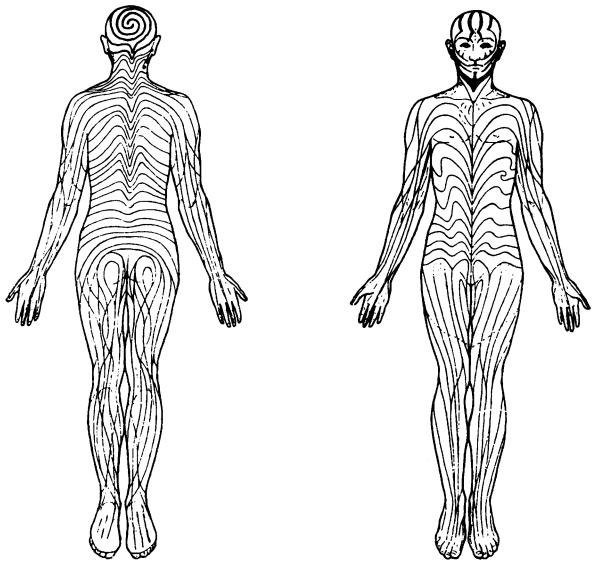

Figure 1 Lines of Blaschko. This figure is a reproduction of Blaschko's original drawing (1901), completed on the scalp according to Happle et al. (1984).

void conditions are considered. For example, the areas of hyperpigmentation present in the McCune-Albright syndrome are very broad and coarse. Nevertheless, there is convincing evidence that these pigmentary lesions can likewise be taken as a variation on the basic paradigm represented in humans by Blaschko lines.

On the other hand, I agree with Thomas et al. that women heterozygous for X-linked genes affecting the skin are as variously patterned as allophenic mice. This view is supported by the results obtained by Cattanach et al. (1972) in a comparative study of the coats of chimeric mice and those of heterozygotes for X-linked genes.

Finally, I disagree with Thomas et al. (1989, fig. 2) with regard to their diagram of Blaschko lines illustrating "the lack of information concerning the pattern over the head and face." The system of lines published by Blaschko (1901) covered the entire body including the face—but not the scalp, because of lack of pertinent case reports regarding this area. In the meantime this blank area has been filled in (Happle et al. 1984). On the scalp the lines of Blaschko are distributed in spiral streaks converging on the vertex. A completed diagram is presented in figure 1.

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Different Clinical Manifestations of Hyperphenylalaninemia in Three Siblings with Identical Phenylalanine Hydroxylase Genes

To the Editor:

Haplotype analysis at the phenylalanine hydroxylase (PAH) locus is currently used in the prenatal diagnosis of phenylketonuria (PKU) (Lidsky et al. 1985). LOD score analysis suggests that less severe serum phenylalanine elevations also result from mutation at the PAH locus (DiSilvestre et al. 1990*c*). We report a documented case of siblings who have the same phenylalanine hydroxylase (PAH) genotype, similar phenylalanine-loading-study results, normal neopterin-to-biopterin ratios, but different clinical manifestations of hyperphenylalaninemia (HPA). The results suggest that one should exercise caution when using genetic analysis at the PAH locus to predict the clinical outcome of HPA.

An informative Southern blot of DNAs isolated

from blood samples of this atypical PKU family is shown in figure 1. The presence of an *Msp*I polymorphic site results in the restriction-enzyme digestion of a 23-kb fragment to a 19-kb fragment. Clearly, all three siblings have inherited the same alleles of 23 kb from both parents. The pattern obtained with *Xmn*I was also completely informative, while *Bgl*II, *Pvu*II, *Eco*RI, and *Eco*RV resulted in partially informative patterns which confirm the *Msp*I result. Haplotype assignment (Woo 1989) indicates that the haplotypes of the mutant and normal alleles are, respectively, 4/1 for the father and 7/1 for the mother. All three siblings have haplotypes of alleles 4 and 7. In summary, on the basis of these data it was concluded that all three siblings have inherited the same PAH alleles. All three siblings are designated as blackened symbols in figure 1, indicating that they all have elevated plasma phenylalanine. As adults on a normal diet, they have average blood phenylalanine levels of 12-16 mg/dl. The natural protein-challenge results for the siblings are shown in figure 2. All three siblings show a pattern indicative of atypical PKU, in that plasma phenylalanine levels rise moderately, peak at about 24 h, and return to their basal level after 72 h (Blaskovics 1986).

Of the three siblings, the two eldest were born before newborn blood phenylalanine testing was routine. The siblings are designated A, B, and C, with A being the eldest and C being the youngest. Sibling A, who was never on a phenylalanine-restricted diet, is normal at age 35 years, as evidenced by an IQ estimated at 130. Sibling B, the proband, was diagnosed at 13 mo and, despite an attempt at dietary therapy, is severely retarded (IQ approximately 30). Sibling C was diagnosed neonatally and was maintained on a phenylalanine-restricted diet until age 6 years. Sibling C is now age 26 years and has an IQ of 114. All IQ measurements are based on the Wechsler Adult Intelligence Scale. Neither medical history of the patient nor complete medical evaluation revealed any other clinical problems in the proband, suggesting that mental retardation is the result of an abnormal phenylalanine level.

As all eight polymorphic sites are within 100 kb, it is unlikely that a crossover occurred. Moreover, the pattern of polymorphic sites is not indicative of a crossover event. We have not determined the specific mutations in the PAH alleles; it has recently been shown (John et al. 1990) that, in some families, the association between specific mutations and haplotypes can be unreliable as a result of recurrent mutation, gene conversion, or a recombination event. Moreover, the analysis we performed is standardly used for PAH genotyping and would normally result in the conclusion that all three siblings had identical PAH genotypes. Illegitimacy was tested by using two probes that hybridize to regions containing VNTRs (see fig. 3).

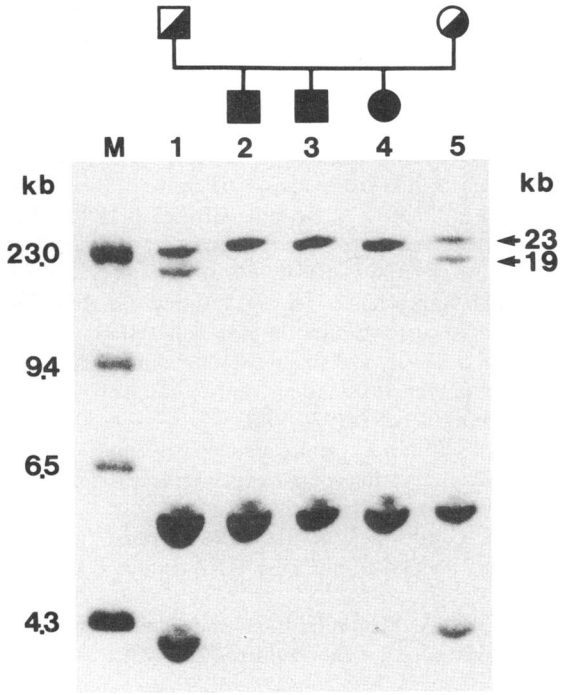

Figure 1 Southern blot analysis using cDNA of PAH as probe. ■ and ● = Elevated serum phenylalanine levels; ◪ and ◕ = carrier. All DNAs were digested with *Msp*I. DNA molecular-weight markers, λ × *Hin*dIII, are shown in lane M. Lanes 1 and 5, Parents. Lanes 2, 3, and 4, Siblings A, B, and C, respectively.

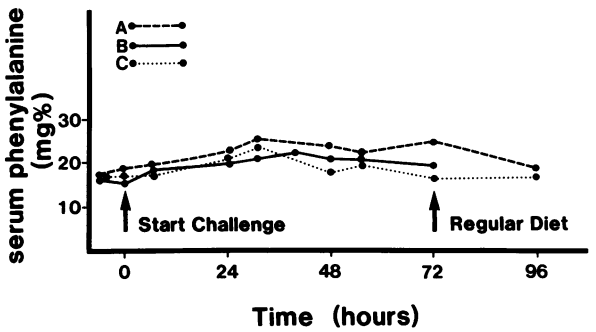

Figure 2 Natural protein challenge results. Phenylalanine (180 mg/kg/d) was given to each individual. The ages at the time of challenge were 17, 14.5, and 9 years for siblings A, B, and C, respectively.

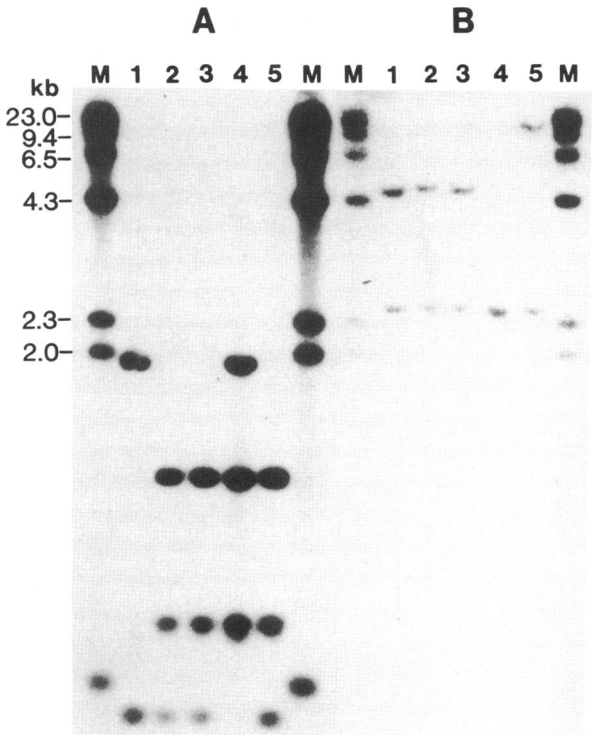

Figure 3 Southern blot analysis using VNTR-B and VNTR-A as probes. The DNAs were digested with *TaqI*. Lanes are labeled as in fig. 1. *A*, Hybridization with VNTR-B. *B*, Same blot stripped in 0.1 N NaOH and hybridized with VNTR-A.

The heterozygosity of VNTR-A is 78% (DiSilvestre et al. 1990*b*), and that of B is 88% (DiSilvestre et al. 1990*a*). Both probes suggest that this is a nuclear family. As the mother has normal phenylalanine levels, maternal PKU is not a problem. Liver biopsy has shown that the proband has 4% of normal PAH activity. Such an activity is suggestive of atypical PKU (Dhont and Farriaux 1987). Normal neopterin/biopterin ratios indicate that there is no problem with either dihydropteridine reductase or the enzymes involved in the synthesis of tetrahydrobiopterin from guanosine triphosphate. We conclude that a presently unidentified subtle difference explains the differences seen in the phenylalanine toxicities of the siblings. Kang et al. (1970), working before PAH RFLPs were recognized, reported siblings who had similar plasma phenylalanine levels but different developmental responses. In the present study we have demonstrated that different clinical phenotypes for the same PAH genotype can be found. We conclude that, although the PAH genotype correctly predicted the biochemical phenotype, the clinical phenotype of this disease can be influenced or altered by additional genetic loci. It will be clinically relevant to learn how the same mutation manifests itself in different individuals. Then the interplay that other molecules have on the serum phenylalanine tolerance levels can be further investigated.

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