



# Estimated numbers and prevalence of PI\*S and PI\*Z alleles of $\alpha_1$ -antitrypsin deficiency in European countries

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**ABSTRACT:** The current study focuses on developing estimates of the numbers of individuals carrying the two most common deficiency alleles, PI\*S and PI\*Z, for  $\alpha_1$ -antitrypsin deficiency (AT-D) in Europe.

Criteria for selection of epidemiological studies were: 1) AT phenotyping performed by isoelectrofocusing or antigen–antibody crossed electrophoresis; 2) rejection of “screening studies”; 3) statistical precision factor score of  $\geq 5$  for Southwest, Western and Northern Europe,  $\geq 4$  for Central Europe,  $\geq 3$  for Eastern Europe; and 4) samples representative of the general population.

A total of 75,390 individuals were selected from 21 European countries (one each from Austria, Belgium, Latvia, Hungary, Serbia-Montenegro, Sweden and Switzerland; two each from Denmark, Estonia and Lithuania; three each from Portugal and the UK; four each from Finland, the Netherlands, Norway and Spain; five each from Russia and Germany; six from Poland; eight from Italy; and nine from France). The total AT-D populations of a particular phenotype in the countries selected were: 124,594 ZZ; 560,515 SZ; 16,323,226 MZ; 630,401 SS; and 36,716,819 MS. The largest number of ZZ (5,000–15,000) were in Italy, Spain, Germany, France, the UK, Latvia, Sweden and Denmark, followed by Belgium, Portugal, Serbia-Montenegro, Russia, The Netherlands, Norway and Austria (1,000–2,000), with  $<1,000$  in each of the remaining countries.

A remarkable lack in number of reliable epidemiological studies and marked differences among these European countries and regions within a given country was also found.

**KEYWORDS:**  $\alpha_1$ -Antitrypsin deficiency,  $\alpha_1$ -protease inhibitor, Europe, genetic epidemiology, protease inhibitor phenotypes

Although  $\alpha_1$ -antitrypsin (AT) deficiency (AT-D) is one of the most common hereditary disorders in Europe, AT-D prevalence varies markedly from one country to another, as well as from one region to another within a given country [1].

AT is the most prevalent proteases inhibitor in the human serum, and is secreted mainly by hepatocytes [2]. The AT gene is highly pleomorphic, with  $\sim 100$  alleles having been 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  $<60\%$ . Most pathology related to AT-D is linked to the Z allele and, in clinical practice, 96% of patients have a ZZ phenotype [3–6]. The remaining 4% mostly

belongs to SZ, MZ and, in a smaller 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 with AT-D-associated diseases has been established to date [2, 5, 6].

AT-D is not properly a disease, but a predisposition for the development of a number of diseases throughout life, mainly pulmonary emphysema and several types of hepatopathies in both children and adults [2, 3].

Knowledge of the AT-D prevalence in every community is essential from a public health perspective. The current study specifically attempts to determine estimates of the prevalence and number of subjects carrying the most common defective alleles, PI\*S and PI\*Z, in each

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of the individual European countries. The current study estimates the total number of ZZ, SZ and MZ individuals in each European country, and goes beyond earlier publications by others [7–10], in which only the allele frequencies for PI\*M, PI\*S and PI\*Z were reported for individual cohorts in individual cities or geographical regions. Moreover, the present approach is a step beyond other recently published reports, where the numbers of subjects at risk were calculated from data reported by a mixture of reliable and unreliable epidemiological studies [1, 11].

## METHODS

### *Sources of the control cohort data used in the present study*

The authors of the present study worked independently and with different methodological approaches on AT-D epidemiology, and have published their research in different peer-reviewed journals [1, 8, 9, 11]. The authors' individual databases were combined to generate a common database used in the present meta-analysis. The present study utilises available data from epidemiological studies performed by others to determine the frequencies of deficiency allele combinations for PI\*S and PI\*Z, in the healthy control cohorts of individual case studies from European countries. The data from these individual cohorts for a given country were combined to obtain mean frequencies for the PI\*M, PI\*S and PI\*Z alleles. The allele frequencies were then used to calculate the total numbers of individuals in each of the five major defective phenotypic classes of interest (namely, PI MS, PI MZ, PI SS, PI SZ and PI ZZ) in the total population of each of these countries and all of Europe.

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 [9, 11]. Allele frequencies have been expressed as the total number of PI\*S and PI\*Z, whether in homo- or heterozygotes, per 1,000 alleles of all PI types.

The prevalence of each phenotype was calculated by applying the Hardy-Weinberg equilibrium statistical formula. The data on the number of individuals in different countries were obtained from the World Factbook database, updated in July 2004 [12].

To assess the statistical reliability of each survey, the coefficient of variation for PI\*S and PI\*Z frequencies in each control cohort was calculated. This coefficient of variation provides an estimate of the precision (or better, the imprecision) of results from each survey. The formulas for developing estimates of numerical precision factor scores (PFS) to obtain a value scale from 0 to 12 with which to assess the statistical quality in terms of precision (or imprecision) of each selected survey were discussed in earlier papers [9, 11].

### *Criteria for selection of studies*

Reliable selected studies for the present meta-analysis should fulfil the following criteria: 1) AT phenotyping performed by IEF or antigen–antibody crossed electrophoresis; 2) rejection of “screening studies”; 3) statistical precision factor score of  $\geq 5$  for Southwest, Western and Northern Europe,  $\geq 4$  for Central Europe,  $\geq 3$  for Eastern Europe; and 4) samples representative of the general population.

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

In most of the selected surveys, phenotypic characterisation was carried out by means of the IEF method. This technique provides a reliable detection of individuals carrying either normal or S and Z variant alleles, but not null alleles. There is no evidence that the phenotypic identification of PI\*S and PI\*Z deficiency alleles in the IEF technique is complicated by phenocopies (*i.e.* mutations in other codons that would give a polypeptide chain with isoelectric points identical to those of the PI\*S and PI\*Z variants) [6]. Thus, present evidence supports the widespread use of IEF for the rapid, inexpensive, and critical identification of the S and Z variants.

Starch gel electrophoresis is a less reliable method. The antigen–antibody crossed electrophoresis technique is an expensive and time-consuming method, and although it does give reliable results, since 1976, antigen–antibody crossed electrophoresis has been gradually replaced by IEF. To the current authors' knowledge, no studies from European IEF diagnosis were later corroborated with follow-up DNA-sequencing studies to provide confirmation at the molecular level.

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, as moderate 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 for assessing the statistical quality in terms of precision (or imprecision) of each selected survey

As the coefficient of variation depends on the sample size and the PI\*S and PI\*Z allelic frequencies, the current authors used different cut-off values of PFS for European countries. In general, PI\*Z frequencies in Europe range between 0 and 30 per 1,000, but PI\*S frequencies fluctuate between a wider range of 5–150 per 1,000. Therefore, 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. Thus, PFS should be adapted for different regions and countries, adjusting the PFS rise by PI\*S frequencies.

Consequently, the current authors considered that an appropriate value for the PFS for the Iberian Peninsula, Western Europe and Northern Europe (where PI\*S frequencies are of  $\sim 25$ –150 per 1,000, and PI\*Z frequencies are  $\sim 12$ –30 per 1,000) should be  $\geq 5$ . An appropriate PFS for Central Europe (where PI\*S frequencies decrease to 15–30 per 1,000, and PI\*Z frequencies are  $\sim 5$ –10 per 1,000) should be  $\geq 4$ . Finally, for Eastern and far distant regions of Southern and Northern Europe (where both PI\*S and PI\*Z frequencies are very low), the current authors have accepted a PFS value of  $\geq 3$  for selection.

Criterion 4: Cohort composition

Only the data of the control group cohort phenotypes in each paper (*i.e.* blood donors, workers, healthy unrelated persons,

**TABLE 1** Estimates of the protease inhibitor (PI)\*S and PI\*Z gene frequency and phenotype prevalence of each of the five phenotypic classes in the 21 European countries studied

Country total population	n <sup>#</sup>	Calculated frequency × 1000 <sup>†</sup>	Calculated prevalence 1/× (Hardy-Weinberg) <sup>*</sup>					Calculated prevalence 1/× (Hardy-Weinberg) <sup>*</sup>		Total PI*S and PI*Z calculated prevalence 1/× (Hardy-Weinberg)
			PI*S	PI*Z	PI MZ	PI SZ	PI ZZ	PI MS	PI SS	
<b>Austria 8174762</b>	868 (6.4)	20 (14–28)		13 (9–20)	1/39 (25–61)	1/1872 (879–4062)	1/5697 (2464–13478)	1/26 (18–37)	1/2460 (1254–4897)	1/15
<b>Belgium 10348276</b>	1345 (10.8)	54 (46–63)		16.7 (12–22)	1/32 (24–44)	1/551 (349–876)	1/3573 (1972–6539)	1/10 (8–12)	1/339 (247–469)	1/7
<b>Denmark 5413392</b>	1096 (12)	28 (25–30)		27 (24–29)	1/20 (18–21)	1/663 (562–783)	1/1368 (1157–1617)	1/19 (17–21)	1/1286 (1091–1517)	1/9
<b>Estonia 1341664</b>	1850 (6.5)	12.7 (9–17)		24 (19–29)	1/22 (17–27)	1/1636 (992–2718)	1/1636 (992–2718)	1/41 (30–55)	1/6197 (3459–1198)	1/14
<b>Finland 5214512</b>	2112 (4.3)	7 (5–10)		6.6 (4–9.7)	1/76 (52–113)	1/10278 (4890–21916)	1/22758 (10621–49527)	1/69 (48–100)	1/18566 (9007–38792)	1/36
<b>France 60424213</b>	8753 (8.3)	76 (72–80)		12.8 (11–14.6)	1/43 (37–49)	1/512 (426–615)	1/6054 (4652–7886)	1/7 (7–8)	1/173 (156–192)	1/6
<b>Germany 82424609</b>	5886 (5.1)	21 (18–23)		9.8 (8–11.8)	1/52 (43–63)	1/2418 (1774–3302)	1/10299 (7120–14931)	1/25 (22–28)	1/2271 (1769–2920)	1/16
<b>Hungary 10032375</b>	1036 (5.9)	25 (19–33)		6.7 (3.8–11)	1/76 (44–135)	1/2949 (1304–6844)	1/21904 (7418–67495)	1/1588 (916–2776)	1/21 (16–27)	1/16
<b>Italy 58057477</b>	12239 (7.6)	23 (21–25)		16 (15–18)	1/32 (29–35)	1/1336 (1115–1601)	1/3708 (3048–4513)	1/23 (21–25)	1/1924 (1631–2272)	1/13
<b>Latvia 2306306</b>	288 (5.6)	31 (19–50)		45 (30–60)	1/12 (8–18)	1/354 (151–861)	1/491 (227–1091)	1/17 (11–29)	1/1024 (402–2718)	1/7
<b>Lithuania 3607899</b>	1995 (6.4)	17 (13–21)		15 (12–19)	1/34 (26–45)	1/1980 (1201–3284)	1/4422 (2644–7443)	1/31 (24–40)	1/3546 (2182–5797)	1/16
<b>The Netherlands 16318199</b>	2539 (4.8)	21 (18–26)		10 (7.7–13)	1/50 (38–67)	1/2275 (1427–3646)	1/9536 (5475–16725)	1/24 (20–29)	1/2170 (1487–3179)	1/16
<b>Norway 4574560</b>	4492 (8.2)	25 (21–28)		18 (16–21)	1/28 (24–33)	1/1095 (824–1458)	1/2929 (2156–3986)	1/21 (18–24)	1/1638 (1258–2134)	1/12
<b>Poland 38626349</b>	9539 (4.9)	15 (13–17)		4 (3–5)	1/123 (98–155)	1/8169 (5800–11529)	1/58319 (37177–91784)	1/34 (31–39)	1/4577 (3619–5792)	1/27
<b>Portugal 10524145</b>	1449 (6.2)	129 (117–141)		13.8 (10–19)	1/42 (30–59)	1/281 (186–428)	1/5249 (2788–9987)	1/5 (4–5)	1/60 (50–73)	1/4
<b>Russia 143782338</b>	2787 (3.5)	10 (7–13)		3 (2–5)	1/149 (93–241)	1/15141 (7243–32167)	1/86065 (33951–23894)	1/52 (40–69)	1/10655 (6181–18486)	1/38
<b>Serbia 10825900</b>	1060 (5.1)	7 (4–11)		12.7 (8–18)	1/40 (27–60)	1/5945 (2350–15500)	1/6165 (2846–13600)	1/77 (45–137)	1/22931 (7764–70661)	1/26
<b>Spain 40280780</b>	2458 (7.7)	104 (96–113)		17 (14–21)	1/33 (26–41)	1/278 (206–375)	1/3334 (2175–5164)	1/5 (5–6)	1/92 (78–109)	1/4
<b>Sweden 8986400</b>	1082 (8.81)	24 (18–32)		23 (17–30)	1/23 (17–31)	1/885 (506–1562)	1/1879 (1066–3345)	1/21 (16–29)	1/1688 (963–2917)	1/11
<b>Switzerland 7450867</b>	1148 (8.1)	38 (31–47)		11 (7–17)	46 (31–70)	1/152 (630–2131)	7798 (3544–17485)	14 (11–17)	681 (448–1039)	1/10
<b>UK 60270708</b>	4775 (6.5)	27 (24–31)		12 (10–14)	44 (36–53)	1/533 (1127–2088)	7018 (4838–10205)	19 (17–22)	1339 (1051–1708)	1/13
<b>European totals</b>	75390 (6.9)	33 (32–34)		14.5 (14–15)	1/36 (35–38)	1/1051 (980–1126)	1/4727 (4348–5139)	1/16 (16–17)	1/934 (884–987)	1/11

Data are presented as n (95% confidence interval), unless otherwise stated. <sup>#</sup>: number of subjects (mean precision factor score); <sup>\*</sup>: numbers in parentheses represent 95% confidence interval.

**TABLE 2** Estimates of the numbers of each of the five phenotypic classes for the deficiency alleles protease inhibitor (PI)\*S and PI\*Z for each of the 21 European countries studied

Country total population	Calculated number of PI MZ, PI SZ and PI ZZ phenotypes			Calculated number of PI MS and PI SS phenotypes		Total number of S- and Z-deficiency phenotypes
	PI MZ	PI SZ	PI ZZ	PI MS	PI SS	
<b>Austria 8174762</b>	209375 (134737–320922)	4367 (2012–9303)	1435 (607–3318)	318615 (223528–449892)	3323 (1669–6520)	537115 (535728–538506)
<b>Belgium 10348276</b>	321642 (235074–437347)	18791 (11814–29687)	2896 (1583–5249)	1043548 (877456–1236788)	30484 (22049–41966)	1417361 (1415194–1419531)
<b>Denmark 5413392</b>	276681 (253574–301755)	8163 (6913–9634)	3958 (3348–4678)	258296 (261816–310740)	4209 (3569–4960)	578507 (576989–579718)
<b>Estonia 1341664</b>	62172 (49966–77105)	820 (494–1353)	776 (508–1180)	32833 (24255–44210)	216 (120–388)	96818 (96231–97407)
<b>Finland 5214512</b>	68166 (46013–100110)	507 (238–1066)	229 (105–491)	75470 (51992–108707)	281 (134–579)	144653 (143919–145391)
<b>France 60424213</b>	1415176 (1234020–1621729)	118094 (98214–141891)	9982 (7662–12989)	8371550 (7908520–8857600)	349296 (314713–387492)	10264097 (10258377–10269820)
<b>Germany 82424609</b>	1574316 (1303024–1899316)	34083 (24965–46452)	8003 (5520–11577)	3352208 (2946324–3810514)	36287 (28225–46597)	5004987 (5000649–5009149)
<b>Hungary 10032375</b>	131254 (74097–227166)	3402 (1466–7696)	458 (149–1352)	487516 (365365–646303)	6319 (3614–10947)	628949 (627445–630456)
<b>Italy 58057477</b>	1832157 (1656272–2025831)	43471 (36263–52085)	15659 (2864–19150)	2543144 (2334411–2769456)	30170 (25555–35602)	4464600 (4460622–4468581)
<b>Latvia 2306306</b>	192303 (125417–288626)	6507 (2679–15267)	4699 (2114–15267)	133133 (79451–217132)	2252 (848–5743)	338894 (337841–339950)
<b>Lithuania 3607899</b>	105054 (80471–136584)	1822 (1099–3004)	816 (485–1365)	117311 (91183–150355)	1017 (662–1654)	226021 (225120–226925)
<b>The Netherlands 16318199</b>	323609 (243025–429096)	7174 (4476–11439)	1711 (976–2980)	678334 (577433–823464)	7519 (5133–10976)	1018346 (1016432–1020264)
<b>Norway 4574560</b>	161750 (138015–189315)	4117 (3137–5554)	1562 (1148–2121)	216316 (188603–247813)	2793 (2143–3635)	386599 (385434–387767)
<b>Poland 38626349</b>	313842 (249643–393827)	4729 (3350–6660)	662 (421–1039)	1120297 (993752–1262178)	8439 (6669–10672)	1447970 (1455657–1450286)
<b>Portugal 10524145</b>	249119 (177783–346754)	37393 (24609–56433)	2005 (1054–3774)	2323032 (2075922)	174344 (143674–202939)	2785893 (2783089–2788700)
<b>Russia 143782338</b>	967379 (597686–1544500)	9496 (4470–19851)	1671 (642–4235)	2749394 (2080061–3619803)	13495 (7778–23272)	3741435 (3737695–3745179)
<b>Serbia 10825900</b>	270421 (180763–400145)	1821 (698–4606)	1756 (796–3804)	140218 (79302–242257)	472 (153–1394)	414689 (413452–415929)
<b>Spain 40280780</b>	1223966 (974300–1533217)	145055 (107396–195346)	12045 (7801–18522)	7369857 (6706733–8085047)	436710 (369639–515054)	9187643 (9182415–9192855)
<b>Sweden 8986400</b>	394910 (292829–529060)	10151 (5753–17744)	4783 (2687–8433)	419089 (313545–566599)	5386 (3080–9334)	834319 (832615–836026)
<b>Switzerland 7450867</b>	160369 (105985–239992)	6468 (3496–11821)	955 (426–2103)	542788 (434701–674626)	10945 (7169–6615)	721526 (719945–723110)
<b>UK 60270708</b>	1382421 (1141469–1671500)	39326 (28872–53464)	8588 (5906–12458)	3165018 (2789984–3586700)	45017 (35284–57362)	4640370 (4636315–4644429)
<b>European totals</b>	16323226 (15637–17038228)	560515 (522960–600730)	124594 (114604–135446)	36716819 (35677978–37783871)	630401 (596592–666087)	54355555 (54341789–54369325)

Data are presented as n (95% confidence interval), unless otherwise stated.



**FIGURE 1.** Distribution of protease inhibitor ZZ prevalence in Europe. The highest prevalence is in the South of the Scandinavian Peninsula, Latvia and Denmark, and it progressively decreases towards the South and the East of Europe. -----: isogenes (lines of equal prevalence).



**FIGURE 2.** Distribution of protease inhibitor SZ prevalence in Europe. The highest prevalence is in the Iberian peninsula and Southern France and gradually decreases towards the North, South and East of the continent. -----: isogenes (lines of equal prevalence).

newborns, school or college students, general population selected at random, *etc.*) were used in the present study. Most individuals from selected cohorts were Caucasians, except a cohort of Lapps from Finland. 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. It should be pointed out that a number of studies carried out in small isolated communities with small sample sizes, significant intermarriage and peculiar genetic traits were rejected due to their low PFS. Since most of these cohorts were not representative of the general population of a given country, these facts should not be considered a methodological defect, but an appropriate approach that should make the estimation more realistic. Examples of these former rejected studies were: Chuetas Jews from Majorca; Gypsies from Hungary; Aromunds, Musequians, Pindonians, Moskopolians, Gramostians and Fraseriots from the Balkans, Romania, Greece, *etc.*

## RESULTS

A total of 68 out of 197 cohorts, having a total of 75,390 individuals, was selected from 21 countries in Europe [13–71]. The mean PFS of these selected control cohorts gave a value of 6.9 on a scale of 0–12 points.

Selected studies were distributed as follows: one each from Austria [13], Belgium [14], Latvia [18], Hungary [34], Serbia-Montenegro [62], Sweden [67] and Switzerland [68]; two each from Denmark [15, 16], Estonia [17, 18] and Lithuania [18, 41]; three each from Portugal [53–56] and the UK [69–71]; four each from Finland [19–22], the Netherlands [42–44], Norway [45–47] and Spain [62–66]; five each from Russia [57–61] and Germany [29–33]; six from Poland [48–53]; eight from Italy [35–42]; and nine from France [23–28].

With an estimated total population of 588,985,731 individuals for these 21 countries, the AT-D total population consisted of

124,594 (95% CI: 114,604–135,446) PI ZZ; 560,515 (95% CI: 522,960–600,730) PI SZ; 16,323,226 (95% CI: 15,637,279–17,038,228) PI MZ; 36,716,819 (95% CI: 35,677,978–37,783,871) PI MS; and 630,401 (95% CI: 596,592–666,087) PI SS phenotypes.

The data on total population, sample size, mean PFS, calculated frequencies for PI\*S and PI\*Z, and calculated prevalence in each country are shown for each of the selected countries (table 1). Estimates of the numbers of each of the five phenotypic classes for the deficiency alleles PI\*S and PI\*Z for each of the 21 countries in Europe are shown in table 2. Estimates of ZZ, SZ and MZ prevalence are given by means of isogenic lines (lines of equal gene prevalence) in maps shown in figures 1–3. The calculated numbers of ZZ, SZ and MZ individuals for every country are given graphically in figures 4–6 for comparison.

## DISCUSSION

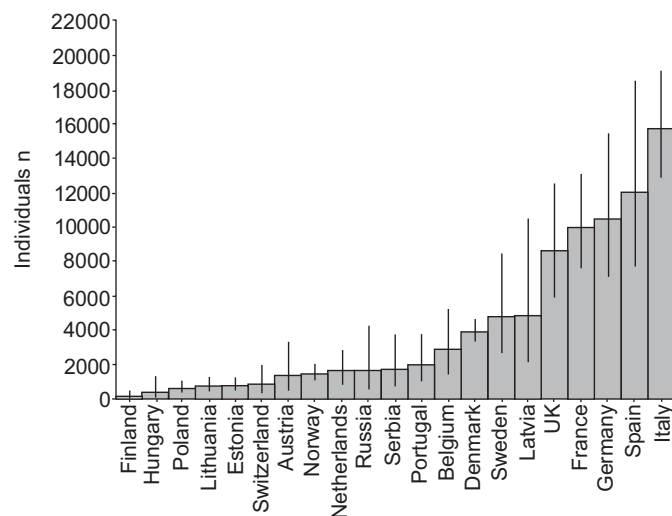
Tables 1 and 2 demonstrate that both the PI\*S and PI\*Z alleles are found in all 21 European countries; very striking differences for the distribution of PI\*S and PI\*Z AT-D alleles are demonstrated among these European countries, and even within different regions of the same country. With an estimated total population of 588,985,731 individuals for the listed European countries, the number of PI ZZ phenotypes consists of 124,594 individuals. The largest numbers of PI ZZ individuals were found in Italy, Spain, Germany, France, the UK, Latvia, Sweden and Denmark, with 5,000–15,000 individuals in each of these eight countries. On the contrary, the lowest number of individuals of the PI ZZ phenotype was found in Finland, Hungary, Poland, Estonia, Lithuania and Switzerland (with <1,000 for every of these six countries). The seven remaining European countries yielded a moderate number of PI ZZ individuals, with ~1,000–2,000 for each of them. These calculated numbers are a reflection of both the specific PI\*Z frequency and the total population of each country.



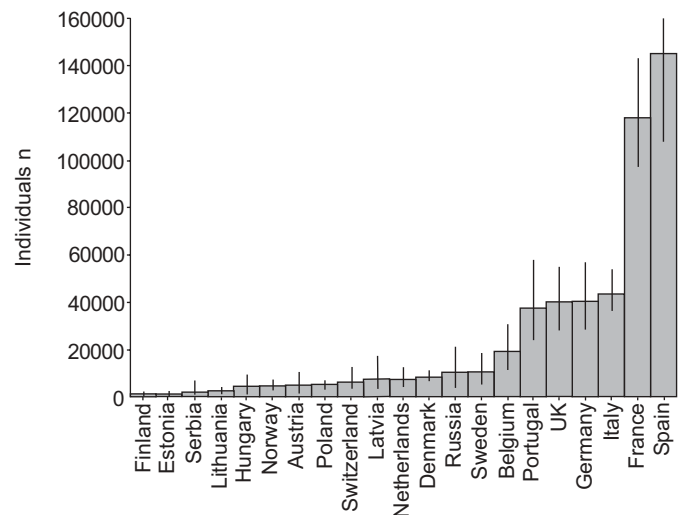
**FIGURE 3.** Distribution of protease inhibitor MZ prevalence in Europe. The highest prevalence is in the South of the Scandinavian Peninsula, Baltic Republics, Denmark and the UK, and progressively decreases towards the East, South and North of the continent. -----: isogenes (lines of equal prevalence).

The current authors are aware that these data should be considered an approximation, since their calculations might have bias related to the samples' 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 geographical regions; there are also marked differences in the contribution of AT-D data in the different regions of the same country. The unbalanced contributions of different regions of a given country should be taken into account for most of the European countries in the present study.

In addition to the protease inhibitor ZZ individuals, the present authors have calculated that there are 560,515 protease

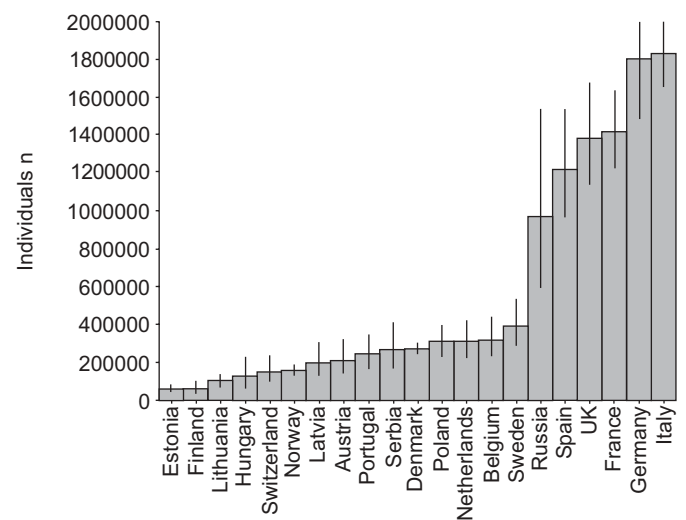


**FIGURE 4.** Estimates of the numbers of individuals of phenotype protease inhibitor ZZ in each of 21 countries in Europe with 95% confidence intervals indicated on each estimate.



**FIGURE 5.** Estimates of the numbers of individuals of phenotype protease inhibitor SZ in each of 21 countries in Europe with 95% confidence intervals indicated on each estimate.

inhibitor SZ and 16,323,226 protease inhibitor MZ individuals in Europe, and an impressive number of almost 37 million individuals with protease inhibitor MS and protease inhibitor SS phenotypes. Although both MS and SS phenotypes are currently not considered to be at increased risk for development of diseases, and that the penetrance (the number of subjects who develop clinical disease) of MZ and SZ phenotypes is clearly lower if compared with protease inhibitor ZZ, it is the authors' intention to provide these numbers to illustrate: 1) the very large numbers of individuals with the S and Z deficiency alleles in the European 21 countries studied; and 2) the need for follow-up epidemiological studies to extend these original observations.



**FIGURE 6.** Estimates of the numbers of individuals of phenotype protease inhibitor MZ in each of 21 countries in Europe with 95% confidence intervals indicated on each estimate.

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