of these patients carry a third CF mutation. Spanish and Turkish patients were analysed for the IVS8-6(T) alleles[11] and the mutation 2183AA→G was found to be associated with the allele 7T, except in patients 1 and 3, who were homozygous for the allele 9T. Spanish and Turkish patients were also studied for the microsatellite loci IVS8CA, IVS17bTA, and IVS17bCA.[12–14] While all six Spanish patients shared the same haplotype (16-30-13) for the mutation 2183AA→G, Turkish patients were homozygous for two other haplotypes, 16-31-13 (patients 1 and 3) and 16-32-13 (patient 2). These three haplotypes are among the most common on normal chromosomes[15] and each can be derived from any of the other two. Alternatively, the mutation may have arisen independently in the two populations or even within the Turkish population. Despite the possible heterogeneous genetic background observed, in particular between the homozygous patients, the severity of the disease is similar.

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Alkaptonuria in Italy: polymorphic haplotype background, mutational profile, and description of four novel mutations in the homogentisate 1,2-dioxygenase gene

EDITOR—Alkaptonuria (AKU, OMIM 203500) is a rare disorder caused by the deficiency of homogentisate 1,2 dioxygenase (HGO, EC 1.13.11.5).[1] HGO catalyses the conversion of homogentisate (HGA) to maleylacetoacetate in the phenylalanine/tyrosine catabolic pathway.[2] As a consequence, affected subjects excrete HGA in their urine, which becomes dark upon exposure to air. The medical interest in this condition stems from its association with ochronosis, or the deposition of a brownish pigment in connective tissues including cartilage, where its accumulation can produce a debilitating degenerative joint disease.[3]

AKU occupies a unique place in the history of human genetics because it was the first disorder to be described as a Mendelian recessive trait.[4–6] Recent advances in the understanding of the molecular basis of AKU[7–9] have verified that loss of function mutations in the *HGO* gene are responsible for the disease. A few mutations have been repeatedly detected in patients from different European countries. Since these mutations segregated with specific haplotypes, they should be considered to be old mutations that have spread throughout western Europe with migration. However, allelic heterogeneity is the main feature emerging from the above and other studies.[7 9–12] Most *HGO* mutations were found in just one family and did not involve CpG dinucleotides. Rather, a preferential occurrence in the CCC sequence motif and its inverted complement GGG has recently been reported.[12] Furthermore, some AKU chromosomes escaped mutation detection within the *HGO* coding region, suggesting the existence of *HGO* alleles whose defect might be related to gene expression.

To determine the extent of allelic heterogeneity in Italian patients, we started a systematic search of AKU families through announcements at relevant National Congresses. We present here the results leading to the identification of four novel mutations. Our data should facilitate future mutation screening in Italian AKU patients and carrier identification by DNA typing.

Ten affected subjects from five unrelated Italian AKU pedigrees were included in the study. In three families it turned out that the patients' parents were consanguineous. Three patients were diagnosed at birth as having AKU through analysis of homogentisic aciduria. The remaining

Table 1 PCR primers for nested PCR analysis of HGO cDNA from blood lymphocytes

Forward primer		*Reverse primer*		*PCR product (bp)*
HTEL	GCAGTGAAGCAGTGGGAACC	HTER	CATTTTAACCAACCCCCTCC	1556
HS1L	GTGGCTTTATATCCTCTGGG	HS9	GGTAGAATCCTATACAGCC	258
HS4	CTTGTCCACGGAGCACC	HS7	GCATCTGTTCTCCATGGAGG	290
HS6	CCTCTGCAATACCTCCATGG	HS3F	TCAAGAAATCACGAGGATTGG	278
HS8	GCCAATGGCTTGGCCAATCC	HS12	ATCAGCAATGGCCACTCCAG	291
HS11F	TTGACTGCTAAGTCTGTCCG	HS10	CATGGTGCCATCGGCAATCC	288
HS13	ATGGACCTGATGCTGACTGC	HS5	CCCCCTCCTCCAATACTACC	314

cases were diagnosed in adulthood on the basis of clinical and radiological examination. Seventeen normal relatives were also investigated. Both genomic DNA and *HGO* cDNA were obtained from peripheral blood by standard methods.

RNA was extracted from peripheral blood lymphocytes by the guanidinium thiocyanate-phenol-chloroform method.[13] cDNA synthesis was performed using both oligo dT and specific primer mapping in the 3'UTR of the *HGO* gene. From the complete sequence of a human *HGO* cDNA (AF045167), primers were designed to obtain overlapping amplicons spanning the entire coding sequence of the *HGO* gene by nested PCR, as described previously.[14 15] Primers HTEL and HTER were used in the first PCR, whereas each of the primer pairs HS1L/HS9, HS4/HS7, HS6/HS3F, HS8/HS12, HS11F/HS10, HS13/HS5 were used in the second PCR. The primer sequences and the expected lengths of the PCR products are shown in table 1.

SSCP analysis was performed according to Orita *et al.*[16] PCR products were heat denatured and subjected to electrophoresis on a non-denaturing 6% polyacrylamide gel and silver stained.[17] All cases were amplified starting from differently obtained cDNA preparations and run independently at least twice with consistent results.

Genomic DNA was used to amplify the exons included in the cDNA regions where abnormal SSCP patterns were found. Moreover, failure to detect mutations in three families necessitated that the genetic lesions were sought at the genomic level by SSCP screening of each exon amplified with intron primers.[9] PCR products were purified by column filtration and sequenced directly with a dye terminator cycle sequencing kit (ABI PRISM Perkin Elmer, Norwalk, USA) using the ABI 377 automated sequencer (Applied Biosystems, Foster City, USA) and its associated analysis software.

Three intragenic STRs, HGO-1 (D3S4496, intron 4), HGO-2 (D3S4497, intron 13), and HGO-3 (D3S4556, intron 4), have been described previously[8 9] and were analysed by PCR with modifications to comply with non-isotopic detection. The PCR products were run on denaturing 6-8% polyacrylamide gels and the alleles were visualised by silver staining. The alleles were numbered consecutively and sized by comparison with known samples. Four SNPs, IVS2+35T/A, IVS5+25T/C, IVS6+46C/A, and c407T/A (exon 4), have also been described[9] and were studied by SSCP on non-denaturing 8% polyacrylamide gel electrophoresis followed by silver staining. Genotype assignment was made possible by comparison with known samples. Familial segregation provided unequivocal derivation of the haplotypes present on the AKU chromosomes.

Five additional unrelated AKU families were analysed for mutations and polymorphisms in the *HGO* gene. The IVS9-56G→A and IVS9-17G→A *HGO* mutations in one Italian patient have already been described.[9] Therefore, the mutations found in 12 AKU chromosomes of Italian ancestry are presented here (table 2). Since consanguineous marriage occurred in three families, only nine chromosomes may be considered to be independent in origin. In fact, patients from these families were homozygous for the AKU mutations G152fs (c621insG), G270R (c975G→A), and G360R (c1245G→C), respectively. The AKU patients in another family were compound heterozygotes for K248R (c909A→G) and IVS7+5G→A (c636+5G→A). Finally, in family VRN, the AKU patient is most likely a compound heterozygote for G360R and an as yet unknown *HGO* mutation. Therefore, as many as eight different *HGO* mutations were found, four of which were novel. We also anticipate that the AKU mutation that remains to be identified will be novel (table 2) because we know that it is different from all previously characterised AKU mutations. We provisionally denoted this mutation as VRN. Three of the four novel mutations (K248R, G270R, and G360R) are missense mutations that affect HGO amino acid residues that are conserved in different species and are likely to be loss of function mutations. K248R is the consequence of an A to G transition at position c909 in exon 10, G270R results from a G to A transition at position c975 in exon 11, and G360R is caused by a G to C transversion at position c1245 in exon 13. This latter mutation was found twice in two unrelated patients. The other novel AKU mutation (IVS7+5G→A) is a G to A transition in the fifth nucleotide position of the donor (5') splice site sequence of intron 7, which most likely causes aberrant splicing of *HGO*. None of these four novel AKU mutations were observed, using SSCP screening, in a sample of 100 control chromosomes. Finally, the mutation G152fs originated from a one base insertion at position c621, which determined a frameshift eventually leading to premature arrest of the protein synthesis. This same mutation was described in two Slovak families.[10] Although the loss of function nature of all these *HGO* mutations was not formally proven, SSCP and sequence analysis of the relevant DNA fragment in family members confirmed in all cases that the pattern of inheritance of AKU was compatible with the segregation of the *HGO* mutations.

Table 2 HGO mutations and haplotypes identified in Italian AKU patients

Mutation	*Type*	*Nucleotide change**	*Associated polymorphisms†*	*No*	*Reference*
G152fs	Frameshift	c621insG	T T 191 161 T C 187	1	10
IVS7+5G→A	Intron change	c636+5G→A	A T 199 161 T C 187	1	This study
IVS9-56G→A	Intron change	c817-56G→A	A T 195 161 T C 181	1	9
IVS9-17G→A	Intron change	c817-17G→A	A T 189 161 T C 191	1	9
K248R	Missense	c909A→G	A T 197 161 T A 171	1	This study
G270R	Missense	c975G→A	T T 195 161 T C 187	1	This study
G360R	Missense	c1245G→C	A A 193 161 T C 197	2	This study
VRN	Unknown	Unknown	A T 193 163 C A 189	1	This study

*Positions of nucleotide changes are from the transcription start site (AF045167).
†The alphanumerical strings represent the haplotypes formed by the following *HGO* intragenic markers: IVS2+35T/A, c407T/A, HGO-3, HGO-1, IVS5+25T/C, IVS6+46C/A, HGO-2.

We managed to perform SSCP analysis of cDNA fragments from two families, one where the G360R mutation was segregating and the other where the patients were compound heterozygotes for the K248R and the IVS7+5G→A mutations. It is interesting to note that this latter supposedly splice site mutation did not affect the SSCP pattern of the cDNA amplicon defined by primer pair HS6/HS3F spanning exons 7 to 9. Furthermore, IVS7+5G→A seemed to have no influence on *HGO* mRNA stability, as judged by the presence of both wild type and mutant bands in the cDNA amplicon defined by primer pair HS8/HS12 containing the K248R site.

In the light of the recent report of a preferential occurrence of *HGO* mutations in the CCC/GGG sequence motifs,[12] we analysed the sequence context of the four novel mutations found in the present work. It could not be coincidental that G270R and G360R mutations take place in tri- and penta-G runs, respectively. Moreover, the G152fs mutation previously described in two Slovak families[10] occurs in a tetra-G run. Whether the G152fs mutation we found in an Italian family has an independent origin remains to be determined. Haplotyping of the Slovak pedigrees as well as comparison with the Italian one could provide strong evidence that the CCC/GGG motif is a mutational hot spot in *HGO*.

Table 2 also shows the haplotypes at the *HGO* intragenic markers IVS2+35T/A, c407T/A, HGO-3, HGO-1, IVS5+25T/C, IVS6+46C/A, and HGO-2 which are associated with each AKU chromosome. Analysis of the *HGO* haplotypes harbouring the purported causative AKU mutations showed that the three intronic mutations were found in a common haplotypic background composed of the very same alleles at four SNPs as well as at HGO-1. Beltrán-Valero de Bernabé *et al*[9] referred to this as haplotype A, the most frequent in European populations. Two other mutations, G152fs and G270R, were detected in a gametic association, haplotype D,[9] which is derived from haplotype A by variation at the SNP IVS2+35T/A. Closely related to haplotype A is also that segregating with mutation G360R and that harbouring the mutation K248R, haplotype B.[9] These haplotypes differ from haplotype A at SNPs c407T/A and IVS6+46C/A, respectively. On the other hand, the mutation VRN was probably within the so-called haplotype E.[9] It has been postulated[9] that haplotype E has a North African origin, an ethnic component that is known to have contributed to the modern Italian population.[18] Whether the VRN mutation has originated in Italy or has been introduced into this country with the different migrations is at present unknown.

Only two of the AKU mutations found in Italians (G152fs and IVS9-56G→A) have been encountered in patients from other European countries. One of them, as indicated before, is the G152fs mutation that was identified in two Slovak AKU pedigrees.[10] It would be interesting to determine whether the G152fs mutation has an eastern European origin and appeared in Italy by migration. The IVS9-56G→A AKU mutation was also identified earlier in an AKU chromosome of a French patient.[9] Interestingly the IVS9-56G→A mutation in the Italian and the French patients are associated with the same *HGO* haplotype. In this case, we postulate an Italian origin for this mutation since the French IVS9-56G→A carrier patient has Italian ancestors.

It is important to note that the mutations P230S, V300G, and M368V, which are relatively common mutations,[7 12 15 19] were absent in our patients. P230S and V300G are typically associated with haplotype E and are thought to be North African in origin.[9] The M368V mutation is widely distributed throughout Europe and is associated with haplotype A.[9] It is also interesting that the mutation G360R was found twice within the same haplotype in two families from different ends of the Italian peninsula; patient VRN was from Calabria (southern Italy), whereas the affected sons of a consanguineous marriage were from South Tyrol, a German speaking region on the Austrian border. Additional *HGO* mutational and polymorphism analyses of AKU patients from many more different countries would be necessary to understand the population genetics of AKU and the migration of the different AKU alleles.

In conclusion, we report here an extensive description of the spectrum of AKU mutations in Italy, including the characterisation of their associated intragenic *HGO* polymorphisms. Four novel mutations were found, which include both missense mutations and subtle intronic changes. The Italian AKU sample confirms the high degree of allelic heterogeneity of the *HGO* gene and illustrates the complications of mutation screening in AKU patients. These data should facilitate the future identification of these AKU alleles in this and other populations.

Note added in proof

The mutation G270R has recently been described by Müller *et al* (*Eur J Hum Genet* 1999;7:645-51).

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Rough skin, brittle hair, and photosensitivity: a mild phenotypic variant of trichothiodystrophy

EDITOR—The trichothiodystrophies (TTD) are named primarily for the hair sulphur deficiency which is their most specific feature and which leads to brittleness of the hair. Other ectodermal tissues may be affected and typically the skin is ichthyotic and the nails dystrophic. Additionally, there may be a distinctive facies and physical and developmental retardation of varying degree of severity. Inheritance is autosomal recessive and at least three loci exist, of which two are known, the excision repair/transcription factor genes *XPD*/*ERCC-2* and *XPB*/*ERCC-3*. We describe an 8 year old girl in whom the diagnosis of a mild and in some respects atypical form of TTD was made on the synthesis of clinical, pathological, and biochemical data. The genotypic basis of this clinical phenotype has yet to be established.

The patient was the second child of a dizygous twin pregnancy born to unrelated, healthy, white parents by emergency caesarean section at 32 weeks because of pre-eclampsia. The family history was unremarkable and her male co-twin was healthy. Birth weight was 2100 g (90th centile for this gestation). Birth length and head circumference were 51.5 cm and 32.5 cm respectively. The skin was dry and flaky from birth (but never "collodion"), and in using a towel her mother had to pat her dry, rather than to rub. Thickening of the palms and soles developed in the first year of life. The nails were brittle from birth. Hair growth has always been slow and she has never had a proper haircut, only trims. Desquamated cells from the external auditory canal failed to clear and she has required periodic syringing.

She was referred to our service at 5 years of age because of concerns related to persistent dermatitis, dermal photosensitivity suggested by easy burning in the sun, mild developmental delay, and distinctive facial appearance. We noted the following features: hair that was "wiry" in texture, fragile, and easy to extract; abnormal scalp hair distribution with temporal recession; prominent forehead with sparse eyebrows (fig 1); a generalised dryness of the skin with areas of keratoderma; and brittle, spoon shaped fingernails and toenails. The keratoderma was particularly marked on the soles and palms (fig 2) and at the popliteal and antecubital flexures. Apart from congenital absence of the second premolars, the teeth were normal. Her weight was 27 kg (90th centile), height 128 cm (97th centile), and head circumference 54 cm (98th centile). These measurements are consonant with the parental heights and weights, which were in the 90th-97th centile range. She was attending a normal school and was in the appropriate class for

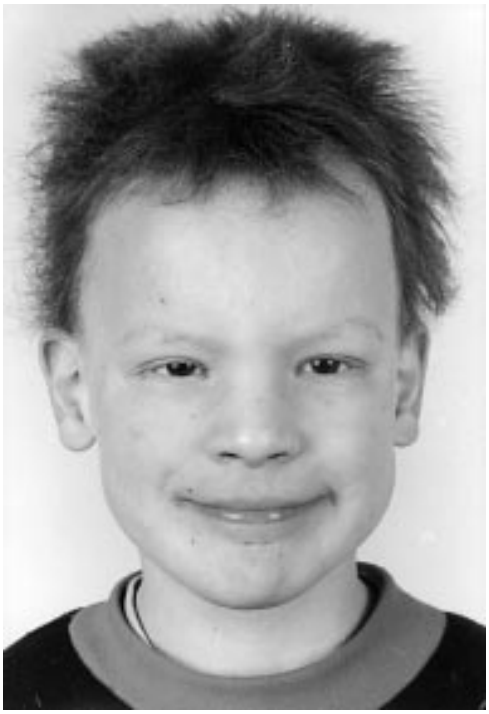

Figure 1 Patient aged 8 years. The hair is short (has only been trimmed) and stands up irregularly. There is temporal recession.

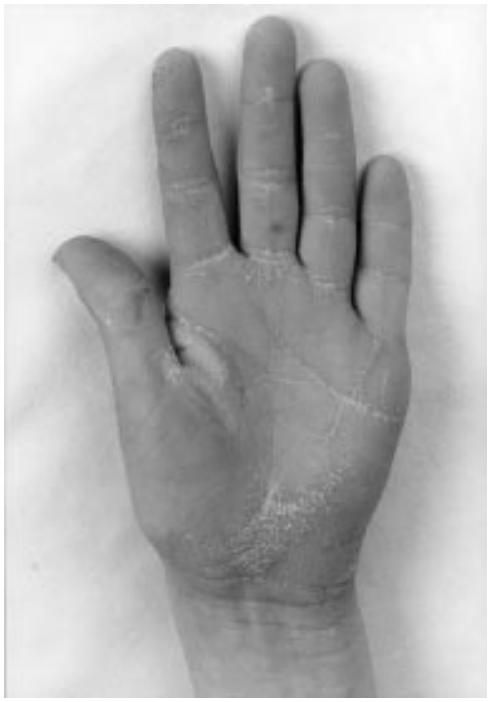

Figure 2 Palmar keratoderma.