### Introduction

Tetrahydrobiopterin (BH4) is an essential cofactor in the enzymatic production of the biogenic amines, dopamine and serotonin. 6-PTPS deficiency is a disorder of tetrahydrobiopterin biosynthesis, leading to low CNS HVA and SHIAA neurotransmitter levels and elevated plasma phenylalanine.1

There is a spectrum of disease severity ranging from the mild / asymptomatic peripheral form with isolated hyperphenylalaninaemia to severe phenotypes secondary to central nervous system neurotransmitter deficiency. There is little known about the “peripheral” cohort; some cases develop a clinical phenotype with time2, but it is unclear what proportion of patients develop such symptoms.

### Case Series – NSW Cohort

Retrospective review of medical records of all ten patients with 6-PTPS deficiency diagnosed in New South Wales (NSW), identified on newborn screening with raised phenylalanine levels. Five patients had neurological abnormalities at the time of diagnosis; a further two patients developed abnormal neurology during infancy.

One patient was not started on neurotransmitter replacement at diagnosis. Two patients developed adverse effects and so neurotransmitter supplementation was withdrawn during early infancy with all three patients being asymptomatic without neurotransmitter replacement.

### Peripheral 6-PTPS Cohort

**Patient 1: 2 year old boy, non-consanguineous Kenyan descent**

**Newborn Screen:** elevated phenylalanine (Phe) (744 umol/L); urine: low urinary biotin (0.66 umol/mmol creat), biotin ratio 5%

**CSF:** SHIAA and HVA levels marginally low, CSF biotin was within the normal range.

**Genotype:** compound heterozygous VUSs in the PTS gene (c.379C>A | p.Leu127Ile and c.245A>G | p.Glu82Glu). The latter is a novel promoter variant

**Management:** After commencing Levodopa and 5-hydroxytryptophan agitation and sleep disturbance developed, hence discontinued without problem. Sapropterin discontinued after 12 months with Phe levels remaining stable despite an unrestricted diet. He has developed no neurological symptoms.

### Patient 2: 14 month girl, non-consanguineous East Asian descent

**Newborn Screen:** elevated phe (692 umol/L); urine: low urine biotin (0.49 umol/mmol creat), biotin ratio 1.9%

**CSF:** collection unsuccessful

**Genotype:** compound heterozygous pathogenic variants in the PTS gene (c.84-291A>G and c.286G>A | p.Asp96Asn), both conferring residual enzyme activity in functional studies2,3

**Management:** Commenced levodopa and 5-hydroxytryptophan but developed sleep cycle irregularities and agitation, and medications ceased at 3 months of age. Continues sapropterin (5mg/kg/day). Now at 14 months of age remains asymptomatic.

### Patient 3: 6 year old boy, non-consanguineous Caucasian Australian descent

**Newborn Screen:** elevated phe (315 umol/L); urine: low urine biotin (0.48 umol/mmol creat), biotin ratio 6%

**CSF:** marginally decreased CSF HIAA, normal HVA, biotin within the normal range

**Genotype:** homozygous likely pathogenic variant in PTS (c.46C>T | p.Arg16Cys), associated with residual enzyme activity in functional studies2. No previous reports of homozygous individuals.

**Animal studies** with this homozygous genotype demonstrated normal brain neurotransmitter and plasma phenylalanine levels despite lower plasma and brain biotin levels compared with wild-type.

**Management:** has never received neurotransmitter or sapropterin supplementation. Remains clinically asymptomatic.

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