. **Studies on the genetic epidemiology of AAT Deficiency has resulted in the development of a unique database that permits a unique analysis of the geographic distribution in 14 different regions located at random from Piemonte to Sicilia.**

Results. **The use of Hardy-Weinberg statistical analysis to evaluate the distribution of these two deficiency alleles has demonstrated striking differences in the frequencies of these two deficiency alleles in these 14 different regions with 23/84 pair wise combinations significantly different (P=0.05) for PIS, and 5/84 combinations for PIZ.**

Conclusions. **These findings demonstrate differences that impact the standards of care and diagnosis of AAT Deficiency in Italy since the prevalence of these deficiency alleles is not uniform throughout the country.**
Monaldi Arch Chest Dis 2005; 63: 3, 133-141.

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

[1] Laboratory of Molecular Toxicology, Environmental Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC (U.S.A.).
[2] Laboratorio di Biochimica e Genetica, Clinica di Malattie dell'Apparato Respiratorio, IRCCS Policlinico San Matteo, Università di Pavia, Italy.
[3] Internal Medicine Division, Respiratory Diseases Branch, Hospital Valle del Nalon, Langreo Principado de Asturias,
[4] Bio-statistics Unit, Hospital Central de Asturias, Oviedo, Principado de Asturias, Spain.

Correspondence: Dr. Frederick J. de Serres, Laboratory of Molecular Toxicology, Environmental Toxicology Program, National Institute of Environmental Health Sciences, PO Box 12233, Research Triangle Park, NC 27709-2233 (U.S.A.); e-mail: deserres@bellsouth.net

Introduction

Critical to the effective diagnosis and management of disease is information on its prevalence in a particular geographic area such as the country of Italy. Alpha-1-antitrypsin deficiency (AAT Deficiency) is one of the most common serious hereditary diseases in the world, since its affects all major racial subgroups worldwide. There are at least 120.5 million carriers and deficient subjects worldwide for the two most prevalent deficiency alleles PIS and PIZ [1]. This genetic disease is known to exist in Italy [2], and it is related to a high risk for development of jaundice in infants, liver disease in children and adults, and pulmonary emphysema in adults [3].

Alpha-1-antitrypsin (AAT) is a 52 kDa alpha-1-glycoprotein, composed of 394 amino acid residues and 3 asparagine-linked complex carbohydrate side chains [4]. It is produced mainly by hepatocytes and secreted into the blood, where it acts as a circulating serine protease inhibitor whose principal substrate is neutrophil elastase (NE) [5]. The AAT gene locus is located on the long arm of chromosome 14, has been mapped to chromosome 14q31-32.3 [6], and is organized in 3 non-coding (Ia, Ib and Ic) exons and 4 (II, III, IV and V) coding exons [7]. The normal gene is designated PIM, and about 100 normal and defective genetic variants are recognizable by isoelectric focusing (IEF) [8, 9]. The two most frequent deficient alleles are PIS (which expresses approximately 50-60% of AAT) and PIZ (which expresses approximately 10-20% of AAT) [6, 10-12].

AAT Deficiency is a heritable autosomal recessive metabolic disease that results in the syn-

thesis and secretion of a defective AAT. AAT Deficiency state by itself is not a disease, but a predisposition to later development of several diseases, both in children and adults. Hepatic accumulation of AAT polymers leads to low serum levels of AAT protein and these, in conjunction with other genetically determined characteristics and environmental influences, might result in early onset of panlobular pulmonary emphysema in adults, especially in habitual tobacco smokers [4, 13, 14]; severe liver diseases in newborns, children and adults [12, 15], and it is also suspected that AAT Deficiency could promote bronchial asthma [16], bronchiectasis [17], multisystemic vasculitis [18], necrotizing panniculitis [19, 20], rheumatoid arthritis [21], intracranial arterial dissections [22], multiple sclerosis [23], and other diseases. Although, evidence from the literature indicates that both carriers and deficiency allele combinations for the PIS and PIZ defective alleles (namely PISS, PIMS, PIMZ, PISZ and PIZZ phenotypes) are at increased risk of developing the above mentioned AAT Deficiency-associated diseases clear scientific evidence of the relationship among PIMS and PISS phenotypes and these diseases remains to be established

Knowledge of the AAT Deficiency prevalence in every community is essential for enhancing awareness of this disease among health-care givers and the general public, for planning health policy and financial medical resources, and to their utilization by the scientific community, governments and the pharmaceutical industry [1]. The present study utilizes data from genetic epidemiological studies performed by others to determine the phenotypes of carriers and deficiency allele combinations for PIS and PIZ in the control cohorts of individual case studies located at random in 14 out of the 20 regions in Italy. This is a unique database that was not found for any country in the original database on 58 countries [1], or our current database on 67 countries worldwide (de Serres, unpublished).

We have used the genetic epidemiological studies to compare the deficiency allele frequencies of PIS and PIZ and their utilization, along with estimates of the population sizes in each of these 14 regions, to develop estimates, using Hardy-Weinberg statistical analyses, of the numbers of carriers (PIMS and PIMZ) and deficiency allele homozygotes and heterozygotes (PISS, PISZ, and PIZZ).

Methods

Sources of the control cohort data used in the present study

The present study utilizes data from genetic epidemiological studies performed by others to determine the frequencies of the phenotypes of carriers and deficiency allele combinations for PI S and PI Z, in the control cohorts of individual case studies from 14 different regions of Italy [2]. The data from these individual cohorts for a given region are combined to get mean frequencies for the PIM, PIS, and PIZ alleles and their prevalences. The allele frequencies are then used to calculate the total numbers of individuals in each of the five major defective phenotypic classes of interest (namely, PIMS, PIMZ, PISS, PISZ, and PIZZ) in the total population of each region. Our approach is a step beyond the data that typically are published, in which the gene frequencies for PIM, PIS, and PIZ were calculated and reported for individual cohorts in individual cities or geographic regions [1].

The papers used in the present study were obtained through a variety of sources, and have been discussed in earlier publications [2].

Estimating allele frequencies of PIM, PIS, and PIZ

The formulas developed by Dr. Bustillo for developing estimates of the allele frequencies and 95% confidence intervals using Hardy-Weinberg statistical analysis were discussed in an earlier paper [24].

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

To assess the statistical reliability of the control cohorts in the surveys for each country, a Precision Factor Score with a scale of 1 to 12 was developed by one of us (EF Bustillo), as described in an earlier publication [2]. Since PFS is inversely proportional to the values of the coefficient of variation (cv), which measures the dispersion of values in respect to the mean, the smaller value of cv the greater PFS.

It is important to have in mind that a cv depends on the total number of alleles (sample size) and on the allele frequencies of PIS and PIZ actually found. Thus, a low score is the result of small numbers of subjects in a given control cohort, or a series of control cohorts each with a small number of subjects, and low values for PIS and/or PIZ allele frequencies. A high score is given to those studies where the number of subjects is high or a series of control cohorts each with a large number of subjects, and high values for PIS and/or PIZ allele frequencies. In addition, a statistical analysis of the total control cohort sample for a given country is performed to provide estimates of the mean, median, standard deviation, and the range (upper and lower values).

Results

Hardy-Weinberg statistical analysis of the control cohort databases for each of the 14 regions

Forty-three cohorts, having a total of 12,143 individuals, have been collected from database searches on each of these 14 regions in Italy [2], These 43 cohorts are distributed as follows: 1 for *Trentino*, 2 for *Piemonte*, 2 for *Liguria*, 5 for *Veneto*, 7 for *Emilia-Romagna*, 5 for *Toscana*, 2 for *Umbria*, 3 for *Lazio*, 1 for *Molise*, 3 for *Campania*, 1 for *Puglia*, 2 for *Calabria*, 2 for *Sicilia*, and 7 for *Sardegna*. The control cohort size and the defi-

ciency allele frequencies for PIS and PIZ in each of 14 regions are given in table 1 and their geographic distributions are given in figs. 1 and 2.

The overall database for each of the 14 regions is given in table 2 where the number of control cohorts in each region is given along with the PF Score, and the deficiency allele frequencies using Hardy-Weinberg statistical analysis with 95% confidence intervals. In addition, estimates are given of the prevalence for each of the 5 phenotypic classes: 3 considered to be at risk for adverse health effects (namely PIMZ, PISZ, and PIZZ) as well as 2 not currently considered to be at risk (namely PIMS and PISS).

Comparison of the deficiency allele frequencies for PIS in each of the 14 regions

When the deficiency allele frequencies for PIS for each of the regions are compared (fig. 3), there are 23 out of 84 comparisons (in black boxes) where the allelic frequencies are statistically different from one another.

Comparison of the deficiency allele frequencies for PIZ in each of the 14 regions

When the deficiency allele frequencies for PIZ for each of the regions are compared (fig. 4), there

Table 1. - Comparison of the results of Hardy-Weinberg statistical analyses of the control cohort data for each of 14 regions in Italy

Region	**PF Score[1]**	**No. of cohorts**	**Cohort size**	**Allele frequency with 95% Confidence Intervals***		
				PIM	PIS	PIZ
Trentino	10.2	1	1,606	0.9533 (0.9453-0.9602)	0.0318 (0.0261-0.0386)	0.0149 (0.0112-0.0199)
Veneto	4.4	5	607	0.9646 (0.9522-0.9740)	0.0288 0.0205-0.0403)	0.0066 0.0031-0.0135)
Liguria	3.3	2	597	0.0.9782 (0.9678-0.9854)	0.0176 (0.0122-0.0272)	0.0042 (0.0015-0.0103)
Piemonte	4.9	2	602	0.9527 (0.9387-0.9636)	0.0399 (0.0298-0.0529)	0.0075 (0.0037-0.0147)
Emilia-Romagna	6.8	7	1,426	0.9709 (0.9639-0.9766)	0.0224 (0.0175-0.0287)	0.0067 (0.0041-0.0106)
Toscana	6.4	5	1,544	0.9655 (0.9576-0.9721)	0.0287 (0.0228-0.0361)	0.0057 (0.0033-0.0097)
Umbria	1.3	2	220	0.9795 (0.9601-0.9900)	0.0182 (0.0085-0.0369)	0.0023 (0.0001-0.0146)
Lazio	11.2	3	1,980	0.9427 (0.9349-0.9496)	0.0.457 (0.395-0.0528)	0.0116 (0.0086-0.0156)
Campania	4.4	3	657	0.9749 (0.9645-0.9824)	0.0175 (0.0114-0.0266)	0.0076 (0.0039-0.0144)
Molise	3.2	1	600	0.9700 (0.9583-0.9786)	0.0267 (0.0186-0.0379)	0.0033 (0.0011-0.0091)
Puglia	1.3	1	420	0.9893 (0.9790-0.9949)	0.0095 (0.0044-0.0195)	0.0012 (0.0001-0.0077)
Calabria	4.5	2	284	0.9930 (0.9808-0.9977)	0.0070 (0.0023-0.0192)	0.0000 (0.0000-0.0065)
Sicilia	2.7	2	375	0.9787 (0.9648-0.9873)	0.0160 (0.0087-0.0286)	0.0053 (0.0017-0.0146)
Sardegna	5.8	7	1,225	0.9543 (0.9451-0.9621)	0.0412 (0.0339-0.0501)	0.0045 (0.0024-0.0083)
Italy*,**	5.0	43	12,143	0.9115 (0.9078-9150)	0.0294 (0.0273-0316)	0.0075 (0.0064-0.0086)

[1] PF score = Precision Factor score, * Hardy-Weinberg Equilibrium statistics, ** Weighted mean values using the data from the 14 regions extrapolated to all 20 regions with a total population in Italy of 57,634,327.

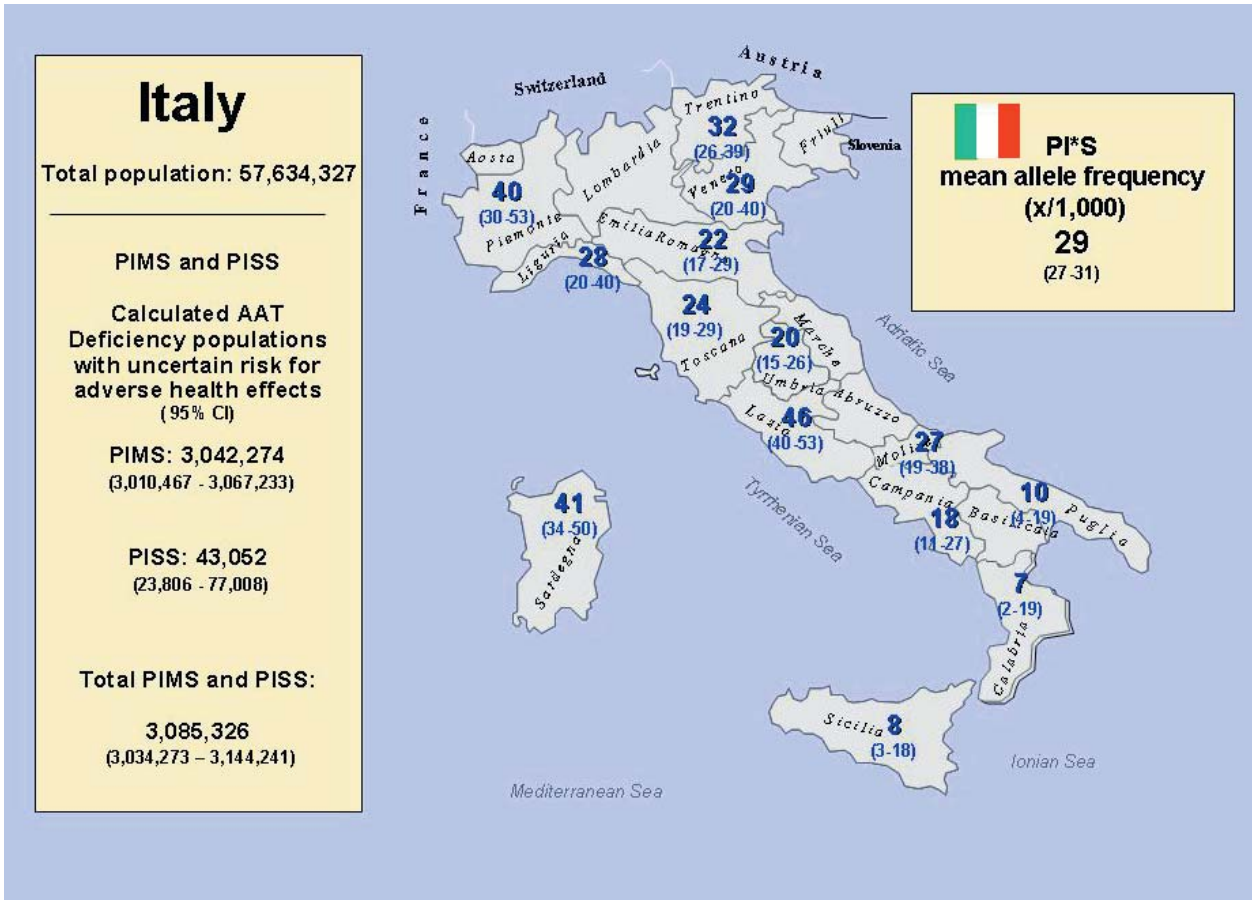

Fig. 1. - PIS geographic distribution in Italy.

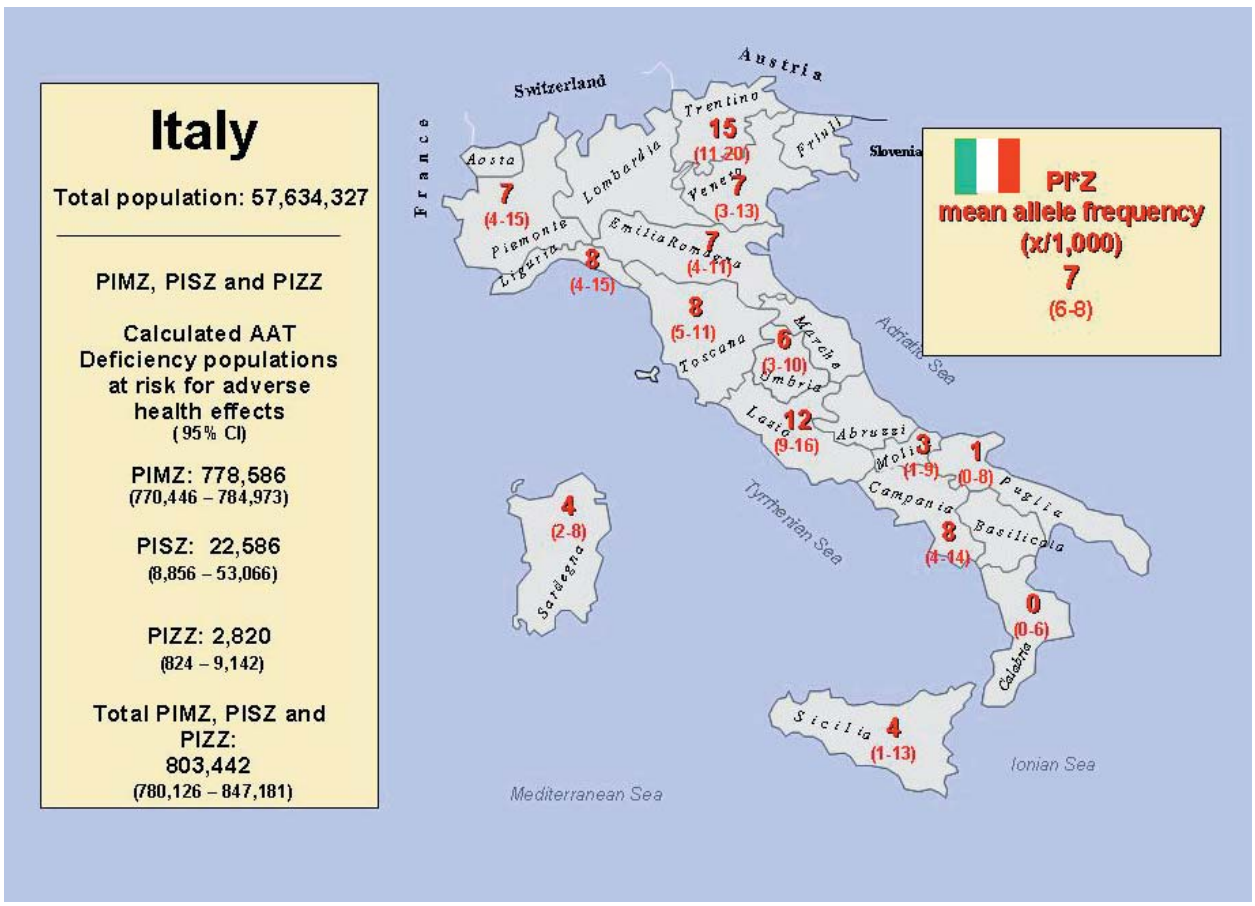

Fig. 2. - PIZ geographic distribution in Italy.

Table 2. - Estimates of the prevalences of each of the 5 phenotypic classes for the deficiency alleles PIS and PIZ for each of 14 regions in Italy

Region	No., type, method, PF Score[1]	Deficiency allele frequency (per 1,000)		Calculated numbers* of carriers and deficiency allele combinations at risk (1/X)			Calculated numbers* of carrier and deficiency allele combinations for PIS (1/X)		Total numbers of phenotypes (1/X)
		PI S	PI Z	MZ	SZ	ZZ	MS	SS	Total
Trentino	1,606, HUP[2], 10.2	32 (26-39)	15 (11-20)	35	1,054	4,478	17	992	6,576
Veneto	607, HUP 4.4	29 (20-40)	7 (3-13)	79	2,632	23,028	18	1,203	26,960
Liguria	597, HUP 4.6	28 (20-40)	8 (4-15)	69	2,329	17,600	18	1,233	21,249
Piemonte	602, HUP 4.9	40 (30-53)	7 (4-15)	70	1,678	17,896	13	629	20,286
Emilia-Romagna	1,426, HUP 6.8	22 (17-29)	7 (4-11)	77	3,345	22,532	23	1,986	27,963
Toscana	2,321, HUP 8.4	24 (19-29)	8 (5-11)	66	2,679	16,261	22	1,766	20,794
Umbria	1,544, HUP 6	20 (15-26)	89 (3-10)	6	4,459	30,322	26	2,623	37,519
Lazio	1,980 11.2	46 (40-53)	12 (9-16)	46	942	7,411	12	479	8,890
Campania	657, HUP 4.4	18 (11-27)	8 (4-14)	67	3,753	17,266	29	3,264	24,379
Molise	600, HUP 3.2	27 (19-38)	3 (1-9)	155	5,625	90,000	19	1,406	97,205
Puglia	420, HUP 1.3	10 (4-19)	1 (0-8)	425	44,100	705,600	53	11,025	761,203
Calabria	284, HUP 4.5	7 (2-19)	0 (0-6)	>1 X 10^6	>1 X 10^6	>1 X 10^6	72	20,164	20,236
Sicilia	375, HUP 2.1	8 (3-18)	4 (1-13)	127	15,625	62,500	63	15,625	93,940
Sardegna	1,225, HUP 5.8	41 (34-50)	4 (2-8)	117	2,701	49,607	13	588	53,026
Italy*,**	13,105 (20-37)	27 (4-13)	7	74	2,615	20,440	19	1,339	24,487

[1] PF score = Precision Factor score, [2] HUP = Healthy unrelated person, * Hardy-Weinberg Equilibrium statistics, ** Weighted mean values using the data from the 14 regions extrapolated to all 20 regions with a total population in Italy of 57,634,327.

are 5 out of 84 comparisons (in black boxes) where the allelic frequencies are statistically different from one another.

Discussion

Geographic distribution of the PIS and PIZ deficiency alleles in Italy

The comparisons of the prevalences of each of the 5 phenotypic classes for both PIS and PIZ in table 2 indicate that there are striking differences from region to region. For example, for PIS there is a difference in prevalence of 1 out of 46 in *Lazio* in contrast to 1 out of 7 in *Calabria*, and for PIMZ there is a difference in prevalence of 1 out of 35 for *Trentino* and less than 1 out of 1 X10^6 in *Calabria*. The lower deficiency allele frequencies for PIZ as well as the sizes of the various control cohorts in some of these 14 regions makes statistical analyses less rigorous than for the deficiency PIS allele. Nevertheless, both comparisons demonstrate that the

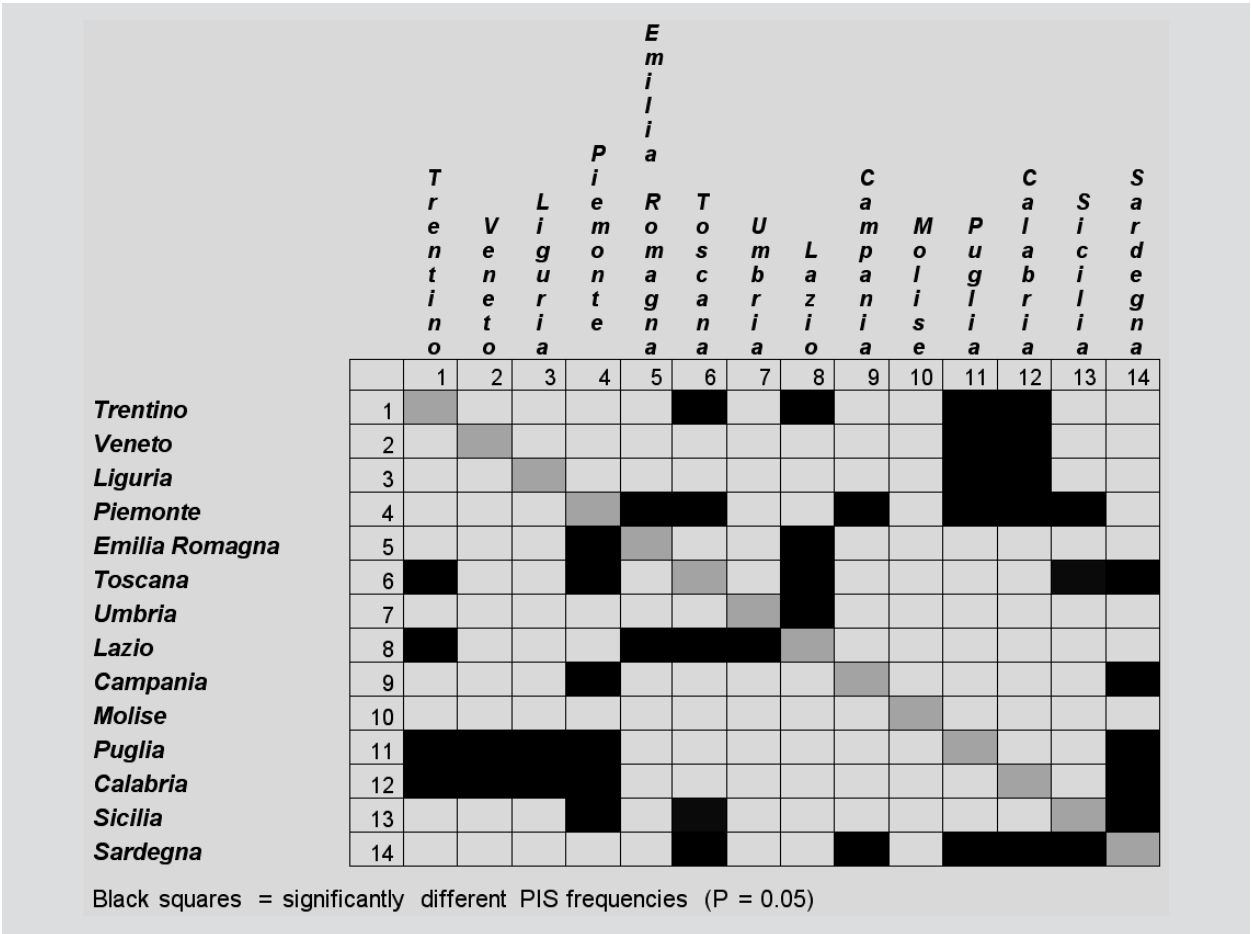

Fig. 3. - Results of Hardy-Weinberg statistical analysis of the deficiency allele frequencies of PIS in 14 regions in Italy.

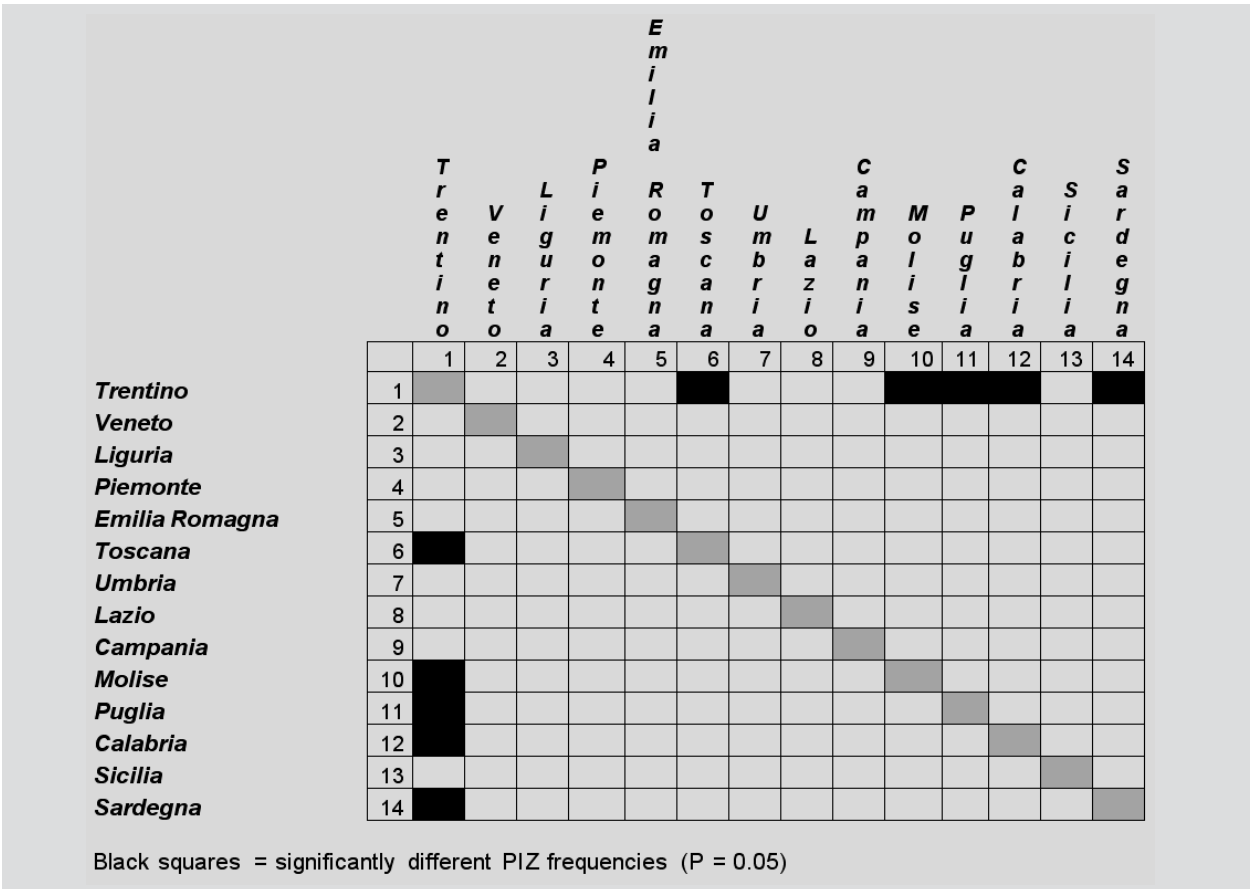

Fig. 4. - Results of Hardy-Weinberg statistical analysis of the deficiency allele frequencies of PIZ in 14 regions in Italy.

distribution of these 2 deficiency alleles throughout the whole country is quite different. Another factor worth noting is the fact that the PF Scores of the control cohort studies selected for this analysis are >4 indicating that they are very reliable.

Earlier studies on the distribution of the PIS and PIZ deficiency alleles [25, 26], based on smaller cohorts suggested higher deficiency allele frequencies for PIS and lower deficiency allele frequencies for PIZ in southern Europe than northern Europe.

In the present study, striking regional differences in the frequency of these two alleles were found for these 14 regions in Italy (figs. 1 and 2).

The high deficiency allele frequencies for PIS found in northern Italian regions are matched by high frequencies in six of the regions in central Italy (*Emilia Romagna*, *Toscana*, *Umbria*, *Lazio*, *Campania*, and *Molise*) (table 2). Lower deficiency allele frequencies for PIS were found for three of the southern Italian regions (*Puglia*, *Calabria* and *Sicilia*). It also is of interest that the deficien-

Table 3. - Estimates of the numbers of carriers and homozygotes/heterozygotes for the deficiency alleles PIS and PIZ in each of 14 regions and extrapolated to all of Italy

Region	**Total population**	**Calculated numbers* of carriers and deficiency allele combinations at risk**			**Calculated numbers* of carrier and deficiency allele combinations for PIS**		**Total numbers of PIS and PIZ phenotypes**
		MZ	SZ	ZZ	MS	SS	Total
Trentino	868,000	59,703 (44,194-80,213)	1,989 (1,220-3,222)	468 (261-833)	126,868 (103,346-155.214)	2,113 (1,426-3,117)	191,140 (190,324-191,959)
Veneto	4,262,000	10,192 (4,683-21,069)	305 (101-872)	35 (8-146)	44,590 (31,230-62,944)	666 (335-1,302)	66,788 (55,343-56,237)
Liguria	1,779,000	5,310 (2,561-10,535)	157 (54-433)	21 (5-80)	20,061 (13,973-28,467)	296 (148-585)	25,846 (25,543-26,152)
Piemonte	4,405,000	14,537 (6,999-28,888)	608 (222-1,587)	57 (14-220)	77,532 (57,182-104,122)	1,622 (909-2,8600)	94,357 (93,784-94,933)
Emilia-Romagna	3,905,000	4,727 (2,911-7,562)	109 (53-223)	16 (6-41)	15,923 (12,298-20,519)	184 (111-302)	20,959 (20.685-21,237)
Toscana	3,528,000	12,863 (7,433-21,818)	217 (95-484)	32 (11-91)	43,734 (32,752-58,088)	369 (209-645)	57,215 (56,757-57,676)
Umbria	799,000	3,558 (182-23,140)	66 (2-863)	4 (0-171)	28,460 (13,008-58,443)	264 (57-1,090)	32,352 (32,008-32,700)
Lazio	4,944,000	5,132 (3,773-6,943)	249 (159-386)	20,192 (17,311-23,496)	20,192 (17,311-23,496)	490 (366-653)	26,093 (25,796-26,394)
Campania	5,384,000	33,755 (16,991-64,547)	606 (201-1,747)	132 (34-474)	77,637 (49,996-118,809)	697 (295-1,607)	112,827 (112,187-113,471)
Molise	326,000	661 (209-1,826)	18 (4-71)	1 (0-9)	5,286 (3,643-7,576)	73 (35-147)	6,038 (5,892-6,188)
Puglia	3,829,000	4,344 (224-28,232)	42 (1-552)	3 (0-109)	34,749 (16,013-71,398)	167 (36-698)	39.304 (38,921-39,691)
Calabria	2,040,000	0 (0-6,271)	0 (0-121)	0 (0-20)	6,790 (2,151-18,612)	24 (2-179)	24 (6,655-6,977)
Sicilia	4,851,000	19,244 (6,082-53,068)	315 (55-1,537)	52 (5-392)	57,733 (30,914-104,082)	472 (139-1,5070)	77,816 (77,282-78,3530)
Sardegna	1,612,000	13,813 (7,200-25,690)	597 (258-1,337)	32 (9-111)	126,832 (103,162-155,282)	23,740 (1,848-4,040)	144,014 (143,305-144,726)
Italy**	57,634,327	778,586 (770,446-784,973)	22,036 (8,856-53,066)	2,820 (824-9,142)	3,042,274 (3,010,467-3,067,233)	43,052 (23,806-77,008)	3,888,768 (3,885,037-3,892,503)

* Hardy-Weinberg Equilibrium statistics, ** Weighted mean values using the data from the 14 regions extrapolated to all 20 regions with a total population in Italy of 57,634,327.

cy allele frequency for PIS in *Sardegna* is comparable to that found in northern Italy (fig. 1).

The deficiency allele frequencies for PIZ are significantly higher in *Trentino* than in *Toscana* and *Sardegna* in central Italy and *Molise*, *Puglia* and *Calabria* in southern Italy (table 2; fig. 2). These same comparisons demonstrate that the PIZ frequencies for the remaining regions are not significantly different from one another (fig. 4). This can be attributed primarily to the low frequencies of the PIZ deficiency allele throughout Italy as well as the larger cohort sample sizes needed to demonstrate any differences in these low PIZ frequencies.

It is well known that the country of Italy was settled in its early history by very diverse ethnic subgroups [27] many of which gave rise to the present names of the 20 individual regiones. 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 [27]. However, since the deficiency allele frequencies for PIS and PIZ were demonstrated to be quite different in the various European countries from which this latter group of immigrants were derived [1], it is not unexpected that these deficiency allele frequencies would be different in the various regions where these immigrants settled.

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 [28]. 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.

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 [1],

Adverse health effects of the deficiency alleles PIS and PIZ

There is not general acceptance of the adverse health effects associated with the PIS deficiency allele as indicted in the ATS/ERS Standards document [29]. As a result we have treated the PIMS and PISS phenotypic classes as “not currently considered at risk”. However, recent research articles [30, 31] provide documentation that both carriers (PIMS and PIMZ) and deficiency allele combinations (PISS, PISZ and PIZZ) may be at risk for various adverse health effects.

Adverse health effects of rare variants for AAT Deficiency in the Italian Registry

Among a total of 2,922 subjects in the Italian AAT Deficiency Registry, there were 155 subjects with severe AAT Deficiency (132 index cases), and 152 with intermediate AAT Deficiency (84 cases) [32]. Among the 132 subjects with severe AAT Deficiency, 15 out of 132 deficient index subjects were identified that were not PIZZ or PISZ, and among the 84 subjects with intermediate AAT Deficiency, 13 out of 84 had genotypes other than the more common genotype PIMZ.

Since these rare variants in the Italian AAT Deficiency Registry [32] have been characterized at the molecular level, they provided a unique and valuable resource for the study of their adverse health effects as well as making possible comparisons with the characteristics of the more common deficiency alleles PIS and PIZ.

Analysis of COPD prevalence and respiratory function indicated, for example, that COPD prevalence was higher in some of the newly discovered rare variant heterozygotes (with the PIM allele) than in PIMZ or PISZ subjects or higher in rare variant heterozygotes (with the PIZ deficiency allele) than PIZZ subjects.

Chronic liver disease, which is the second most common feature associated with AAT Deficiency, also was found to be comparable in the newly discovered rare heterozygotes (with the PIZ deficiency allele) as with PIZZ, PISZ and PIMZ subjects [32].

Additional comparisons of the adverse health effects associated with these rare variants are particularly relevant since they have been found either in the same or closely related ethnic subgroups in different parts of the country of Italy.

AAT Deficiency Research needs

New research initiatives are needed to gain a better understanding of the differences in the adverse health effects associated with the same five phenotypic classes of AAT Deficiency in different individuals associated with the two most prevalent deficiency alleles PIS and PIZ. Equally important is the need to investigate any differences associated with the expression of this genetic disease in different racial subgroups. Such an approach may well resolve apparent differences in the adverse health effects reported in the medical literature on each of the five phenotypic classes of the PIS and PIZ deficiency alleles. The addition of large numbers of rare variants found within various regions in Italy stored in the Italian AAT Deficiency Registry provides a new and unique resource for the further investigation of the adverse health effects associated with other rare AAT Deficiency variants.

Acknowledgements: One of the authors (ML) is a member of the Council of the Alpha One International Registry.

References

1. de Serres FJ. Worldwide Racial and Ethnic Distribution of Alpha-1-antitrypsin Deficiency: Details of an Analayis of Published Genetic Epidemiological Surveys. *Chest* 2002; 122: 1818-1829.
2. de Serres FJ, Blanco I, Bustillo EF. Genetic Epidemiology of Alpha-1 Antitrypsin Deficiency: France, Italy, Portugal, and Spain. *Clin Genet* 2003; 63: 1-20.
3. Brantly ML, Paul LD, Miller BH, Falk RT, Wu M, Crystal RG. Clinical features and history of the destructive lung disease associated with alpha-1-antitrypsin deficiency of adults with pulmonary symptoms. *Am Rev Respir Dis* 1988; 138: 327-336.
4. Brantly M, Nukiwa T, Crystal RG. Molecular basis of alpha-1-antitrypsin deficiency. *Am J Med* 1988; 84: 13-31.
5. Pierce JA. Antitrypsin and emphysema. Perspective and prospects. *JAMA* 1988; 259: 2890-2895.
6. Byth BC, Billingsley GD, Cox DW. Physical and genetic mapping of the serpin gene cluster at 14q32.1: allelic association and a unique haplotype associated with alpha 1-antitrypsin deficiency. *Am J Hum Genet* 1994; 55: 126-133.
7. Blank CA, Brantly M. Clinical features and molecular characteristics of alpha 1-antitrypsin deficiency. *Ann Allergy* 1994; 72: 105-120; quiz 120-102.
8. WHO [alpha 1-Pi deficiency. World Health Organization]. *Pneumologie* 1997; 51: 885-918.
9. WHO AAT Deficiency, World Health Organization, Geneva, 1996.
10. Long GL, Chandra T, Woo SL, Davie EW, Kurachi K. Complete sequence of the cDNA for human alpha 1-antitrypsin and the gene for the S variant. *Biochemistry* 1984; 23: 4828-4837.
11. Nukiwa T, Satoh K, Brantly ML, *et al*. Identification of a second mutation in the protein-coding sequence of the Z type alpha 1-antitrypsin gene. *J Biol Chem* 1986; 261: 15989-15994.
12. Carrell RW, Lomas DA. Alpha1-antitrypsin deficiency - a model for conformational diseases. *N Engl J Med* 2002; 346: 45-53.
13. Lee JH, Brantly M. Molecular mechanisms of alpha1-antitrypsin null alleles. *Respir Med* 2000; 94: S7-11.
14. Brantly M. Alpha 1-Antitrypsin Genotypes and Phenotypes. *In:* R.G. Crystal (Ed.), Alpha 1-Antitrypsin Deficiency: Biology, Pathogenesis, Clinical Manifestations, Therapy, Marcel Dekker, Inc., New York, 1996, pp. 45-59.
15. Parmar JS, Mahadeva R, Reed BJ, *et al*. Polymers of alpha(1)-antitrypsin are chemotactic for human neutrophils: a new paradigm for the pathogenesis of emphysema. *Am J Respir Cell Mol Biol* 2002; 26: 723-730.
16. Eden E, Mitchell D, Mehlman B, *et al*. Atopy, asthma, and emphysema in patients with severe alpha-1-antitrypysin deficiency. *Am J Respir Crit Care Med* 1997; 156: 68-74.
17. King MA, Stone JA, Diaz PT, Mueller CF, Becker WJ, Gadek JE. Alpha 1-antitrypsin deficiency: evaluation of bronchiectasis with CT. *Radiology* 1996; 199: 137-141.
18. Griffith ME, Lovegrove JU, Gaskin G, Whitehouse DB, Pusey CD. C-antineutrophil cytoplasmic antibody positivity in vasculitis patients is associated with the Z allele of alpha-1-antitrypsin, and P-antineutrophil cytoplasmic antibody positivity with the S allele. *Nephrol Dial Transplant* 1996; 11: 438-443.
19. Phelps RG, Shoji T. Update on panniculitis. *Mt Sinai J Med* 2001; 68: 262-267.
20. Pianka JD, Ricci P. Cirrhosis associated with heterozygous alpha-1-antitrypsin deficiency preceded by a remote history of panniculitis. *Am J Gastroenterol* 2000; 95: 1848.
21. Michalski JP, McCombs CC, Scopelitis E, Biundo JJ Jr, Medsger TA Jr. Alpha 1-antitrypsin phenotypes, including M subtypes, in pulmonary disease associated with rheumatoid arthritis and systemic sclerosis. *Arthritis Rheum* 1986; 29: 586-591.
22. Schievink WI, Katzmann JA, Piepgras DG. Alpha-1-antitrypsin deficiency in spontaneous intracranial arterial dissections. *Cerebrovasc Dis* 1998; 8: 42-44.
23. Lolin YI, Ward AM. Alpha-1-antitrypsin phenotypes and associated disease patterns in neurological patients. *Acta Neurol Scand* 1995; 91: 394-398.
24. 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. *Clin Genet* 2003; 64: 382-397.
25. Luisetti M, Seersholm N. Epidemiology of alpha (1)-antitrypsin deficiency. *Thorax* 2004; 59: 164-169.
26. Hutchison DC. The epidemiology of alpha 1-antitrypsin deficiency. *Lung* 1990; 168: 535-542.
27. Zwingle E. Italy before the Romans, National Geographic (January 2005), pp. 52-77.
28. Lindmark B, Eriksson S. Regional Differences in the Idiopathic Hemochromatosis Gene Frequency in Sweden. *Acta Med Scand* 1985; 218: 299-304.
29. 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 Respir Crit Care Med* 2003; 168: 818-855.
30. Sandford AJ, Chagani T, Weir TD, Connett JE, Anthonisen NR, Pare PD. Susceptibility genes for rapid decline of lung function in the Lung Health Study. *Am J Respir Crit Care Med* 2001; 163: 469-473.
31. Sigsgaard T, Brandslund I, Omland O, *et al*. S and Z alpha1-antitrypsin alleles are risk factors for bronchial hyperresponsiveness in young farmers: an example of gene/environment interaction. *Eur Respir J* 2000; 16: 50-55.
32. Ferrarotti I, Baccheschi J, Zorzetto M, *et al*. Prevalence and phenotype of subjects carrying rare variants in the Italian Registry for alpha-1-antitrypsin deficiency. *J Med Genetic* 2005; 42: 377-382.