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Diet and the frequency of the alanine:glyoxylate aminotransferase Pro11Leu polymorphism in different human populations

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Abstract The intermediary metabolic enzyme alanine:glyoxylate aminotransferase (AGT) contains a Pro11Leu polymorphism that decreases its catalytic activity by a factor of three and causes a small proportion to be mistargeted from its normal intracellular location in the peroxisomes to the mitochondria. These changes are predicted to have significant effects on the synthesis and excretion of the metabolic end-product oxalate and the deposition of insoluble calcium oxalate in the kidney and urinary tract. Based on the evolution of AGT targeting in mammals, we have previously hypothesised that this polymorphism would be advantageous for individuals who have a meat-rich diet, but disadvantageous for those who do not. If true, the frequency distribution of Pro11Leu in different extant human populations should have been shaped by their dietary history so that it should be more common in populations with predominantly meat-eating ancestral diets than it is in populations in which the ancestral diets were predominantly vegetarian. In the present study, we have determined frequency of Pro11Leu in 11 different human populations with divergent ancestral dietary lifestyles. We show that the Pro11Leu allelic frequency varies widely from 27.9% in the Saami, a population with a very meat-rich ancestral diet, to 2.3% in Chinese, who are likely to have had a more mixed ancestral diet. F_{ST} analysis shows that the differences in Pro11Leu frequency between some populations (particularly Saami vs Chinese) was very high when compared with neutral loci, suggesting that its frequency might have been shaped by dietary selection pressure.

Introduction

Although the prevalence of calcium oxalate (CaOx) kidney stone disease is high, especially in Western societies, its causes have not been clearly defined (Danpure 2000). It is likely that in most cases its origins are multifactorial, but in a few instances CaOx stones have well-established monogenic origins. One example is the autosomal recessive disease primary hyperoxaluria type 1 (PH1, MIM 259900). PH1 is caused by mutations in the *AGXT* gene, which encodes the intermediary metabolic enzyme alanine:glyoxylate aminotransferase (AGT) (Danpure 2001). AGT is a liver-specific pyridoxal-phosphate-dependent enzyme which catalyses the conversion (detoxification) of the intermediary metabolite glyoxylate to glycine. This is an important reaction because its failure, as occurs in PH1, leads to increased oxidation of glyoxylate to oxalate. Oxalate cannot be further metabolised and its increased synthesis leads to its increased urinary excretion and the deposition of insoluble CaOx in the kidney and urinary tract.

In mammals, the intracellular distribution of AGT differs between different species in a manner that is related to natural diet (Danpure et al. 1990; Danpure et al. 1994b; Holbrook et al. 2000; Birdsey et al. 2004). Thus, AGT tends to be mainly mitochondrial in carnivores, peroxisomal in herbivores, and both mitochondrial and peroxisomal in omnivores. In order to detoxify glyoxylate efficiently, AGT must be present at the site of glyoxylate synthesis (i.e. in the same intracellular compartment). However, there are two main dietary precursors of glyoxylate and two different sites of synthesis. In herbivores, glycolate is thought to be the major precursor and is converted to glyoxylate in the peroxisomes (Noguchi 1987), whereas in carnivores hydroxyproline is the major precursor and is converted to glyoxylate in the mitochondria (Takayama et al. 2003). Therefore, the best location for AGT is in the peroxisomes in plant-eating species and the mitochondria for meat-eating species. On average, humans are probably

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best considered to be omnivores, but their AGT is usually targeted only to the peroxisomes (Cooper et al. 1988), a distribution more typical of herbivores. Therefore, for most individuals (i.e. those who have omnivorous diets) AGT would appear to be in a non-ideal location. It has been suggested previously that the peroxisomal location of AGT in humans might be a reflection of the herbivorous ancestry of hominoids (Holbrook et al. 2000).

There are two principal polymorphic variants of human AGT, encoded by the “major” and “minor” *AGXT* alleles, which differ in a number of respects. The minor *AGXT* allele, which has a frequency of 15–20% in ethnically-uncharacterised Europeans and North Americans, differs from the major allele due to the presence of Pro11Leu and Ile340Met amino acid substitutions, a 74-bp duplication in intron 1, and a VNTR in intron 4 (Purdue et al. 1990, 1991; Danpure et al. 1994a). Of these differences, only the Pro11Leu replacement is known to affect the properties of AGT significantly. For example, the Pro11Leu polymorphism generates a weak mitochondrial targeting sequence which, in an individual homozygous for this allele, leads to about 5% of AGT being targeted to mitochondria (Purdue et al. 1990; Motley et al. 1995; Lumb et al. 1999). In addition, Pro11Leu decreases the specific catalytic activity of purified recombinant enzyme by a factor of three, and partially interferes with its dimerization following *in vitro* translation (Lumb and Danpure 2000). The presence of the Pro11Leu polymorphism also sensitises AGT to the untoward effects of a wide range of PH1-specific mutations, which are predicted to be innocuous in its absence (Lumb and Danpure 2000). This is best exemplified by the synergistic interaction between Pro11Leu and the most common PH1 mutation Gly170Arg, which results in 90% or more of the AGT being mistargeted from its normal location in the peroxisomes to the mitochondria (Danpure et al. 1989). Although the mistargeted AGT is still catalytically active, the 10% remaining in the peroxisomes appears to be insufficient to detoxify the glycolate-derived glyoxylate, allowing increased amounts to be oxidised to oxalate.

Most of the effects of the Pro11Leu replacement are predicted to be detrimental. Therefore, at first sight, it is difficult to understand why the minor *AGXT* allele should occur at such a high frequency, at least in European and North American populations. However, the evolutionary history of mammals suggests that the redirection of a small proportion (i.e. 5%) of AGT from peroxisomes to mitochondria in humans might lead to a subcellular distribution of AGT that was more compatible with an omnivorous, rather than herbivorous, lifestyle (Danpure 1997).

In an attempt to reconcile this apparent dichotomy, we have advanced the hypothesis that the Pro11Leu replacement in AGT is advantageous for individuals who have a high proportion of meat in their diet, but disadvantageous for individuals who do not (Danpure 1997). If correct, one consequence might be that the

frequency of this polymorphism in different populations would be shaped, at least in part, by their ancestral diets. If a locus has been under directional selection for one allele in one population and the opposite direction in another, then this would have the effect of driving the allelic frequency difference beyond that expected under neutrality (Cavalli-Sforza 1996; Lewontin and Krakauer 1973; Akey et al. 2002). Therefore, in the present study, we have determined the frequency of Pro11Leu in 11 different human populations, including some which are known to have very divergent ancestral diets (Haglin 1991, 1999; Kiple and Ornelas 2000). We have quantified differences in allele frequencies using the genetic distance measure F_{ST} (Weir 1996) and compared this value to a null distribution of F_{ST} based on previously published SNP polymorphism data for a large number of loci in geographically matched populations (Sachidanandam et al. 2001).

Materials and methods

Samples

DNA samples were typed for the Pro11Leu polymorphism from 80 Mongolians, 76 Norwegians (Weale et al. 2002), 82 North Welsh (Weale et al. 2002), 73 Ashkenazi Jews (Thomas et al. 2003), 73 Armenians (Weale et al. 2001), 62 Nigerians from the Cross-River region, 69 Ethiopians (Thomas et al. 2003), 88 Anatolian Turks, 34 Swedish Saami, 86 Sichuan Chinese and 84 Indians from Mumbai (Thomas et al. 2003). Informed consent was obtained from all donors. All donors provided details of self-defined ethnic identity, first and second language and place of birth with similar information on his mother, father, maternal grandmother and paternal grandfather. Buccal cells were collected from men using sterile swabs and stored in 1 ml of 0.05 M EDTA/0.5% SDS preservative solution. DNA was purified using standard phenol/chloroform extraction and isopropanol precipitation methods.

Detection of Pro11Leu polymorphism

The Pro11Leu c32C>T polymorphism (previously described as C₁₅₄T) was typed by PCR-RFLP as follows: PCR was carried out in a total reaction volume of 10 μ l containing 0.3 μ M of primers MIT 2 (5'-GCACAGATAAGCTTCAGGGA-3') and EX-2R (5'-CTTGAAGGATGGATCCAGGG-3') (Purdue et al. 1990, 1991), 200 μ M dNTPs, 10 mM Tris-HCl (pH 9.0), 0.1% Triton X-100, 0.01% gelatin, 50 mM KCl, 2.2 mM MgCl₂, 0.13 units Taq polymerase (HT Biotech, Cambridge, UK), 9.3 nM TaqStart monoclonal antibody (Mab) (BD Biosciences/Clontech San Jose, Calif., USA) and 1 μ l of DNA. The Taq and TaqStart Mab were premixed prior to being added to the other reagents. Cycling parameters were as follows: preincubation at 95°C for 5 min

followed by 37 cycles of 94°C for 1 min, 58°C for 1 min, 72°C for 1 min; and then a final incubation step of 72°C for 10 min.

Restriction endonuclease digestion was carried out overnight at 37°C in a final volume of 15 µl, and contained 10 µl of PCR product, 10 units of *StyI*, 0.01 µg/µl acetylated BSA and NEB Buffer 3 as recommended by the manufacturer. Digestion products were then run on 2% agarose gel and DNA bands were visualised using ethidium bromide staining. Bands on the gel corresponding to 512 and 619 bp were interpreted as the major *AGXT* allele and minor *AGXT* allele, respectively (see Introduction) (Danpure and Rumsby 1996). To ensure data quality and the accurate sizing of digestion products, some samples were also PCR amplified and *StyI* digested as above but using a version of the EX-2R primer that had been fluorescently labelled with the dye NED. These digestion products were then run on an ABI-377 automated sequencer (5% acrylamide denaturing gel) along with a ROX-labelled size standard.

Data analysis

A contour map of the geographic distribution of the Pro11Leu T allele (i.e. that encoded by the minor *AGXT* allele) was estimated and visualised by surface interpolation (tension factor=0.9) using the Generic Mapping Tools software (Wessel and Smith 1998; <http://gmt.soest.hawaii.edu/>).

To generate a null-distribution of F_{ST} between Europeans and East Asians, and between Europeans and Africans, for presumed neutral SNPs, data for 42 African Americans, 42 East Asians and 42 European Americans (Sachidanandam et al. 2001; Akey et al. 2002) were taken from a dataset of 33,487 SNPs typed by the Orchid Laboratory, publicly available at the SNP Consortium web site (http://snp.cshl.org/allele_frequency_project/panels.shtml). We carefully selected SNPs from the larger dataset, such that each SNP was (1) either polymorphic or variable between populations, (2) mapped only once onto the genome, and (3) separated by at least 50 kb from the next nearest SNP, to minimise correlation in F_{ST} values. This left 11,024 SNPs for the European/East Asian comparison and 11,970 SNPs for European/African American comparison. We note that this SNP set will, by chance, contain some loci

that are under selection, but unless the proportion of loci under balancing selection is large then this will have only a conservative effect on the comparisons presented here. All F_{ST} values were calculated using the unbiased 'random populations' formula for haploid data given by Weir (1996). All statistical analyses were carried out using the statistical package 'R' (<http://www.R-project.org/>).

Results

The frequencies of the Pro11Leu T allele in different human populations are shown in Table 1. There is a marked South East–North West cline in the frequency of the Pro11Leu polymorphism (see Fig. 1). It was low (2.3–6.9%) in eastern and southern Asia, intermediate (8.9–10.9%) in Africa, and high (14.6–27.9%) in Europe and the Middle East. It is notable that of the populations studied, the one predicted to have the most meat-based ancestral and current diet, the Saami (Haglin 1991, 1999), has the highest estimated frequency of the Pro11Leu T allele (27.9%). On the other hand, the population with the lowest frequency (2.3%), the Chinese, is likely to have had a more mixed ancestral diet. The frequency was also low (3.0%) in Indians, a population whose ancestral diet is presumed to have been much more vegetarian than populations living at higher latitudes (Eaton and Eaton 2000).

The Saami are the only population in our sample for which there is good evidence for a long history of a meat-rich diet (Haglin 1991, 1999). To examine whether the observed differences in Pro11Leu T allele frequency between the Saami and non-European populations are within the range expected for neutral alleles, we quantified allele frequency difference using the genetic distance measure F_{ST} (Weir 1996), and compared this with null-distributions of F_{ST} for comparable populations (see Materials and methods). Currently, large data sets of SNPs, from which null distributions of F_{ST} can be constructed, are only available for European Americans, African Americans and East Asians (Sachidanandam et al. 2001; Akey et al. 2002). Although the populations examined in this study are not identical to those for which large data sets of SNPs are available, it can be argued that a comparison of the Saami/Chinese Pro11Leu allele F_{ST} against the null-distribution of F_{ST} for the

Table 1 Frequency of *AGXT* genotypes in 11 human populations. Allele C corresponds to the *AGXT* major allele, encoding Pro11; allele T corresponds to the *AGXT* minor allele, encoding Leu11 (*ANT* Anatolian Turks, *ARM* Armenians, *ASH* Ashkenazi Jews,

CHI Chinese, *ETH* Ethiopians, *IND* Indians (from Mumbai), *MON* Mongolians, *NIG* Nigerians, *NOR* Norwegians, *NOW* North Welsh, *SAM* Saami)

	CHI	IND	MON	NIG	ETH	NOW	ANT	ARM	NOR	ASH	SAM
CC	82	79	69	52	55	60	68	48	50	47	19
CT	4	5	11	9	13	20	14	22	22	23	11
TT	0	0	0	1	1	2	6	3	4	3	4
Number of alleles	172	168	160	124	138	164	176	146	152	146	68
Frequency of T allele	0.0233	0.0298	0.0688	0.0887	0.1087	0.1463	0.1477	0.1918	0.1973	0.1986	0.2794

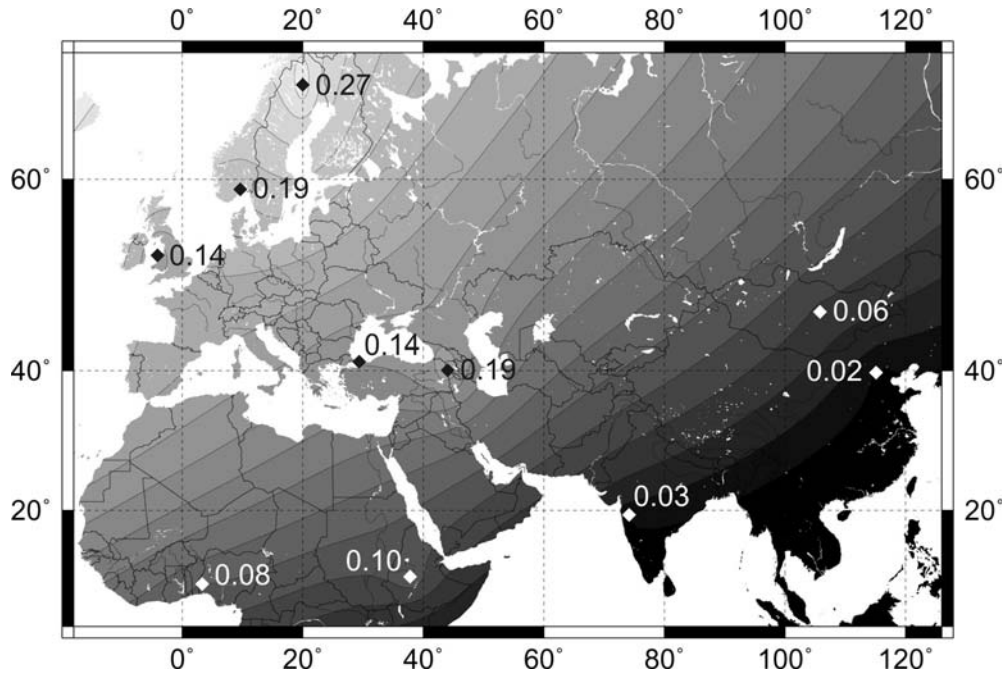


Fig. 1 Contour map of the distribution of the Pro11Leu polymorphism. The *numbers* indicate the frequencies of the *AGXT* minor allele in the populations studied (i.e. the Pro11Leu T allele). The

European/East Asian data sets is a conservative one. This is because previous studies of a large number of classical polymorphic markers (Cavalli-Sforza et al. 1988, 1994) have shown that the F_{ST} between Saami and

Ashkenazi Jewish sample is not plotted on this map due to the diverse geographical origin of the population (Thomas et al. 2002). The North West–South East cline can be easily seen

East Asian populations are typically lower than those between continental European and East Asian populations. However, a comparison of the Saami/Nigerian Pro11Leu allele F_{ST} against the null-distribution of F_{ST} for the European/African American data sets is likely to be biased in favour of F_{ST} outlier status for the Pro11Leu allele. This is because a number of studies have shown African Americans to be an admixed group between Europeans and West Africans, with the greater ancestry component (between 80 and 90%) being West African in origin (Parra et al. 1998). As a consequence, the European/African American comparison is likely to produce an underestimate of the true null-distribution of F_{ST} between the Saami and Nigerian populations.

When compared with the null distribution for Europeans and East Asians the F_{ST} for the Saami vs Chinese (0.3024) was in the top 7.40% (see Fig. 2). The F_{ST} for the Saami vs Nigerians was 0.1184, which was in the top 26.57% of the European/African American F_{ST} distribution.

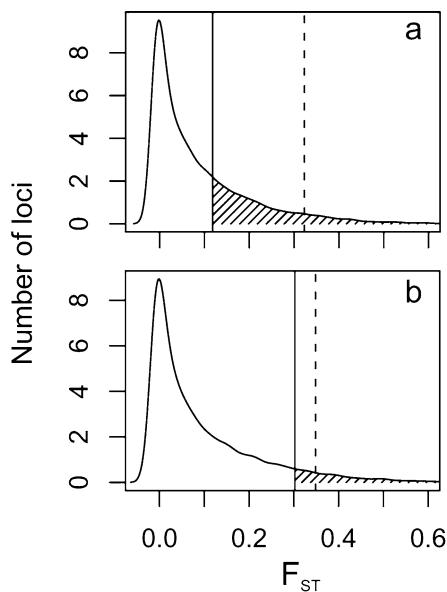


Fig. 2 F_{ST} analysis for **a** Saami vs Nigerians and **b** Saami vs Chinese. The curves show the frequency distribution of F_{ST} for 11,970 SNPs for European and African American populations (**a**) and 11,024 SNPs for European American and East Asian populations (**b**). The vertical solid lines indicate the F_{ST} values for the Pro11Leu polymorphism and the dashed lines indicate the top 5% of the null distribution values. The crosshatched areas indicate the top 26.57% of F_{ST} values in **a** and the top 7.40% in **b**

Discussion

The different frequencies of the Pro11Leu polymorphism in different human populations could be the result solely of genetic drift shaped by demographic history, or could also be shaped by environmental selection pressure, such as diet (see Introduction). The Pro11Leu replacement is unique, even among non-synonymous polymorphisms, in so far as it leads to significant changes to the catalytic properties and intracellular compartmentalisation of an essential intermediary

metabolic enzyme (i.e. AGT). Decrease in specific catalytic activity to one third of normal (Lumb and Danpure 2000) would be expected to be disadvantageous irrespective of diet. Such a reduction would significantly decrease the ability of AGT to detoxify glyoxylate, whatever its source. However, the redirection of 5% or so from the peroxisomes to the mitochondria (Purdue et al. 1990) would be expected to have little effect in vegetarians because they would rely mainly on peroxisomal AGT, the level of which would hardly change, to detoxify glyoxylate derived from glycolate. On the other hand, the appearance of AGT, albeit in small amounts (i.e. 5%), in the mitochondria, where none existed before, could be a significant advantage for humans whose diet contains a high proportion of meat, as they could now detoxify glyoxylate derived from hydroxyproline with greater efficiency. Presumably, in these populations the benefits of a partial AGT redistribution would outweigh the disadvantage of lower specific activity.

We have investigated differences in Pro11Leu allele frequency between traditionally meat-eating populations and those with ancestrally mixed or more vegetarian diets to look for evidence for natural selection. Given the availability of data on presumed neutral SNP for the construction of null-distributions of F_{ST} (Sachidanandan et al. 2001), the only reasonable comparisons we were able to make were between the Saami and the Chinese, and between the Saami and the Nigerians. While in neither case did the Pro11Leu allele F_{ST} reach formal outlier status (i.e. in the top 5% of the null-distribution) (Akey et al. 2002), the difference between the Saami and the Chinese is high ($F_{ST} = 0.3024$). This is in the top 7.40% of the European vs. East Asian null-distribution. Given the lower average F_{ST} observed between Saami and East Asians than between continental Europeans and East Asians, based on classical markers (Cavalli-Sforza et al. 1988, 1994), the European vs East Asian comparison is likely to generate higher values than the true null-distribution of F_{ST} between the Saami and the Chinese for neutral loci. We also note that polarity of the difference in Pro11Leu allele frequency, with a higher frequency of the T allele in the Saami, is consistent with our hypothesis. When we generate a null distribution that accounts for the polarity of allele frequency difference, by randomly assigning a minus or plus sign to each neutral SNP F_{ST} , we find that the Pro11Leu allele F_{ST} is in the top 3.7% of the null distribution. However, it should also be noted that the Saami population is considerably smaller than either the continental European or the Chinese populations and is therefore more susceptible to drift. As a result, the true null-distribution of F_{ST} between Saami and Chinese may have a lower mean but a higher variance.

These results suggest that at least some of the population differences in the frequency of the Pro11Leu polymorphism may have been shaped by natural selection. In addition, its high frequency in high meat-eating populations and low frequency in a presumed mainly vegetarian or low meat-eating populations, together

with a substantial amount of evolutionary data (see Introduction), suggests that ancestral diet is likely to have provided the main selection pressure. Although there are no definitive data currently available for the incidence of idiopathic CaOx kidney stone disease in most of the populations investigated in the present study, it is well recognised that the incidence of stones in Western societies is, in general, greater than that in less affluent societies, and has increased over the past few decades (Robertson 1993). Increasing affluence is paralleled by increased meat-eating, and increased meat-eating is associated with increased risk of CaOx stones (Robertson et al. 1979a, b). Whether this increase in Western societies has been attenuated in any way by the high frequency of the Pro11Leu polymorphism is at present unclear, as is whether its low frequency in Eastern societies might accentuate the effect of any increase in meat eating on stone formation.

The wide variations in allelic frequency of the Pro11Leu polymorphism in different populations also has implications for the phenotypic expression of PH1. Its allelic frequency is about 50% in ethnically uncharacterised European and North American PH1 patients (Rumsby 2000). This high frequency, compared with the normal population, reflects its genetic linkage and functional synergism with the two most common PH1-specific mutations Gly170Arg and Ile244Thr (Lumb and Danpure 2000), which have frequencies of about 30 and 9%, respectively (Danpure 2001). The mistargeting of 90% or more of the AGT from peroxisomes to mitochondria, which is the single most common cause of PH1 in European and North American patients, results from the combined presence of Pro11Leu and Gly170Arg replacements (see Introduction). The very low frequency of Pro11Leu in Chinese and Indian Hindus might suggest that this phenotype is much less likely to occur in these populations. Whether this results in decreased overall incidence of PH1 is at present unknown.

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