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## Report of four novel variants in *ASNS* causing asparagine synthetase deficiency and review of literature

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Asparagine synthetase deficiency (ASNSD, MIM 615574) is a recently delineated rare neurometabolic disorder caused by mutations in *ASNS* (MIM 108370) (Ruzzo et al., 2013). It is characterized by congenital and/or postnatal progressive microcephaly, global developmental delay, seizures, growth retardation, cerebral atrophy and simplified gyral pattern. We hereby describe four novel variations ascertained by exome sequencing in three individuals from three unrelated families (Figure S1). We summarize the genotype and phenotype of 22 individuals from 14 families with 16 mutations in *ASNS* (Alfadhel et al., 2015, Ben-Salem et al., 2015, Gataullina et al., 2016, Gupta et al., 2017, Palmer et al., 2015, Ruzzo et al., 2013, Seidahmed et al., 2016, Sun et al., 2016, Yamamoto et al., 2017). Informed consents from the families were obtained for the study. The study was approved by the Institutional Ethics Committee. Detailed clinical information, exome sequencing methodology and analysis are provided as supplementary information.

All three individuals showed congenital microcephaly, progressive post-natal microcephaly and spasticity whereas seizures were noted only in patients 1 and 3 (Supplementary table 1). Magnetic resonance imaging of brain revealed simplified gyral pattern, cerebral atrophy and ponto-cerebellar hypoplasia in all (Figure 1). WES analysis in patient 1, revealed a novel homozygous missense variant, c.1211G>A [p.(Arg404His)] in exon 10 of *ASNS* gene. Analysis of patient 2 disclosed novel compound heterozygous variants, c.224A>G [p.(Asn75Ser)] in exon 3 and c.413A>C [p.(Asp138Ala)] in exon 4 of *ASNS* gene. In patient 3, a novel homozygous variant, c.1649G>A [p.(Arg550His)] was observed. These variants are not present in either homozygous or heterozygous states in databases of normal population.

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Disclosures

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These variants are also not observed in our in-house database of 357 families. These variants occur at a highly conserved region and predicted as damaging to ASNS protein function. Further analysis by *in silico* or any other functional assay could not be performed for these variants.

A review of 25 individuals including our patients revealed significant global developmental delay (22/23) in most individuals. Congenital microcephaly and simplified gyral pattern on brain imaging was evident in a significant proportion (19/25) of individuals. Other frequent brain imaging findings were ponto-cerebellar hypoplasia/reduced pons size (16/25) and progressive cerebral atrophy seen in all the individuals. Spastic quadraparesis (19/24) and seizures (18/25) are the other common findings in individuals with ASNSD (Supplementary table 1). High degree of inbreeding observed in the local population is the possible cause of homozygous variants in non-consanguineous families in our study.

We herein emphasize the utility of whole exome sequencing as an important tool in delineating the genetic etiology in individuals with rare and clinically heterogeneous phenotypes. We also add four novel mutations, thus expanding the *ASNS* mutation spectrum. The presence of variable degree of congenital microcephaly underscores that this condition should be considered among the various genetic disorders presenting with primary microcephaly.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

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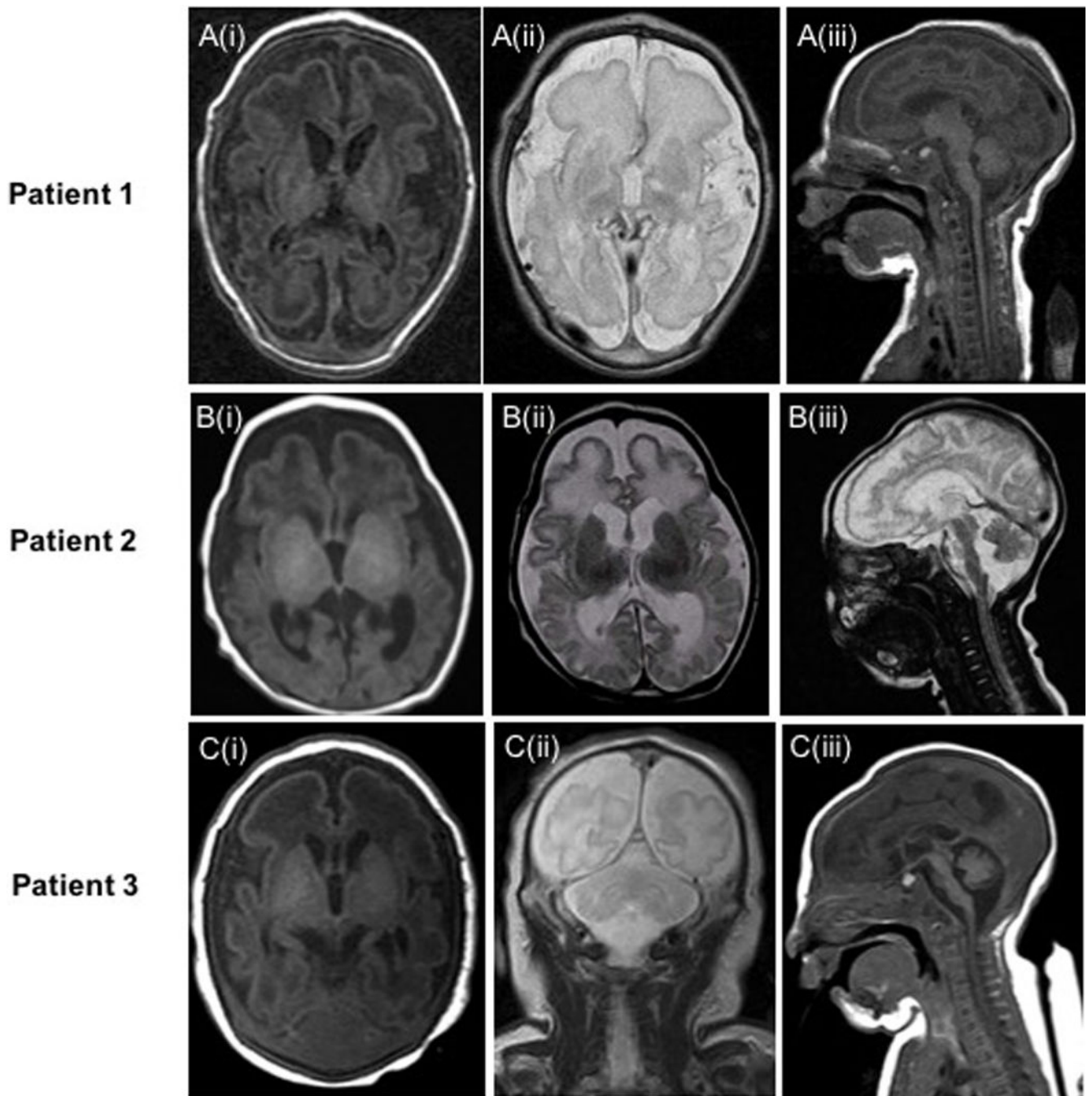
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**Figure 1:**

(A) Brain magnetic resonance imaging (MRI) of patient 1 taken on day 2 of life. Axial T1 (i), axial T2 (ii) and sagittal T1 (iii) weighted images show microcephaly with overlapping of sutures, simplified gyral pattern, delayed myelination, reduced volume of the pons and mild cerebral atrophy are observed. (B) Brain MRI images of patient 2 taken at 1 month of age. Axial T1 (i), axial T2 (ii) and sagittal T2 (iii) weighed images show microcephaly with overlapping sutures, mild delayed myelination, reduced size of the pons and cerebral atrophy are observed. (C) Brain MRI images of patient 3 on day 2 of life. Axial T1 (i), coronal T2

(ii) and sagittal T1 (iii) weighted images show microcephaly with overlapping of sutures, simplified gyral pattern, reduced volume of the pons and cerebral atrophy are observed.

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