Mitochondrial studies in a novel disorder associated with NUBPL-associated mitochondrial Complex I deficiency in patients with global developmental delays, ataxia, cerebellar and pons hypoplasia

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ABSTRACT

The NUBPL gene (OMIM 603525) was first reported as a cause of NUBPL disease (Complex I deficiency, OMIM 252300) in 2010, and only seven families have been reported worldwide. We now report clinical features of 15 cases in 8 families, representing the largest number of patients diagnosed worldwide with NUBPL complex I (C10). Patients were diagnosed using whole exome Sequencing (WES) and all were found to be compound heterozygous for a NUBP1 (OMIM 603525) splicing mutation (c.827-27C>T) that is common in the population (<0.1% frequency), plus a novel non-synonymous or splicing mutation (in-frame) as follows: c.2151T>G (p.I711V) in families 1 (cases 1 and 2) and 6 (case 5); c.655+4G>insA (family 2 panel 3); and c.5457T>G (p.I1822V) in family 4 case 4. We note that in 3 of 6 families, the grand or great-grand family has a de novo case. We performed whole genome sequencing (WGS) in 5 of 8 families, which revealed pathogenic variants in other genes including those associated with autosomal recessive cases, and congenital or early onset disorders. We have observed no clear genotype-phenotype correlation between NUBPL 1 and 2 mutations and report a novel c.166G>A mutation associated with a more severe cerebellar and pontine phenotype.

Case 5 (Family 4)

CLINICAL HISTORY: Case 5 is a 19-year-old young man who was healthy until age 18 months. Following an acute episode he became spastic, wheelchair bound and severely dysarthric. He had an elevated CSF lactate and was diagnosed with a Leigh-like mitochondrial disorder. His CSF was tested in the "mild mental retardation range". His brain MRI is shown in Figure 4. A repeat brain MRI (image not shown) at age 14 years showed severe atrophy and abnormal signal in the pons and cerebellum, with normal cerebellum volume.

MOLECULAR DIAGNOSIS: Clinical exome sequencing was ordered by the University of Texas Medical School and he was found to be compound heterozygote: c.827-27C>T and c.166G>A (in cis) from his mother and c.3117T>G (p.I1039P) from his father, the same missense mutation found in Family 1.

Figure 4: Brain MRI image case 5

CASE 5 FINDINGS: Shows cerebellar vermiform hypoplasia with severe atrophy of the cerebellum and pons.

CLINICAL SUMMARY OF 5 CASES WITH NUBPL CI DEFICIENCY

FUNCTIONAL ANALYSIS OF MISSENSE NUBPL MUTATIONS

CONCLUSIONS

1. Clinical presentation in these 5 cases is consistent with previously reported NUBPL Complex I deficiency cases that had pathogenic NUBPL findings (Calvo et al., 2010; Kevelam et al., 2013; Tenisch et al., 2012). Branch point mutation c.815-27C> T (1% frequency, European ancestry) is seen in all families, possibly due to founder haplotype.

2. Missense variant c.166G>A (p.G55E) is present in cis with c.815-27C>T in all previous/current cases, except newly reported cases 1 and 4, and its contribution to the disease remains uncertain (Tucker et al., 2012).

3. Mutant NUBP1 protein is non-functional in a yeast model for ODLP2 (human LSAD). No effect was found for M180B (human V182A), but experiments in a mammalian model may be informative. We also note that Case 4 may have a milder version of the disease (see Figure 3, brain MRI was normal).

Mitochondrial clinical trial may have resulted in clinical improvements.

REFERENCES:

2. Pedigree of families: 3. "c.2151T>G (p.I711V) in families 1 (cases 1 and 2) and 6 (case 5); c.655+4G>insA (family 2 panel 3); and c.5457T>G (p.I1822V) in family 4 case 4.

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See also ASHD 2016 poster 1403/F: NUBP1-linked to late-onset movement disorders

CLINICAL FINDINGS IN PATIENTS WITH NUBPL DISEASE

Case 1 and 2 (Family 1)

CLINICAL HISTORY: Case 1 is a 16-year-old girl with ataxia, developmental delay, and cerebellar abnormalities. She developed in-utero in 30 weeks and progressive cerebellar atrophy. Prior brain MRI at 6 months of age revealed cerebellar atrophy. A cerebellar biopsy at age 1 year showed enlarged Purkinje cells, non diagnostic. Follow-up brain MRIs show progressive cerebellar abnormalities (Figure 1). ECG analysis on a related muscle biopsy sample tested normal for complex IV although an elevated citrate synthase level was noted. Her sister, Case 2, is a 5-year-old girl with similar clinical features (ataxia, developmental delay, and cerebellar abnormalities) developing at age 3 months. Her brain MRI at age 7 months showed similar cerebellar abnormalities (Figure 1).

MOLECULAR DIAGNOSIS: Diagnostic exome sequencing confirmed compound heterozygosity of two alterations in the NUBP1 gene: c.815-27C>T, and c.3117T>G (p.I1039P). In both affected siblings. Variant c.815-27C>T (father) is a branch site splicing mutation that was previously reported in Complex I deficiency patients (Calvo et al., 2010; Kevelam et al., 2013) and it is present at 1% frequency in European ancestry subjects (Luk et al., 2016). Both patients are currently on a mitochondrial cocktail therapy (Coenzyme Q10, carnitine, alpha lipoic acid, and vitamins E, C, and B complex) and this has resulted in improvement, particularly in the younger sibling.

Case 3 and 4 (Family 2)

CLINICAL HISTORY: Case 3 is a 4-year-old boy presenting with ataxia, developmental delay, and cerebellar abnormalities. Regression in motor skills were noted at age 13-14 months. She lost ability to stand without support and became clumsy. Hypotonia and speech articulation difficulties were also noted, but she has normal cognition. ECG analysis (skin fibroblasts) was essentially normal. Her brain MRIs are shown in Figure 1. Neuroimaging (image not shown) also showed stable largely symmetric punctate areas of signal abnormality and restricted diffusion of the genu of the corpus callosum. Her spectroscopy revealed a lactate peak within the cerebellum.

Figure 1: Brain MRI images for cases 1 and 2.

MOLECULAR DIAGNOSIS: She was initially diagnosed with Infantile Neuronal Axonal Dystrophy (INAD, OMIM 256690) because of her MRI findings; however, genetic testing for PLAD1 mutations was negative. Clinical exome sequencing was ordered by the Cleveland Clinic and she was found to be a compound heterozygote: c.815- 27C>T and c.166G>A (in cis) from her mother and c.655+4G>insA from her father, a combination previously reported in 1 case from the US (Koong et al., 2015).

We were unable to establish if the two families are related (Kevelam et al. family did not wish to participate in further research at this time). She is currently on a mitochondrial cocktail. Her fibroblasts showed a clinical response to EPI-743 (Eidson Pharmaceuticals).

Case 4 (Family 3)

CLINICAL HISTORY: Case 4 is a 4-year-old boy with global developmental delay, abnormal movements, nystagmus and lactic acidaemia. After birth, he was noted to have generalized hypotonia, clonus, a weak cry, and poor feeding. He is non-verbal and has mild dysmorphic features in his brain MRI as shown in Figure 3.

Figure 3: Brain MRI image for case 4, age 12 months.

MOLECULAR DIAGNOSIS: Clinical exome sequencing was ordered by the Baylor College of Medicine and he was found to be a compound heterozygote: c.827-27C>T from his mother and c.5457T>G (p.I1822V) from his father. Array CGH (CMA-HPK/NP: 21.3) also revealed a 2p16.3 microdeletion (see Girirajan et al.), which may be contributing to the patient’s symptoms.