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SHORT REPORT

Heterogeneous clinical spectrum of DNAJC12-deficient hyperphenylalaninemia: from attention deficit to severe dystonia and intellectual disability

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ABSTRACT

Background Autosomal recessive mutations in *DNAJC12*, encoding a cochaperone of HSP70 with hitherto unknown function, were recently described to lead to hyperphenylalaninemia, central monoamine neurotransmitter (dopamine and serotonin) deficiency, dystonia and intellectual disability in six subjects affected by homozygous variants.

Objective Patients exhibiting hyperphenylalaninemia in whom deficiencies in hepatic phenylalanine hydroxylase and tetrahydrobiopterin cofactor metabolism had been excluded were subsequently analysed for *DNAJC12* variants.

Methods To analyse DNAJC12, genomic DNA from peripheral blood (Sanger sequencing), as well as quantitative messenger RNA (Real Time Quantitative Polymerase Chain Reaction (RT-qPCR)) and protein expression (Western blot) from primary skin fibroblasts were performed.

Results We describe five additional patients from three unrelated families with homozygosity/compound heterozygosity in *DNAJC12* with three novel variants: c.85delC/p.Gln29Lysfs*38, c.596G>T/p.*199Leuext*42 and c.214C>T/p.(Arg72*). In contrast to previously reported DNAJC12-deficient patients, all five cases showed a very mild neurological phenotype. In two subjects, cerebrospinal fluid and primary skin fibroblasts were analysed showing similarly low 5-hydroxyindolacetic acid and homovanillic acid concentrations but more reduced expressions of mRNA and DNAJC12 compared with previously described patients. All patients responded to tetrahydrobiopterin challenge by lowering blood phenylalanine levels.

Conclusions DNAJC12 deficiency appears to result in a more heterogeneous neurological phenotype than originally described. While early identification and institution of treatment with tetrahydrobiopterin and neurotransmitter precursors is crucial to ensure optimal neurological outcome in DNAJC12-deficient patients with a severe phenotype, optimal treatment for patients with a milder phenotype remains to be defined.

INTRODUCTION

Today, many countries have adopted newborn screening for phenylketonuria (PKU; phenylalanine hydroxylase (PAH) deficiency, OMIM 261600), which is based on high phenylalanine (Phe) concentrations (hyperphenylalaninemia (HPA)) in dried blood spots (DBSs).[1 2] Immediate institution of treatment can effectively reduce plasma Phe concentrations and prevent classical PKU symptomatology.[1 2]

About 1%–2% of all cases identified with HPA in newborn screening are due to disorders affecting BH_4 metabolism.[3 4] While patients with classical PKU present with very high blood Phe concentrations, BH_4 deficiencies present with dopamine and serotonin deficiencies besides HPA (for a broader view of BH_4 in enzyme function see[5]). Central dopamine and serotonin deficiencies are reflected by low homovanillic acid (HVA) and 5-hydroxyindolacetic acid (5HIAA) in cerebrospinal fluid (CSF), respectively. Accordingly, treatment consists of BH_4 to normalise plasma Phe concentrations as well as with L-dopa/carbidopa and 5-hydroxytryptophan precursors to reduce neurological symptoms caused by the dopamine and serotonin deficiencies.[6]

Recently, autosomal recessive deficiency of DNAJC12, which is thought to act as a cochaperone for PAH, tyrosine hydroxylase and tryptophan hydroxylase, has been described as a cause for HPA.[7] Similar to disorders of BH_4 metabolism (and classic PKU), *DNAJC12* variants cause dopamine and serotonin deficiency in addition to HPA. Clinically, the six consanguineous patients with homozygous *DNAJC12* mutant alleles who have been reported thus far showed intellectual disability and severe neurological symptoms including dystonia.[7] Herein, we present five additional patients with HPA without *PAH* mutations or any known defect in BH_4 metabolism, who turned out to have biallelic *DNAJC12* deficiency. The two siblings of Caucasian background (Dutch) with compound heterozygous *DNAJC12* variants and the three children of Saudi origin with a homozygous genotype described here all showed a very mild neurological phenotype.

METHODS

Subjects

All clinical data were obtained with written informed consent from the parents of all investigated subjects, in agreement with the Declaration

of Helsinki and approved by the Ethical Committees of the centres participating in this study, where biological samples were obtained.

Family 1

Patient 1-A is a boy and was born at term after an uneventful pregnancy from non-consanguineous parents with a Caucasian pedigree (Dutch). He was identified with HPA at day 5 by newborn screening (NBS) with a blood Phe concentration of 500 µmol/L. The neonatal BH_4 loading test (20 mg/kg) showed a reduction in plasma Phe concentrations from 330 to 120 µmol/L after 8 hours, suggesting BH_4 deficiency. However, a BH_4 defect was ruled out by a normal urinary pterin profile and normal dihydropteridine reductase (DHPR) activity in DBS. He was therefore considered to have mild PAH deficiency, although genotyping did not show any mutations in the *PAH*. A Phe-restricted diet kept plasma Phe concentrations <360 µmol/L. Development in infancy was normal. From the age of 2.5 years, he showed behavioural issues of hyperactivity and attention deficit. At age 6 years, neuropsychological assessment showed a disharmonic intelligence profile (Wechsler Intelligence Scale for Children- III (WISC-III): full scale IQ 108; verbal 125; performance 88) and attention deficit hyperactivity disorder (ADHD) (inattention type) with a differential diagnosis of Asperger's. In 2009, a 48-hour BH_4-loading test (20 mg/kg) was performed, which reduced plasma Phe concentrations from 350 to 95 µmol/L. He was subsequently treated with BH_4 (11–13 mg/kg/day), which allowed him to have an unrestricted diet (plasma Phe concentrations ranging between 49 and 475 µmol/L). Neuropsychological assessment at 10 and 13 years of age showed a normal IQ and executive functions but minor problems in facial recognition and the identification of facial emotions, thinking problems and both social and internalising problems. Neurological examination at 13 years of age showed a low passive tone, but normal active tone, subtle signs of dystonia when walking (on toes) and suboptimal alternating hand movements with the non-dominant hand. CSF analysis (at the age of 13 years) revealed normal pterins but low biogenic amines (5HIAA and HVA; see table 1). Due to the fact that that the CSF results rather than the clinical symptoms clearly support central dopamine deficiency, it was considered unnecessary to start L-dopa/carbidopa treatment.

Patient 1-B is a girl (sister of patient 1A) and was born after an uneventful pregnancy and delivery and was diagnosed with HPA following a blood Phe concentration of 433 µmol/L on the second day after birth. Given the history of her brother, pterin and DHPR analyses were not performed, and a Phe-restricted diet was immediately initiated. Early development was slow but within the normal limits. From the age of 4 years, it was noted at school that she had difficulty interacting with other children. Neuropsychological assessment showed indications for autism spectrum disorder, but this was not further investigated. At the age of 5 years, a 48-hour BH_4-loading test (20 mg/kg) showed a reduction in plasma Phe concentrations from 346 to 109 µmol/L, and she was treated with BH_4 (15–20 mg/kg/day), which allowed her to have an unrestricted diet (plasma Phe concentrations largely <360 µmol/L). Neuropsychological assessment at 8 and 11 years of age showed a normal IQ and executive functions, and only minor problems in facial recognition and the identification of facial emotions as well as increased social problems. Neurological examination performed at the age of 11 years showed a low passive tone and suboptimal alternating hand movements with the non-dominant hand. CSF analysis (at the age of 11 years) revealed normal pterins but low biogenic amines (5HIAA and HVA; see table 1). Due to the fact that that the CSF results rather than the clinical symptoms clearly support central dopamine deficiency, it was considered unnecessary to start L-dopa/carbidopa treatment.

More information on the subjects and on materials and methods are described in the online supplementary materials and methods.

RESULTS

We report on five patients with HPA from three unrelated families in whom neither *PAH* variants nor any known defect in BH_4 metabolism was identified, that is, pterins analysis and DHPR enzyme activity were in the normal range and no mutations were identified, who turned out to have biallelic *DNAJC12* deficiency. A summary of genetic and biochemical data as well as clinical characteristics and current treatment of our patients is summarised in table 1. For comparison, the biochemical and clinical characteristics from the first six previously described DNAJC12-deficient patients are also listed. Blood Phe levels in our DNAJC12-deficient patients were between 420 and 526 µmol/L, similar to previously described subjects. They all responded to an oral challenge with BH_4 (20 mg/kg) by lowering their blood Phe concentrations to almost normal. In two patients from family 1, CSF investigations revealed low concentrations of 5HIAA and HVA, comparable with previously published patients.[7] Nevertheless, in all our patients, the clinical phenotype was much milder than described previously. Apparently, neither blood Phe levels nor CSF neurotransmitter metabolites are a good predictor of the severity of neurological disease in DNAJC12-deficient patients. In the two siblings from non-consanguineous parents (family 1), a compound heterozygous genotype with two novel *DNAJC12* variants (c.85delC/p.Gln29Lysfs*38 and c.596G>T/p.*199Leuext*42) was identified. The other three patients from consanguineous parents (families 2 and 3) were all homozygous for another novel *DNAJC12* variant c.214C>T (p.Arg72*). In summary, the three novel variations include one frameshift mutation, a non-sense mutation and a 42-nucleotides extension due to the stop codon mutation. While the frameshift and the non-sense mutations are predicted to be deleterious or disease causing, the effect of the stop codon mutation may be less obvious. Theoretically, the stop-codon variant results in a slightly longer protein with an extra tag on the C-terminus. However, it is believed that quality surveillance mechanisms protect the cell from such potentially harmful mutant proteins by mRNA elimination and/or protein degradation.[8] Degradation of such a DNAJC12 mutant is corroborated by the analysis of fibroblasts from patients 1-A and 1-B, where both the DNAJC12 transcript (mRNA) and protein expression in fibroblasts were markedly reduced as compared with healthy controls (figure 1A and B).

The variants are deposited in the locus-specific database PNDdb at http://www.biopku.org.

DISCUSSION

We report on five individuals in three families in whom HPA is caused by the recently identified DNAJC12 deficiency.[7] In contrast to the previously reported six DNAJC12-deficient patients, who all presented with severe neurological symptoms if not treated early with a combination of BH_4 and neurotransmitter precursors L-DOPA/carbidopa and 5-hydroxytryptophan,[7] the here presented patients show only mild neurological symptoms, behavioural problems and/or mild hypotonia, if any symptoms at all. The patients of family 1, in succession, have

Table 1 Overview of genetic, biochemical and clinical characteristic of subjects identified thus far with DNAJC12 deficiency

						Patients (n=6)
Characteristic	**1-A**	**1-B**	**2-A**	**2-B**	**3**	**Anikster *et al* 2017[7]**
DNA variation	c.[85delC];[596G>T]	c.[85delC];[596G>T]	c.[214C>T];[214C>T]	c.[214C>T];[214C>T]	c.[214C>T];[214C>T]	
Location in exon #	E2;E5	E2;E5	E3;E3	E3;E3	E3;E3	
Protein alteration	p.[Gln29Lysfs*38];[*199Leuext*42]	p.[Gln29Lysfs*38];[*199Leuext*42]	p.[Arg72*];[Arg72*]	p.[Arg72*];[Arg72*]	p.[Arg72*];[Arg72*]	
Age (at diagnosis)	13 years	11 years	25 months	3 years	10 years	2–20 years
First blood Phe (µM)	500	433	526	509	420	84–460
BH_4 loading test	Responsive	Responsive	Responsive	Responsive	Responsive	6/6 (responsive)
CSF analysis			n.d.	n.d.	n.d.	
5HIAA (nmol/L)	28 (↓)	20.3 (↓)	n.d.	n.d.	n.d.	6/6 (↓)
(ref. range: 74–163)						
HVA (nmol/L)	108 (↓)	86 (↓)	n.d.	n.d.	n.d.	6/6 (↓)
(ref. range: 133–551)						
Neopterin (nmol/L)	14.5 (n)	11.3 (n)	n.d.	n.d.	n.d.	1/4 (↑)
(ref. range: 9–20)						
Biopterin (nmol/L)	19.1 (n)	15.0 (n)	n.d.	n.d.	n.d.	1/2 (↑)
(ref. range: 10–30)						
Dystonia	+ (subtle)	None	None	None	None	4/6
Speech delay	None	None	None	None	None	2/6
Intellectual disability	None	None	None	None	None	3/6
Axial hypotonia	+ (mild)	+ (mild)	None	+ (mild)	+ (mild)	1/6
Limb hypertonia	None	None	None	None	None	1/6
Parkinsonism	None	None	None	None	None	1/6
Nystagmus	None	None	None	None	None	1/6
Oculogyric crisis	None	None	None	None	None	1/6
Attention difficulties	+	None	None	None	None	1/6
Autistic features	?	?	None	None	None	1/6
Current treatment	Yes (BH_4)	Yes (BH_4)	None	None	Yes (BH_4 plus NT)	Yes (BH_4 plus NT)

?, unclear; ↓, reduced; n, normal; ↑, elevated; 5HIAA, 5-hydroxyindolacetic acid; CSF, cerebrospinal fluid; HVA, homovanillic acid; n.d., not done; NT, neurotransmitter precursors; Phe, phenylalanine.

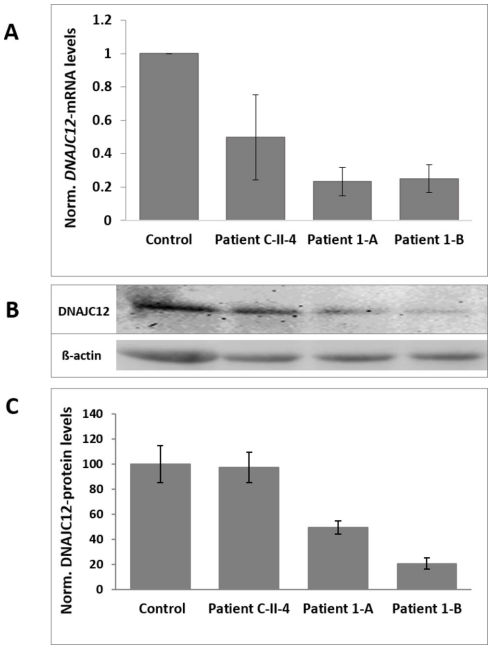

Figure 1 DNAJC12 expression in patient's fibroblasts. (A) *DNAJC12* (mRNA) expression in patient's fibroblasts in relation to reference *Rab7* gene expression (n=3). Besides control fibroblasts, the DNAJC12-deficient patient with the homozygous *DNAJC12* variations c.[215G>C]; [215G>C]/p.[Arg72Pro];[Arg72Pro] previously published by Anikster *et al* as patient C-II-4,[7] and patients 1-A and 1-B from the here described family 1 are shown. Relative mRNA expression revealed a significant but variable reduction of around 0.5 (±0.25) in patient C-II-4. The here described Dutch siblings, that is, patient 1-A and patient 1-B (family 1) with the compound heterozygous variations c.[85delC];[596G>T]/p.[Gln29Lysfs*389]; [*199Leuext*42] resulted in a more significant reduction of mRNA expression levels of around 0.23 (±0.09) and 0.25 (±0.08) compared with control, respectively. (B and C) Corresponding DNAJC12 protein expression in patient's fibroblasts. Western Blot analysis (100 µg total protein) of DNAJC12 in patients' fibroblasts detected no significant difference between control and patient C-II-4, similarly to what was reported before,[7] but strongly diminished protein levels in patients 1-A and 1-B (family 1) compared with control fibroblasts (normalised against β-actin). Values after protein normalisation (in C): control 100±14.9%, C-II-4 97.5±12.1%, patient 1-A 49.4±5.3%, patient 1-B 20.6±4.5%.

been treated with a Phe-restricted diet and with BH_4 monotherapy without substitution of neurotransmitter precursors. Most of the time, patients in family 2 have received no treatment at all, while the patient in family 3 is doing well on moderate dosages of BH_4, L-DOPA/carbidopa and 5-hydroxytryptophan. Despite the very mild clinical phenotype, however, CSF neurotransmitter metabolite concentrations in the two patients from family 1 were remarkably similarly low as the previously reported in DNAJC12-deficient patients. Patients described in this study are, however, slightly younger (family 2) than those previously described and the patient from family 3 was already on treatment for several years at the time of molecular diagnosis, which may have affected the natural course of the disease. One may speculate that a long-term exposure to elevated blood and brain Phe levels (inhibition of other large-neutral amino acids at the blood–brain barrier), together with impaired CNS synthesis of biogenic amines (competitive inhibition of tyrosine and tryptophan hydroxylases) could result in a more severe neurological presentation, including intellectual disability and Parkinsonism. Moreover, our studies in primary skin fibroblasts from these same two patients with the milder phenotype exhibited a more reduced expression of both mRNA and DNAJC12 than with one of the previously described patients with a more severe phenotype. Therefore, a potential reverse relation between DNAJC12 expression and severity of phenotype needs further functional studies and investigations.

The very recently published key statements of the first European PKU guidelines state that in every child who is referred for HPA, both pterins and DHPR activity should be assessed to exclude disorders of BH_4 metabolism.[1] Non-classical HPA (BH_4 deficiencies) is a rather rare group of disorders with overall prevalence of 1:500 000 newborns,[4] and it is probably too early to estimate prevalence of DNAJC12 deficiency. Together with the previously reported DNAJC12-deficient patients, the here described cases show that, besides disorders of BH_4 metabolism, DNAJC12 deficiency should also be included in the differential diagnosis of HPA. This is especially warranted if a (neonatal) BH_4-loading test is performed and normalises plasma Phe concentrations, while disorders of BH_4 metabolism have been ruled out, and genetic testing for PAH deficiency has not revealed any variant. The previously reported cases showed that early identification and prompt institution with $BH_4$and dopamine and serotonin precursors was crucial to prevent intellectual disability and severe neurological symptoms including movement disorders such as dystonia.[7] The here presented cases, having a much milder neurological phenotype, raise the question whether such treatment should be initiated in all DNAJC12-deficient patients to optimise neurological outcome. Investigations of biogenic amines in CSF are essential for such decisions.

In view of the defective DNAJC12 itself, it is known that the DNAJ heat shock protein family (HSP40) member C12 undergoes functional interactions with chaperones of the HSP70 family by stimulating their ATPase activity.[9] The finding of DNAJC12-deficient patients presenting with HPA and abnormal brain catecholamines has identified the PAH enzyme but also tyrosine and tryptophan hydroxylases as interacting 'client' proteins (see also discussion in ref 7). In this context, it is interesting to note that ectopic expression of the HSP40/HSP70 complex was reported to rescue GTPCH activity of the *GCH1* variant p.Gly201Glu that was found in a Dopa-responsive dystonia patient[10] and that *DNAJC6* and *DNAJC13* were associated with, respectively, autosomal recessive and dominant juvenile Parkinsonism[11 12] (for an overview on defects in trafficking and Parkinson's disease, see ref 13). A more detailed physiological analysis is obviously required to fully understand these various interactions and interdependences.

To conclude, we report on five additional cases with HPA due to DNAJC12 deficiency in whom neurological symptoms are much milder than in the six patients who have been previously reported. Thereby, *DNAJC12* variants seem to cause a heterogeneous neurological phenotype, of which the severity is not reflected by plasma Phe nor CSF neurotransmitter metabolite levels. While early identification and institution of treatment with BH_4 and neurotransmitter precursors is crucial to ensure optimal neurological outcome in DNAJC12 deficiency patients with a severe phenotype, optimal treatment for patients with a milder phenotype remains to be defined.

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