

## Correspondence

# Tetrahydrobiopterin-responsive hyperphenylalaninaemia due to homozygous mutations in the phenylalanine hydroxylase gene

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**Sir:** Steinfeld et al. [3] reported on three infants with tetrahydrobiopterin (BH<sub>4</sub>)-responsive phenylalanine hydroxylase (PAH) deficiency, one of them with a common homozygous Y414C mutation. They questioned the concept of decreased cofactor affinity as a valid explanation for BH<sub>4</sub> responsiveness. Recently, we published the first patient with a homozygous L48S mutation presenting with a BH<sub>4</sub>-responsive PAH deficiency [1]. While some of mutations in the *PAH* gene may produce Km variants which can be activated by BH<sub>4</sub> (I65T, V190A, A241C, R261Q, A313T, A373T, E390G, A395P, A403V, P407S, Y414C) the L48S mutation is not located in the DNA coding region for the catalytic domain. Previously described patients were all compound heterozygotes for the above listed mutations and most of these mutations proteins showed 20%-30% residual activity when recombinantly expressed in eukaryotic cell systems[1]. Thus, mechanisms different from the low cofactor affinity may be responsible for the phenotype in patient with the L48S mutation.

The recent finding that BH<sub>4</sub> (200 mg/kg ip) increases the PAH mRNA, enzyme activity and protein levels by 50% in a *hph-1* mouse suggested the BH<sub>4</sub> can regulate *PAH* gene expression [2]. We proposed that in patient with the L48S mutation, and this may also be true for some other homozygous mutations, BH<sub>4</sub> increases enzyme activity by inducing the gene expression. However, one cannot exclude that in some patients the BH<sub>4</sub> responsiveness is due to both a Km variant and increased *PAH* gene expression.

These data stress the importance of the BH<sub>4</sub> loading test and of BH<sub>4</sub> as a potential practical alternative in the treatment of mild hyperphenylalaninaemia. Our preliminary data indicate that BH<sub>4</sub>-responsive PAH deficiency is more common than initially assumed. Around 70% of patients with initial plasma phenylalanine levels below 800 µmol/l respond to the loading test with 20 mg BH<sub>4</sub>/kg body weight (C. Bernegger and N. Blau, unpublished observation).

## References

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