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European ACP1*C Allele Has Recessive Deleterious Effects on Early Life Viability

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Abstract

The acid phosphatase locus (ACP1) is a classical polymorphism that has been surveyed in hundreds of human populations worldwide. Among individuals of European ancestry, the *ACP1**C allele occurs with an average frequency of approximately 0.05, whereas it is nearly absent in all other human populations. It has been hypothesized that this allele is maintained by over dominant selection among European populations. Here, we analyze ACP1 protein polymorphism data from more than 50,000 individuals previously surveyed in 67 populations across Europe as well as inheritance data from more than 6,000 European parent–offspring pairs to assess the signature of natural selection currently acting on this allele. Although we see a significant excess of *ACP1**C heterozygotes relative to Hardy–Weinberg expectations, we find no evidence that natural selection favors *ACP1**C heterozygotes. Instead, *ACP1**C appears to have a strongly deleterious and recessive fitness effect. We observed only 48.9% of expected homozygous offspring from heterozygous parents and significantly fewer homozygotes than expected within populations. Because parent–offspring pairs indicate a significant deficiency of *ACP1**C homozygotes, we infer that viability selection is acting on *ACP1**C homozygotes very early in life, perhaps before birth. We estimate that approximately 1.2% of all couples of European ancestry are composed of individuals who both carry the *ACP1**C allele. As such, selection against *ACP1**C homozygotes may represent a nonnegligible contribution to the overall number of spontaneous abortions among women of European ancestry and may cause substantial fertility reductions among some combinations of parental genotypes.

Keywords

ACP1; ACID PHOSPHATASE; OVERDOMINANCE; NATURAL SELECTION; SPONTANEOUS ABORTION; EUROPEAN POPULATIONS

The acid phosphatase locus (ACP1) is a polymorphic enzyme system that has been surveyed in hundreds of thousands of individuals worldwide (Mourant et al. 1976; Roychoudhury and Nei 1988). ACP1 has four major codominant alleles that reach polymorphic frequencies, two with global distributions (*ACP1**A and *ACP1**B) and two with regional geographic distributions (*ACP1**C and *ACP1**R, which are restricted to Europe and sub-Saharan Africa, respectively). In addition, a number of minor alleles reach polymorphic frequencies in individual populations, such as *ACP1**GUA among the Guaymi of Costa Rica and *ACP1**TIC among the Ticuna of Brazil (Neel et al. 1980; Barrantes et al. 1982).

ACP1 encodes two separate isozyme products through alternative splicing of the primary RNA transcript (Dissing and Sensabaugh 1987; Dissing et al. 1991; Lazaruk et al. 1993). Allele variants of ACP1 differ in their production of these isozymes with respect to both the total quantity and the ratio of isozymes produced [reviewed by Greene et al. (2000)]. Thus ACP1 genotypes appear to have distinct phenotypes with regard to enzyme production,

making them potential targets of natural selection. Here, we focus on identifying whether there is a signature of natural selection on the European *ACPI**C allele. Correlation studies have shown that carriers of *ACPI**C may experience fitness advantages over individuals who do not carry the allele, leading to the suggestion that *ACPI**C may be maintained through overdominance as a balanced polymorphism (Greene et al. 2000).

The *ACPI* locus encodes the low-molecular-weight protein tyrosine phosphatase, the function of which remains poorly understood. It is expressed ubiquitously among human tissues and is thought to play an important role in signal transduction, acting to down-regulate a number of cellular processes related to growth and differentiation (Wo et al. 1992; Raugei et al. 2002). Functional differences between the two *ACPI* isozymes, termed fast (F) and slow (S), have yet to be identified. These enzymes are identical, with the exception of 33 amino acids that are the products of the alternatively spliced third and fourth exons, respectively (Dissing and Johnsen 1992). Changes in the amount of F and S isozymes produced by each allele have been associated with mutations that interrupt exonic splicing enhancers (Rudbeck et al. 2000). *ACPI**C is the only allele to produce more S than F isozyme, and it also produces approximately six times more S isozyme (and somewhat less F isozyme) than any other major allele (Dissing 1987). These differences in isozyme production have been suggested to be the result of a single silent substitution in the third exon of *ACPI**C that alters motifs recognized by human splicing factors SRp40 and SRp55 (Rudbeck et al. 2000).

Patterns of *ACPI* allele frequency variation have been interpreted as evidence that particular genotypes may be adaptive in certain environments. This pattern is most striking for the *ACPI**A and *ACPI**B alleles. The frequencies of these alleles vary clinally on every continent, with *ACPI**A appearing to be relatively advantageous at high latitudes (Ananthakrishnan and Walter 1972; Piazza et al. 1981; Sokal et al. 1989; Cavalli-Sforza et al. 1994). The *ACPI**C allele does not show such striking patterns of geographic variability. It is relatively uncommon in nearly all European populations, with a mean frequency of 0.053 (Mourant et al. 1976). Despite its rarity, *ACPI**C is of considerable interest because several studies have suggested that the allele confers increased fitness to heterozygous carriers. One study of Italian women showed that heterozygous female *ACPI**C carriers are significantly less likely to have recurrent spontaneous abortions than women of other genotypes, indicating a possible fertility advantage for heterozygous women (Gloria-Bottini et al. 1996).

A second apparent advantage occurs at birth; rates of macrosomia (extremely high birth weights) are significantly lower among infant carriers of the *ACPI**C allele (Gloria-Bottini et al. 1988). Macrosomia is of considerable risk to both infants and mothers and has been shown to occur more frequently than expected among carriers of the *ACPI**A allele (Gloria-Bottini et al. 1988; Bottini et al. 1990). Because European populations typically have high frequencies of the *ACPI**A allele, Greene et al. (2000) hypothesized that *ACPI**C may be maintained through heterozygote advantage in *ACPI**A/*C individuals, acting to check rates of infant macrosomia without fully diminishing the cold-adapted benefits of carrying the *ACPI**A allele.

Both the Greene et al. (2000) hypothesis and the correlation between spontaneous abortion rates and *ACPI* genotype suggest a possible role of heterozygote advantage in the maintenance of *ACPI**C. Here, we examine protein polymorphism data from more than 50,000 individuals, representing populations from all regions of Europe, to determine whether overdominance maintains the *ACPI**C allele.

Materials and Methods

We assembled all available polymorphism surveys in which genotypic proportions (of all possible genotypes) were reported for the *ACPI* locus from European populations. We included only populations where both sexes were sampled from a minimum of 150 individuals. In total, we obtained genotypic data from 50,528 individuals sampled from 67 populations spanning the entire European continent. These data sets are shown in Appendixes 1 and 2. Individual studies used a diverse range of sampling strategies, with some considering populations to be units as small as a single village and others pooling data from entire countries. In this analysis we deferred to the original investigators to define the population composition.

To isolate the possible signature of natural selection acting only on *ACPI**C, we combined the two other alleles present in Europeans (*ACPI**A and *ACPI**B), creating three genotypic classes: *ACPI**C homozygotes (hereafter abbreviated CC), *ACPI**C heterozygotes (XC), and non-*ACPI**C homozygotes (XX). This method may cause us to miss potentially interesting patterns of selection operating within the lumped allele classes; however, it allows us to test hypotheses relating to the action of natural selection on *ACPI**C in a simple two allele system.

Expected Hardy–Weinberg genotypic proportions were calculated from the observed frequency of *ACPI**C and non-*ACPI**C alleles. Deviations from these proportions were analyzed using standard chi-square tests. The fact that populations are not defined uniformly in our analysis may cause spurious deviations from expected Hardy–Weinberg values because some populations are almost certainly internally subdivided (thus violating the assumption of random mating within defined study units). However, this phenomenon will produce a Wahlund effect (Wahlund 1928), or an apparent excess of homozygotes within populations. If overdominance maintains the *ACPI**C allele, we expect to observe the opposite pattern, making the bias introduced by pooling subdivided populations conservative with regard to our study.

A second source of data used in our analysis is published *ACPI* genotype data for 6,039 parent–offspring pairs, as reported by Sørensen (1973). This data set includes the combined results of data collected in a number of northern European populations. Although a large portion of this data set was screened for cases where paternity could not be confirmed, any errors in paternity assignment do have the potential to influence the observed result. Based on the subset of data in which paternity was confirmed (Sørensen 1973, Table III), we believe that this source of error is unlikely to influence our interpretations here.

Of the total number of parent–offspring pairs, 1,281 are children of parental types that could potentially produce XC heterozygotes or CC homozygotes, with 90 of these composed of parents who are both XC heterozygotes (i.e., parents who could potentially produce CC children). No parents with the CC genotype were present in the Sørensen (1973) data set. We analyzed deviations from expected Mendelian inheritance patterns using standard chi-square tests. All non-*ACPI**C alleles were pooled in this analysis, as described earlier.

It is important to emphasize that both our Hardy–Weinberg and Mendelian analyses are tests of selection acting only in the present generation and that they do not allow us to test hypotheses regarding the role of selection in the past.

Results

ACP1 Genotype Frequencies

Our analysis of genotype frequencies among 67 individual European populations showed only a single significant deviation from Hardy–Weinberg expectations. The single exceptional population was composed of 2,402 individuals from eastern Slovakia sampled by Juícková et al. (1994). In this population the significant deviation from Hardy–Weinberg expectations ($\chi^2 = 7.42$, $df = 2$, $P = 0.024$) is caused primarily by a deficiency of CC homozygotes (0 observed, 6.66 expected) and an excess of XC heterozygotes (253 observed, 239.68 expected), whereas the number of observed XX homozygotes is close to that expected (2,149 observed, 2,155.66 expected).

Despite only a single population having ACP1 genotype frequencies that deviated significantly from expectations, analysis of all populations revealed a significant skew toward an excess of heterozygotes and a deficiency of CC homozygotes. Of the 67 populations, more heterozygotes than expected were observed in 55 populations (sign test, $P = 1.03 \times 10^{-7}$). Similarly, among the 40 populations where at least a single CC homozygote was expected, 32 populations showed a deficiency of homozygotes (sign test, $P = 1.82 \times 10^{-4}$).

Pooling all 67 European populations yielded a highly significant deviation from Hardy–Weinberg expectations ($\chi^2 = 25.02$, $df = 2$, $P = 3.70 \times 10^{-6}$). There was a slight deficiency of XX homozygotes (45,010 observed, 45,069 expected), an excess of XC heterozygotes (5,421 observed, 5,303 expected), and a deficiency of CC homozygotes (97 observed, 156 expected).

ACP1*C Allele Frequencies

The frequencies of the *ACP1**C allele within the 67 European populations, shown in Figure 1, were approximately normally distributed (Kolmogorov–Smirnov test, $P = 0.39$), with a mean frequency of 0.052 (SD = 0.018). Five populations are suspected outliers [as defined by Tukey (1977)]. Three of these populations have *ACP1**C frequencies less than 0.010: the Norwegian Saami (Lie and Teisberg 1973), Spanish Basques from the Biscay region (Aguirre et al. 1991), and a population from southwest Germany (Goedde et al. 1966). The remaining two suspected outliers have *ACP1**C frequencies greater than 0.095: the Skolts from northern Finland (Mourant et al. 1976) and a sample of Poles from Krakow, Wroclaw, and Rzeszow (Wyslouchowa 1970).

Mendelian Inheritance

Comparisons between parent and offspring genotypes revealed a significant deviation in offspring genotypes relative to Mendelian expectations when all mating types were considered together (Table 1, row 1: $\chi^2 = 7.30$, $df = 2$, $P = 0.026$). We observed an excess of XX homozygotes (644 observed, 618 expected) and a deficiency of both XC heterozygotes (626 observed, 640.5 expected) and CC homozygotes (11 observed, 22.5 expected).

When we restricted the pedigree analysis to mating types in which both parents are XC heterozygotes (Table 1, row 2), we still observed significant deviations from Mendelian expectations ($\chi^2 = 9.73$, $df = 2$, $P = 7.70 \times 10^{-3}$). In this case there was a deficiency of both homozygous classes (XX: 21 observed, 22.5 expected; CC: 11 observed, 22.5 expected) and an excess of heterozygotes (58 observed, 45 expected).

Finally, considering only mating types in which one parent is an XC heterozygote and one is an XX homozygote, we saw no significant deviation from Mendelian expectations ($\chi^2 =$

2.54, $df = 1$, $P = 0.111$), although there was a trend toward a deficiency of heterozygotes (Table 1, row 3).

Discussion

Patterns of variation at the *ACPI* locus are inconsistent with those expected of a neutrally evolving locus. Among European populations we observed systematic deviations from Hardy–Weinberg genotype expectations, with significantly more populations having an excess of *ACPI**C heterozygotes (and a deficiency of *ACPI**C homozygotes) than expected by chance. Further, when we pooled all 50,528 European individuals in this study, we observed a highly significant deficiency of *ACPI**C homozygotes and an excess of heterozygotes. This observation is particularly surprising in our pooled data set, where we expected a Wahlund effect to bias the data toward an excess of *homozygotes*. Nonneutral patterns were also evident when we compared parent–child genotypes with the expected predictions of Mendelian inheritance. Among parents who are both *ACPI**C heterozygotes, we observed only 48.9% of the expected number of homozygous *ACPI**C children and an excess of heterozygous children (Table 1, row 2).

Before considering the possibility that natural selection is acting on the *ACPI* locus, we need to examine the potential for biases with regard to data collection as a possible cause of the observed skew in genotype frequencies. In particular, Brinkmann et al. (1971) suggested that *ACPI**B/*C and *ACPI**C/*C genotypes may be difficult to distinguish based on their electrophoretic staining patterns (but not *ACPI**A/*C, which has a distinct banding pattern). Indeed, Brinkmann and colleagues hypothesized that ambiguity between these two genotypes may be the cause of an apparent excess of XC heterozygotes.

Examination of the present data set, however, reveals no indication of this type of systematic bias. In fact, counter to the pattern described, the *ACPI**A/*C genotype appears to make up the numerical bulk of the excess heterozygotes in our pooled European sample (*ACPI**A/*C: 1,959 observed, 1,860 expected; *ACPI**B/*C: 3,462 observed, 3,443 expected) (see Appendix 2). Furthermore, when we excluded all data sets in which there were more *ACPI**B/*C heterozygotes than expected, we still observed a significant excess of populations with a deficit of *ACPI**C/*C homozygotes (21 out of 25 populations, sign test $P = 9.11 \times 10^{-4}$).

Similarly, we saw no signature of typing error in the analysis of Mendelian inheritance. There was an excess of both *ACPI**A/*C and *ACPI**B/*C children from matings of two heterozygous parents [*ACPI**A/*C: 24 observed, 19.5 expected; *ACPI**B/*C: 34 observed, 25.5 expected; data from Sorenson (1973, Table IV)]. In contrast, there was no excess of heterozygous XC offspring in mating types where an *ACPI**B/*C parent is paired with a non-*ACPI**C homozygote (XX), as would be expected if some *ACPI**B/*C parents truly carried the *ACPI**C/*C genotype.

Based on these observations, we do not believe that ambiguity in distinguishing *ACPI**B/*C and *ACPI**C/*C genotypes causes the observed deficit of *ACPI**C/*C homozygotes in either the population surveys or the analysis of Mendelian inheritance; therefore the pattern most likely represents the action of natural selection.

On the basis of only the deviations between observed and expected genotype frequencies among European populations, it is difficult to assess the form of natural selection acting on the *ACPI**C allele. An excess of heterozygotes is often interpreted as evidence of balancing selection at a locus, operating through overdominance. However, a relatively underappreciated quirk in the interpretation of Hardy–Weinberg deviations is that a significant excess of heterozygotes occurs whenever the geometric mean of homozygous

genotypic fitnesses is less than that of the heterozygote (Wallace 1958; Lewontin and Cockerham 1959). In other words, the existence of a strongly deleterious allele, such as a recessive lethal allele, will cause a considerable excess of heterozygotes. Thus either overdominance *or* selection against a homozygous genotype is sufficient to produce the pattern observed among our European populations. Comparison of parent and offspring genotypes allows us to distinguish between these alternatives, because different sets of parental genotypes can be used to test each hypothesis. Interestingly, there is no excess of heterozygous children from parental pairings of *ACPI**C heterozygotes (XC) and non-*ACPI**C homozygotes (XX), as would be expected if overdominance plays a role in maintaining the *ACPI**C allele. In contrast, there is a strong deficiency of *ACPI**C homozygous children (48.9% of the expected number) from matings of heterozygous parents (XC × XC). Thus we see no evidence that the *ACPI**C allele is currently maintained by overdominance and strong evidence that *ACPI**C homozygotes have greatly reduced fitness.

From this analysis of the data it is clear that *ACPI**C is a deleterious allele segregating among European populations, which in turn causes the observed deviation from Hardy–Weinberg expectations in our population data. Its persistence is almost certainly due to the fact that its fitness effects appear to be largely recessive, as evidenced by the agreement between observed data and Mendelian expectations from parental pairings of *ACPI**C heterozygotes and non-*ACPI**C homozygotes (Table 1, row 3).

An open question then is how *ACPI**C arose to polymorphic frequencies in nearly every European population, despite its negative fitness effects. Interestingly, Cavalli-Sforza et al. (1994) found that *ACPI**C has one of the strongest correlations (>0.90) of all polymorphic gene systems with their first principal component of European gene frequencies. Cavalli-Sforza et al. (1994) hypothesized that the genes underlying their first principal component reflect migrations into Europe from the Middle East during the Neolithic. Specifically, this migration event is thought to correspond to the spread of modern agricultural technology. It is particularly interesting that two of the three population outliers with low *ACPI**C frequencies (the Norwegian Saami and the Spanish Basque) are among the few populations in Europe that appear to be remnants from pre-Neolithic Europe (Cavalli-Sforza et al. 1994). Based on this evidence, the relatively high frequency of *ACPI**C may simply reflect a founder event associated with the arrival of agriculture in Europe. Genetic drift may have allowed the *ACPI**C allele to increase in frequency in the founder population, and it has since persisted at low frequency (albeit as an unstable polymorphism) because of its recessive influence on fitness.

Alternatively, we cannot rule out a historical role for natural selection favoring the *ACPI**C allele. The two tests we use here, deviations from Hardy–Weinberg equilibrium and deviations from Mendelian patterns of inheritance, detect the action of natural selection only in the current generation and do not address the possibility of selection in the past. Indeed, given the relatively high frequency of *ACPI**C in extant European populations, a historical role for selection acting to maintain the allele in the past remains an intriguing hypothesis.

It is important to consider the extent to which the continued segregation of the *ACPI**C allele has noticeable fitness effects among extant European populations (and European-derived populations in other portions of the world). Based on our analysis of the data, approximately 10.7% of all Europeans are heterozygous carriers of the *ACPI**C allele. Assuming random mating, we estimate that 1.2% of European couples are composed of two heterozygous individuals. It is among these couples where we see only 48.9% of the expected number of offspring with the CC genotype (which account for 25% of the expected number of total offspring from these couples). The point at which this viability selection

occurs during development remains unknown. However, the observation that deviations from expected Mendelian patterns of inheritance are present among children indicates that this selection is likely to occur before birth.

Among humans, it has been estimated that 50–80% of all embryos are lost in utero as a result of both environmental and genetic factors (Diamond 1987). Our analyses indicate that viability selection against *ACPI**C homozygotes may represent a nonnegligible contribution to this phenomenon among Europeans. Indeed, among couples where both individuals are heterozygous for the *ACPI**C allele, as many as 12.3% of all embryos may be lost because of this single genetic factor. Further, when *ACPI**C homozygotes are paired with either each other or with *ACPI**C heterozygotes, viability selection acting through the *ACPI* locus may present a real barrier to fertility. This result appears somewhat paradoxical considering the study of Gloria-Bottini et al. (1996), which showed that *ACPI**C carriers have lower rates of spontaneous abortion than noncarriers. However, less than 5% of the parental pairs in that study were of the type where both individuals carried the *ACPI**C allele, making the fitness effect we describe here undetectable.

Our results indicate that *ACPI**C is a recessively deleterious allele that reduces viability during early life stages and is not maintained at present by overdominant selection. The relationship between *ACPI* and human fertility clearly needs to be examined in more detail. The action of natural selection on this single locus has the power to explain a significant proportion of spontaneous abortions among people of European ancestry and may even act as a molecular mechanism limiting the fertility of some couples. Relatively few individual genes have been implicated directly as causes of early-life-stage nonviability, and those genes that have been identified typically operate through immune system pathways (Stephenson 1996). The proteins encoded by *ACPI*, on the other hand, primarily play a role in the regulation of cell growth, differentiation, and metabolism (Raugei et al. 2002). It may be through these growth-limiting functions that *ACPI**C acts to decrease viability. *ACPI**C differs from other *ACPI* alleles in that it produces a much higher amount of the S isozyme and much less of the F isozyme (Dissing 1987). Elucidating the functional roles of these isozymes may provide important insights into the metabolic processes underlying early-life-stage viability.

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Appendix 1. Populations in Which ACP1 Genotype Frequencies Are Reported from at Least 150 European Individuals

Population	N	Observed Frequency				Expected Frequency				χ^2	Reference
		XX	XC	CC	p(X)	p(C)	XX	XC	CC		
Austria (Vienna)	410	359	51	0	0.938	0.062	360.6	47.8	1.6	1.80	Speiser and Pausch (1967)
Belgium (Liège)	1,000	899	98	3	0.948	0.052	898.7	98.6	2.7	0.04	Brocteur et al. (1980)
Belgium (Liège)	500	447	51	2	0.945	0.055	446.5	52.0	1.5	0.18	Brocteur et al. (1970)
Corsica	274	253	20	1	0.960	0.040	252.4	21.1	0.4	0.77	Memmi et al. (1998)
Croatia (Brac)	744	660	84	0	0.944	0.05	666.2	79.3	2.4	2.66	Roberts et al. (1992)
Czech Republic	300	262	38	0	0.937	0.063	263.2	35.6	1.2	1.37	Salak and Palousova (1971)
Czech Republic (Prague)	307	272	35	0	0.943	0.057	273.0	33.0	1.0	1.12	Herzog and Bohatová (1969)
Denmark	3,734	3,266	453	15	0.935	0.065	3,266.6	451.8	15.6	0.03	Dissing and Svensmark (1976)
Denmark	470	417	53	0	0.944	0.056	418.5	50.0	1.5	1.68	Lamm (1970)
Denmark (Copenhagen)	852	727	118	7	0.923	0.077	725.1	121.8	5.1	0.82	Sørensen (1973)
England	880	780	100	0	0.943	0.057	782.8	94.3	2.8	3.19	Hopkinson and Harris (1969)
Faroe Islands	662	602	60	0	0.955	0.045	603.4	57.3	1.4	1.49	Tills et al. (1985)
Finnish Skolts	288	232	56	0	0.903	0.097	234.7	50.6	2.7	3.34	Mourant et al. (1976)
France	487	448	39	0	0.960	0.040	448.8	37.4	0.8	0.85	van Cong and Mouleec (1967)
Georgia (Zemo Alisubani)	209	197	12	0	0.971	0.029	197.2	11.7	0.2	0.18	Nasidze (1995)
Germany (Bayern)	1,625	1,403	217	5	0.930	0.070	1405.9	211.1	7.9	1.25	Gussmann (1970)
Germany (Berlin)	1,188	1,048	135	5	0.939	0.061	1047.4	136.2	4.4	0.08	Radian and Strauch (1966)
Germany (Berlin)	1,043	927	113	3	0.943	0.057	927.4	112.2	3.4	0.05	Prokop and Uhlenbruck (1969)
Germany (Freiburg)	1,800	1,569	229	2	0.935	0.065	1574.5	217.9	7.5	4.65	Hummel et al. (1970)
Germany (Hamburg)	7,059	6,163	878	18	0.935	0.065	6174.6	854.8	29.6	5.19	Brinkmann et al. (1971)
Germany (Köln)	500	441	58	1	0.940	0.060	441.8	56.4	1.8	0.40	Hummel et al. (1970)
Germany (southwest region)	300	272	28	0	0.953	0.047	272.7	26.7	0.7	0.72	Wille et al. (1968)
Germany (southwest region)	171	168	3	0	0.991	0.009	168.0	3.0	0.0	0.01	Goedde et al. (1966)
Greece	610	555	55	0	0.955	0.045	556.2	52.5	1.2	1.36	Stamatoyannopoulos et al. (1975)
Hungary	168	148	20	0	0.940	0.060	148.6	18.8	0.6	0.67	Goedde et al. (1987)
Ireland	1,787	1,624	162	1	0.954	0.046	1,626.8	156.5	3.8	2.23	Tills (1977)
Italy (Aquila)	383	338	45	0	0.941	0.059	339.3	42.4	1.3	1.49	Scozzari et al. (1970)
Italy (Bari)	470	423	47	0	0.950	0.050	424.2	44.7	1.2	1.30	Rickards et al. (1995)
Italy (Calabria)	203	176	27	0	0.933	0.067	176.9	25.2	0.9	1.03	Rickards et al. (1990)

Population	N	Observed Frequency				Expected Frequency				Reference	
		XX	XC	CC	p(X)	p(C)	XX	XC	CC		χ^2
Italy (Sardinia)	243	201	41	1	0.912	0.088	201.9	39.2	1.9	0.52	Modiano et al. (1967)
Italy (Ferrara)	1,361	1,240	119	2	0.955	0.045	1,240.8	117.4	2.8	0.24	Beretta et al. (1989)
Italy (Friuli)	518	454	64	0	0.938	0.062	456.0	60.0	2.0	2.25	Fuciarelli et al. (2000)
Italy (Garfagnana)	238	212	26	0	0.945	0.055	212.7	24.6	0.7	0.79	Paoli et al. (1993)
Italy (Lazio)	390	352	38	0	0.951	0.049	352.9	36.1	0.9	1.02	Vecchi (1969)
Italy (Oristano)	264	231	33	0	0.938	0.063	232.0	30.9	1.0	1.17	Bottini et al. (2001)
Italy (Penne)	351	312	39	0	0.944	0.056	313.1	36.8	1.1	1.21	Gloria-Bottini et al. (2000)
Italy (Rome)	417	351	65	1	0.920	0.080	352.7	61.6	2.7	1.26	Modiano et al. (1967)
Italy (Rome)	350	310	38	2	0.940	0.060	309.3	39.5	1.3	0.49	Gloria-Bottini et al. (2000)
Italy (Sicily)	289	262	27	0	0.953	0.047	262.6	25.7	0.6	0.69	Rickards et al. (1992)
Northern Ireland	315	292	23	0	0.963	0.037	292.4	22.2	0.4	0.45	Mourant et al. (1976)
Netherlands (Leiden)	782	708	74	0	0.953	0.047	709.8	70.5	1.8	1.93	Fraser et al. (1974)
Norway (Fredrikstad)	210	182	28	0	0.933	0.067	182.9	26.1	0.9	1.07	Mourant et al. (1976)
Norwegian non-Saami	1,698	1,503	189	6	0.941	0.059	1,502.9	189.1	5.9	0.00	Lie and Teisberg (1973)
Norwegian Saami	196	193	3	0	0.992	0.008	193.0	3.0	0.0	0.01	Lie and Teisberg (1973)
Poland	213	182	31	0	0.927	0.073	183.1	28.7	1.1	1.31	Wolanski et al. (1983)
Poland (Krakow, Wroclaw, Rzeszow)	1,064	862	199	3	0.904	0.096	868.9	185.3	9.9	5.86	Wyslouchowa (1970)
Portugal	1,516	1,357	152	7	0.945	0.055	1,354.5	156.9	4.5	1.49	Amorim et al. (1994)
Russia (Bryansk)	209	187	20	2	0.943	0.057	185.7	22.6	0.7	2.81	Spitsyn et al. (2001)
Russia (Moscow)	217	187	29	1	0.929	0.071	187.1	28.8	1.1	0.01	Spitsyn et al. (2001)
Russia (Sverdlovsk)	328	301	27	0	0.959	0.041	301.6	25.9	0.6	0.60	Spitsyn et al. (2001)
Scotland (southwest)	825	738	87	0	0.947	0.053	740.3	82.4	2.3	2.56	Mitchell et al. (1976)
Slovakia (eastern)	2,402	2,149	253	0	0.947	0.053	2,155.7	239.7	6.7	7.42	Juricková et al. (1994)
Spain (Andalusia)	213	203	10	0	0.977	0.023	203.1	9.8	0.1	0.12	Goedde et al. (1972)
Spain (Basque Biscay)	847	833	14	0	0.992	0.008	833.1	13.9	0.1	0.06	Aguirre et al. (1991)
Spain (Castilles)	295	281	14	0	0.976	0.024	281.2	13.7	0.2	0.17	de Pancorbo et al. (1986)
Spain (Galicia)	253	236	16	1	0.964	0.036	235.3	17.4	0.3	1.55	Goedde et al. (1972)
Spain (Ibiza)	390	365	25	0	0.968	0.032	365.4	24.2	0.4	0.43	Miguel and Petitpierre (1989)
Spain (Madrid)	190	170	20	0	0.947	0.053	170.5	18.9	0.5	0.59	Goedde et al. (1972)
Spain (Mallorca)	2,122	2,005	117	0	0.972	0.028	2,006.6	113.8	1.6	1.71	Miguel and Petitpierre (1990)

<i>Population</i>	<i>N</i>	<u>Observed Frequency</u>			<i>p(X)</i>	<i>p(C)</i>	<u>Expected Frequency</u>			χ^2	<i>Reference</i>
		<i>XX</i>	<i>XC</i>	<i>CC</i>			<i>XX</i>	<i>XC</i>	<i>CC</i>		
Spanish Basque (Berneo)	288	273	15	0	0.974	0.026	273.2	14.6	0.2	0.21	Goedde et al. (1972)
Swedish Saami	210	197	13	0	0.969	0.031	197.2	12.6	0.2	0.21	Beckman et al. (1971)
Switzerland (mostly Bern)	1,365	1,237	123	5	0.951	0.049	1,235.2	126.5	3.2	1.06	Pflugshaupt et al. (1970)
United Kingdom	274	253	21	0	0.962	0.038	253.4	20.2	0.4	0.44	Hopkinson et al. (1964)
West Germany	401	367	34	0	0.958	0.042	367.7	32.6	0.7	0.79	Fuhrmann and Lichte (1966)
Yugoslavian Hungarians	342	289	51	2	0.920	0.080	289.2	50.6	2.2	0.02	Kalimanovska, Dacin et al. (1990)
Yugoslavian Rumanians	307	267	40	0	0.935	0.065	268.3	37.4	1.3	1.49	Kalimanovska, Jelic-Ivanovic et al. (1990)
Yugoslavian Slovaks	211	192	18	1	0.953	0.047	191.5	19.1	0.5	0.64	Kalimanovska et al. (1988)
Pooled Europe	50,528	45,010	5,421	97	0.944	0.056	45,069	5,303	156	25.01	

Appendix 2. Full Enumeration of All Observed and Expected Genotype Frequencies in ACP1 Population Data Setsa

Population	Observed Frequency						Expected Frequency								
	*A/*A	*A/*B	*B/*B	*A/*C	*B/*C	*C/*C	p(A)	p(B)	p(C)	*A/*A	*A/*B	*B/*B	*A/*C	*B/*C	*C/*C
Austria (Vienna)	46	185	128	22	29	0	0.365	0.573	0.062	54.5	171.4	134.7	18.6	29.2	1.6
Belgium (Liege)	114	404	381	41	57	3	0.337	0.612	0.052	113.2	411.5	373.9	35.0	63.6	2.7
Belgium (Liege)	61	209	17	718	33	2	0.349	0.596	0.055	60.9	208.0	177.6	19.2	32.8	1.5
Corsica	4	48	201	0	20	1	0.102	0.858	0.040	2.9	48.0	201.6	2.2	18.9	0.4
Croatia (Brac)	118	274	268	52	32	0	0.378	0.566	0.056	106.1	318.0	238.2	31.7	47.5	2.4
Czech Republic	36	111	115	10	28	0	0.322	0.615	0.063	31.0	118.7	113.5	12.2	23.4	1.2
Czech Republic (Prague)	49	116	107	10	25	0	0.365	0.578	0.057	40.9	129.5	102.6	12.8	20.2	1.0
Denmark	489	1,591	1,186	186	267	15	0.369	0.566	0.065	508.2	1,560.5	1,198.0	178.2	273.6	15.6
Denmark	61	178	178	21	32	0	0.341	0.602	0.056	54.8	193.3	170.4	18.1	31.9	1.5
Denmark (Copenhagen)	115	364	248	39	79	7	0.371	0.551	0.077	117.6	348.8	258.7	49.0	72.7	5.1
England	119	379	282	39	61	0	0.373	0.570	0.057	122.3	374.2	286.4	37.3	57.0	2.8
Faroe Islands	100	244	258	34	26	0	0.361	0.594	0.045	86.3	283.8	233.3	21.7	35.6	1.4
Finnish Skolts	18	96	118	14	42	0	0.253	0.649	0.097	18.5	94.8	121.4	14.2	36.4	2.7
France	47	203	198	16	23	0	0.321	0.639	0.040	50.3	199.9	198.6	12.5	24.9	0.8
Georgia (Zemo Alisubani)	17	82	98	2	10	0	0.282	0.689	0.029	16.7	81.3	99.2	3.4	8.3	0.2
Germany (Bayern)	220	621	562	81	136	5	0.351	0.579	0.070	200.6	661.0	544.3	79.8	131.4	7.9
Germany (Berlin)	145	516	387	55	80	5	0.362	0.577	0.061	156.0	496.5	395.0	52.5	83.6	4.4
Germany (Berlin)	133	452	342	51	62	3	0.369	0.574	0.057	141.7	441.6	344.0	43.9	68.3	3.4
Germany (Freiburg)	199	707	663	80	149	2	0.329	0.606	0.065	195.0	718.2	661.3	76.7	141.2	7.5
Germany (Hamburg)	877	2,922	2,364	314	564	18	0.353	0.582	0.065	881.9	2,903.2	2,389.5	323.1	531.8	29.6
Germany (Köln)	51	211	179	17	41	1	0.330	0.610	0.060	54.5	201.3	186.1	19.8	36.6	1.8
Germany (southwest region)	21	134	117	10	18	0	0.310	0.643	0.047	28.8	119.7	124.2	8.7	18.0	0.7
Germany (southwest region)	13	64	91	2	1	0	0.269	0.722	0.009	12.4	66.4	89.2	0.8	2.2	0.0
Greece	61	250	244	21	34	0	0.322	0.633	0.045	63.3	248.7	244.3	17.7	34.8	1.2
Hungary	17	64	67	2	18	0	0.298	0.643	0.060	14.9	64.3	69.4	6.0	12.9	0.6
Ireland	210	733	681	54	108	1	0.338	0.616	0.046	203.8	744.0	679.0	55.4	101.1	3.8
Italy (Aquila)	21	97	220	11	34	0	0.196	0.745	0.059	14.7	111.8	212.8	8.8	33.5	1.3
Italy (Bari)	47	153	223	15	32	0	0.279	0.671	0.050	36.5	175.9	211.8	13.1	31.6	1.2
Italy (Calabria)	15	75	86	9	18	0	0.281	0.653	0.067	16.0	74.4	86.5	7.6	17.6	0.9

Population	Observed Frequency						Expected Frequency								
	*A/*A	*A/*B	*B/*B	*A/*C	*B/*C	*C/*C	p(A)	p(B)	p(C)	*A/*A	*A/*B	*B/*B	*A/*C	*B/*C	*C/*C
Italy (Sardinia)	17	77	107	13	28	1	0.255	0.656	0.088	15.8	81.4	104.7	11.0	28.2	1.9
Italy (Ferrara)	98	536	606	35	84	2	0.282	0.673	0.045	108.1	516.2	616.5	34.7	82.8	2.8
Italy (Friuli)	51	217	186	29	35	0	0.336	0.602	0.062	58.4	209.6	187.9	21.5	38.5	2.0
Italy (Garfagnana)	18	102	92	9	17	0	0.309	0.637	0.055	22.7	93.6	96.4	8.0	16.6	0.7
Italy (Lazio)	39	159	154	10	28	0	0.317	0.635	0.049	39.1	156.8	157.1	12.0	24.1	0.9
Italy (Oristano)	13	76	142	7	26	0	0.206	0.731	0.063	11.3	79.7	141.1	6.8	24.1	1.0
Italy (Penne)	36	125	151	19	20	0	0.308	0.637	0.056	33.2	137.5	142.3	12.0	24.8	1.1
Italy (Rome)	36	132	183	14	51	1	0.261	0.658	0.080	28.5	143.5	180.7	17.5	44.1	2.7
Italy (Rome)	34	118	158	8	30	2	0.277	0.663	0.060	26.9	128.6	153.8	11.6	27.8	1.3
Italy (Sicily)	24	113	125	13	14	0	0.301	0.652	0.047	26.2	113.5	122.9	8.1	17.6	0.6
Northern Ireland	31	137	124	10	13	0	0.332	0.632	0.037	34.7	132.0	125.7	7.6	14.5	0.4
Netherlands (Leiden)	99	343	266	30	44	0	0.365	0.588	0.047	104.2	335.5	270.0	27.0	43.5	1.8
Norway (Fredrikstad)	33	83	66	10	18	0	0.379	0.555	0.067	30.1	88.2	64.6	10.6	15.5	0.9
Norwegian non-Saami	248	726	529	71	118	6	0.381	0.560	0.059	246.1	724.2	532.6	76.5	112.6	5.9
Norwegian Saami	43	96	54	2	1	0	0.469	0.523	0.008	43.2	96.2	53.6	1.4	1.6	0.0
Poland	16	53	113	10	21	0	0.223	0.704	0.073	10.6	66.9	105.6	6.9	21.8	1.1
Poland (Krakow, Wroclaw, Rzeszow)	147	309	406	76	123	3	0.319	0.585	0.096	108.3	396.9	363.6	65.4	119.8	9.9
Portugal	123	556	678	55	97	7	0.283	0.663	0.055	121.1	567.8	665.6	46.9	110.0	4.5
Russia (Bryansk)	36	81	70	4	16	2	0.376	0.567	0.057	29.5	89.0	67.2	9.0	13.6	0.7
Russia (Moscow)	28	74	85	10	19	1	0.323	0.606	0.071	22.6	84.8	79.7	10.0	18.8	1.1
Russia (Sverdlovsk)	34	111	156	8	19	0	0.285	0.674	0.041	26.7	126.0	148.9	7.7	18.2	0.6
Scotland (southwest)	92	360	286	28	59	0	0.347	0.601	0.053	99.1	343.5	297.6	30.2	52.3	2.3
Slovakia (eastern)	256	1,000	893	88	165	0	0.333	0.614	0.053	266.4	982.8	906.4	84.3	155.4	6.7
Spain (Andalusia)	28	107	68	6	4	0	0.397	0.580	0.023	33.5	98.0	71.6	4.0	5.8	0.1
Spain (Basque Biscay)	70	324	439	2	12	0	0.275	0.717	0.008	64.1	334.0	435.0	3.9	10.0	0.1
Spain (Castiles)	31	90	160	7	7	0	0.269	0.707	0.024	21.4	112.4	147.4	3.8	9.9	0.2
Spain (Galicia)	19	107	110	6	10	1	0.298	0.666	0.036	22.5	100.6	112.2	5.4	12.0	0.3
Spain (Ibiza)	17	156	192	4	21	0	0.249	0.719	0.032	24.1	139.5	201.7	6.2	18.0	0.4
Spain (Madrid)	18	77	75	10	10	0	0.324	0.624	0.053	19.9	76.7	73.9	6.5	12.5	0.5
Spain (Mallorca)	143	736	1,126	30	87	0	0.248	0.725	0.028	130.4	762.2	1,114.0	29.0	84.8	1.6

Population	Observed Frequency						Expected Frequency								
	*A/*A	*A/*B	*B/*B	*A/*C	*B/*C	*C/*C	p(A)	p(B)	p(C)	*A/*A	*A/*B	*B/*B	*A/*C	*B/*C	*C/*C
Spanish Basque (Bermeo)	20	104	149	4	11	0	0.257	0.717	0.026	19.0	106.1	148.1	3.9	10.8	0.2
Swedish Saami	57	91	49	8	5	0	0.507	0.462	0.031	54.0	98.4	44.8	6.6	6.0	0.2
Switzerland (mostly Bern)	147	604	486	41	82	5	0.344	0.607	0.049	161.5	570.3	503.5	45.7	80.8	3.2
United Kingdom	29	132	92	7	14	0	0.359	0.602	0.038	35.4	118.6	99.4	7.5	12.6	0.4
West Germany	51	150	166	11	23	0	0.328	0.630	0.042	43.1	165.6	159.0	11.1	21.4	0.7
Yugoslavian Hungarians	41	130	118	13	38	2	0.329	0.591	0.080	37.0	132.9	119.3	18.1	32.5	2.2
Yugoslavian Rumanians	43	129	95	21	19	0	0.384	0.550	0.065	45.4	129.9	93.0	15.4	22.0	1.3
Yugoslavian Slovaks	21	87	84	4	14	1	0.315	0.637	0.047	21.0	84.8	85.7	6.3	12.7	0.5
Pooled Europe	5,711	20,091	19,308	1,959	3,462	97	0.331	0.613	0.056	5,543	20,526	19,000	1,860	3,443	156

^a See Appendix 1 for reference information.

Figure 1. Histogram representing the distribution of *ACP1**C allele frequencies among 66 European populations.

Table 1

ACP1 Genotypes of Parents and Offspring

<i>Parental Genotype</i>	<i>N</i>	<i>Offspring Genotype^a</i>			χ^2
		XX	XC	CC	
All mating types	1,281	644 (618)	626 (640.5)	11 (22.5)	7.30 ^b
XC × XC	90	21 (22.5)	58 (45)	11 (22.5)	9.73 ^c
XX × XC	1,191	623 (595.5)	568 (595.5)	0 (0)	2.54

^a Observed numbers of offspring genotypes are listed, with expected Mendelian values in parentheses. Deviations from expected values were analyzed with a chi-square goodness-of-fit test.

^b $P < 0.05$.

^c $P < 0.01$.