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Pontocerebellar Hypoplasia Type 9: A New Case with a Novel Mutation and Review of Literature

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Abstract

Pontocerebellar hypoplasia type 9 (PCH-9) is a very rare autosomal recessive neurodegenerative disorder. Affected infants present early with severe developmental delay, spasticity, with the unique magnetic resonance imaging picture of thin corpus callosum, atrophied pons, and cerebellum. It is caused by loss of function mutations in the *AMPD2* gene, encoding for the adenosine monophosphate deaminase enzyme-paralog 2. This gene is expressed in different somatic tissues with high level of expression in cerebellum and its encoded enzyme catalyzes a critical step in *de novo* biosynthesis of purines and its deficiency in the developing neurons severely affects neuronal differentiation and cell viability. We clinically evaluated an Emirati patient presented with severe developmental and growth delay, as well as corpus callosum agenesis and atrophy of brainstem and cerebellum. We performed exome sequencing, Sanger sequencing, and segregation analysis to identify the genetic cause of the phenotype, followed by *in silico* and *in vitro* analysis. We identified the novel variant (NM_004037.9:c.1471G > A) in *AMPD2* gene leading to a single amino acid substitution (p.Gly491Arg) in adenosine monophosphate deaminase-2 enzyme. This variant is predicted to be pathogenic using several *in silico* tools, and resulted in a decrease in the enzyme function in the patient's polymorphonuclear cells by 82% (95% confidence interval: 73.3–91.7%, $p = 0.029$) compared with the control. This data establishes that the affected child is affected by PCH-9. Furthermore, we review all reported cases in literature to summarize the main clinical features of this rare disease.

Keywords
- pontocerebellar hypoplasia
- corpus callosum agenesis
- adenosine monophosphate deaminase 2

Introduction

Pontocerebellar hypoplasia (PCH) syndromes are a group of inherited neurodegenerative disorders that involve mainly the cerebellum and pons, but may progress to other regions of the brain parenchyma. As it is characterized by an early onset in the prenatal period, it was previously misinterpreted as hypoplasia, but Namavar et al have provided evidence of a segmental degeneration of the cerebellar cortex neurons and of the ventral nuclei and transverse

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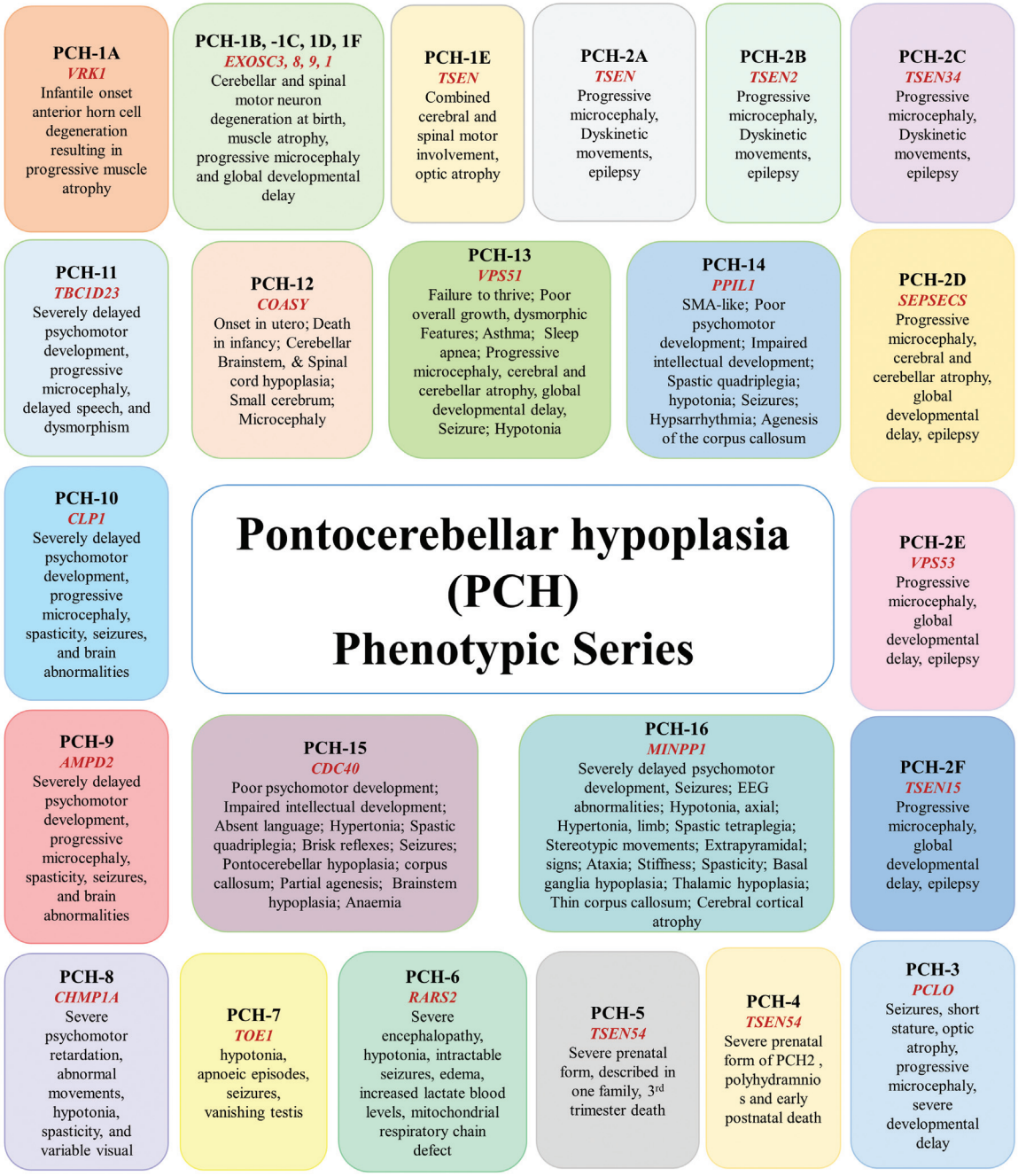

Fig. 1 A schematic summarizing pontocerebellar hypoplasia syndrome phenotypic series described so far in OMIM (PS607596), with the causative gene defect involved and key clinical features.

fibers of the pons.[1,2] Many subtypes of PCH have been described according to the clinical presentation and the genetic causes of the disease.[1] Currently known PCH syndromes and their underlying genetic heterogeneity are summarized in ►**Fig. 1** (MIM Phenotypic Series—PS607596).

Akizu et al[2] described a new PCH subtype in eight patients from five consanguineous Middle-Eastern families, designating as PCH-type 9 (MIM: 615809). This type has been shown to be caused by homozygous mutations in *AMPD2* gene that encodes the enzyme adenosine monophosphate deaminase (AMPD) 2, a key enzyme in *de novo* purine biosynthesis.[2] AMPD catalyzes the deamination of adenosine monophosphate (AMP) to inositol monophosphate (IMP). Three forms of the enzyme are expressed in various mammalian tissues: AMPD 1 to 3, being AMPD2 the dominant paralog in the brain, highly expressed in the cerebellum.[2] *AMPD2* is also expressed in the pituitary gland, spleen, kidneys, intestine, among other tissues, and is overexpressed notably in blood polymorphonuclear cells.[3–5]

Akizu et al[2] also provided evidence that AMPD2 activity is critical during neurogenesis and loss of function mutations renders the neuronal progenitor cells derived from patients-

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specific induced pluripotent stem cells vulnerable and exquisitely sensitive to adenosine resulting in neuronal cell growth restriction and apoptosis. Moreover, Guanosine-5'-triphosphate (GTP) deficiency in cytoplasm as a result of IMP absence inhibits mRNA translation initiation and impairs protein synthesis that indicate the pathogenic mechanism for neurodegeneration.[2]

In this report, we describe the clinical presentation and elucidate the pathogenicity of a novel missense mutation (NM_004037.9:c.1471G > A; p.Gly491Arg) in *AMPD2* detected by exome sequencing in a 3 years old Emirati child with corpus callosum agenesis, cerebellar and brainstem atrophy, and severe developmental and growth delay, confirming PCH-9 diagnosis. So far, several causative mutations have been reported with PCH-9, but our patient is the first to be reported from the Emirati population (►**Table 1**).

Case Report

This study has been approved by Al-Ain Medical Human Research Ethics Committee according to the national regulations (Approval numbers 10/09 and ERH-2015–3241 15–115) (**Supplementary Data File**, available in the online version only). The affected child in this report is the third of four children to a consanguineous Emirati couple. At the time of examination, the patient was 3 years old. The pregnancy period was complicated by gestational diabetes, and antenatal scan showed ventriculomegaly with absent corpus callosum and questionable cerebellar hypoplasia. His birth was at term by spontaneous vaginal delivery with growth parameters: weight 2,990 g (z-score= −0.94 standard deviation [SD]), length 48.5 cm (z-score= −0.56 SD), head circumference 32 cm (z score= −2 SD), and Appearance, Pulse, Grimace, Activity, Respiration (APGAR) scores were 9 and 10 at 1 and 5 minutes, respectively. He required only initial clearing airway and stimulation. His neurological examination at birth revealed normal head and fontanelle with no apparent dysmorphic features. Tetraplegic hypertonia and spasticity with fisting were noted. Eye examination showed convergent squint with hypoplastic discs. His brain magnetic resonance imaging (MRI) at 2 days of age showed agenesis of the corpus callosum and atrophy of the pons and cerebellum (►**Fig. 2A**). Examination at 3 years showed a height of 85 cm (z-score= −3.024 SD), weight of 9.5 kg (z-score= −4.376 SD), and weight for height ratio of 11.12 (z= −2.9 SD). He had microcephaly (head circumference is 46 cm, z= −2.4 SD), with bitemporal narrowing, hypotonic facies, open mouth, central hypotonia, peripheral hypertonia, and generalized hyperreflexia. He was not fixing or following light or objects. He had limitation in elbow extension, knee extension, and ankle dorsiflexion. There were surgical scars of tendons released on the ankle joints and right hip dislocation surgery. Depigmented areas on the right side of his face just below the right eye and a smaller area near the left corner of the mouth were noted and diagnosed as vitiligo (►**Fig. 2B**). His developmental milestones were as follows: gross/fine motor: he could not roll, had momentarily head control for few seconds, was not using his hands, his limbs were stiff with fisting hands. Social/language: he responded to sounds when calling his name, he was able to smile, laugh, and make sounds but was unable to babble or talk. He suffered from excessive drooling and constipation. His parents recently noticed him having abnormal movements suggestive of seizures just before/as he is falling to sleep with brief eye deviation and raising arms for few seconds only. Electroencephalography showed very frequent spike and slow wave discharges from left frontocentral region. The patient cannot feed himself so he is fed by G tube.

Apart from a maternal first cousin with a history of ocular coloboma and developmental delay, family history is otherwise insignificant. Several investigations were done including a microarray that showed a 509kb duplication at 17p13.2; his father has the same duplication and he is healthy. In addition, loss of heterozygosity of the entire chromosome 22 was also detected that was also detected in father and a healthy sibling. No imprinting disorder has been mapped to chromosome 22. Regarding his stunted growth, serum insulin-like growth factor-1 was 266 ng/dL (normal range for his age: 95 confidence intervals [CI]: 88.3–149.1 ng/dL).[6]

Using whole exome sequencing, we identified high-quality rare missense, in-frame indels, and loss-of-function (frameshift, stop, stop-less, start-less, splicing) variants (►**Fig. 3A**; **Supplementary Date File**, available in the online version only). Then we looked for variants falling in genes known to cause developmental disorders (►**Supplementary Table S1**, available in the online version only). Out of these, we prioritized a homozygous variant (GRCh37; Chr1:110171328) in *AMPD2* (NM_004037.9):c.1471G > A; p.Gly491Arg. This variant segregated with the disease in all family members as confirmed by Sanger sequencing (►**Fig. 3B, C**). It has not been reported in the Genome Aggregation Database (gnomAD), a reference database encompassing the sequencing data of more than 140,000 individuals.[7] Additionally, *in silico* prediction tools reported this mutation as a disease causing in MutationTaster, deleterious (score −7.82) in PROVEAN, damaging (score 0.00) in SIFT, probably damaging (score 1.0—sensitivity 0.0, specificity 1.00) in POLYPHEN2, and has high functional impact in Mutation Assessor (FI score 3.88). The position Gly491 in *AMPD2* is highly conserved among species (MSA height is 138). The patient phenotype highly overlaps with the disease PCH-9 caused by *AMPD2* mutations, noting that no other variant detected in other PCH syndromes associated genes (►**Fig. 1**).

To further establish the pathogenicity of the mutation, we tested the enzyme activity in the patient's leukocytes using AMPD2 dependent assay (►**Fig. 4A**; **Supplementary Date File**, available in the online version only). As AMPD2 is expressed in immune cells, we isolated peripheral blood leukocytes from fresh blood samples from the patient and his asymptomatic mother, a heterozygous carrier of Gly491Arg mutation, as a control. The end point absorbance at 340 nm was around 40% less in the patient sample compared with the control (95% CI: 29–60%, $p = 0.006$). The enzyme activity calibrated by the NADH+H+(nicotinamide adenine dinucleotide (NAD) + hydrogen (H)) absorbance and cell count

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Table 1 Clinical presentation of patients reported with *AMPD2* mutations in PCH-9

	Akizu et al, 2013[2]	Akizu et al, 2013[2]	Akizu et al, 2013[2]	Akizu et al, 2013[2]	Akizu et al, 2013[2]	Farwell et al, 2015[11]	Marsh et al, 2015[12]	Marsh et al, 2017[13]	Accogli et al, 2017[14]	Kortüm et al, 2018[16]	Kortüm et al, 2018[16]	Kortüm et al, 2018[16]	Kortüm et al, 2018[16]	Kortüm et al, 2018[16]	Kortüm et al, 2018[16]	Karaca et al, 2018-[17]	Hengel et al, 2020[15]	Current study
General																		
Ethnicity	Egyptian	Saudi	Egyptian	Saudi	Turkish	Middle Eastern	Middle Eastern	Middle Eastern	Middle Eastern	Kurdish	Northern European	Middle European	Indian	Sri Lankan	Afghan	N/A	Arab Israel/ Palestinian	Emirati
Number of patients	1	1	1	1	1	1	5	1	3	1	2	2	1	1	1	1	3	1
Pontocerebellar hypoplasia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Microcephaly	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Global developmental delay	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Growth delay	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+	+	+	+	+	−	+	+	+
Age/age at death	N/A	N/A	N/A	N/A	N/A	Alive at 2 yr	2 Alive at 22 &17 yr, 3 Died at 9, 11 & 22m	Died at 26mo	Alive at 9, 8 & 7y	Died at 13mo	Alive at 4yr & 17mo	Alive at 6yr & 3mo	Alive at 4yr	Alive at 6yr	Alive 11mo	N/A	N/A	Alive at 3.5 yr
Cause of death							Sepsis/ pneumonia	Pneumonia		Respiratory failure								
Dysmorphic features																		
Bitemporal narrowing	N/A	N/A	N/A	N/A	N/A	N/A	+	−	−	N/A	N/A	N/A	N/A	N/A	N/A	+	N/A	+
Sloping forehead	N/A	N/A	N/A	N/A	N/A	N/A	−	N/A	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+
Hypotonic facies	N/A	N/A	N/A	N/A	N/A	N/A	+	−	−	N/A	N/A	N/A	N/A	N/A	N/A	+	N/A	+
Macroglossia	N/A	N/A	N/A	N/A	N/A	N/A	+	−	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+	N/A	+
Downslanting palpebral fissures	N/A	N/A	N/A	N/A	N/A	N/A	+	−	−	N/A	N/A	N/A	N/A	N/A	N/A	+	N/A	−
Bilateral epicanthus	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+	+	+	N/A	N/A	N/A	+	N/A	+
Broad nasal bridge	N/A	N/A	N/A	N/A	N/A	N/A	+	−	−	+	N/A	+	N/A	N/A	N/A	+	N/A	−
Abnormal ears	N/A	N/A	N/A	N/A	N/A	N/A	+	−	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	−
Teeth abnormalities	N/A	N/A	N/A	N/A	N/A	N/A	N/A		+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+
Joint contractures	+	+	+	+	+	N/A	+	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+	N/A	+
Mandibular hypoplasia	N/A	N/A	N/A	N/A	N/A	N/A	−	N/A	+	N/A	N/A	N/A	N/A	N/A	N/A	−	N/A	+
Clinodactyly	N/A	N/A	N/A	N/A	N/A	N/A	−	N/A	+	N/A	N/A	N/A	N/A	N/A	N/A	−	N/A	−
Neurological features																		
Seizures	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	N/A	+
Spasticity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N/A	+
Extrapyramidal movements	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	−	N/A	N/A	N/A	N/A	N/A	+	N/A	+
Impaired swallowing	+	+	+	+	+	N/A	+	+	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+
Axonal neuropathy	N/A	N/A	N/A	N/A	N/A	N/A	+	−	−	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	−−

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Table 1 (*Continued*)

	Akizu et al, 2013[2]	Akizu et al. 2013[2]	Akizu et al, 2013[2]	Akizu et al, 2013[2]	Farwell et al, 2015[11]	Marsh et al, 2015[12]	Marsh et al, 2017[13]	Accogli et al, 2017[14]	Kortüm et al, 2018[16]	Kortüm et al, 2018[16]	Kortüm et al, 2018[16]	Kortüm et al, 2018[16]	Kortüm et al, 2018[16]	Karaca et al, 2018-17	Hengel et al,[15] 2020	Current study
Optic atrophy/ cortical visual impairment	+	+	+	+	N/A	+	+	+	+	N/A	N/A	N/A	N/A	+	N/A	+
Skin changes																
Vitiligo	N/A	N/A	N/A	N/A	N/A	–	–	–	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+
Pigmented nevi	N/A	N/A	N/A	N/A	N/A	+	–	–	N/A	N/A	N/A	N/A	N/A	N/A	N/A	–
Trophic skin	N/A	N/A	N/A	N/A	N/A	+	–	–	N/A	N/A	N/A	N/A	N/A	N/A	N/A	–
Reported causative variant	p. Glu778Asp	p.Tyr349*	p. Asp793Tyr	p. Arg674His	pArg 378Pro/p. N411S	p.Tyr752*	p. Arg251Trp	p.Arg1 65fs*21	p. Asp 480Glyfs *13	p.Arg378 Pro/p. Asn411Ser	p.Glu228*/ p. Arg843His	p. Arg378Trp	p. Glu550lys	p. Gly710Arg	p. Ser 805 Arg	p. Gly49 1Arg

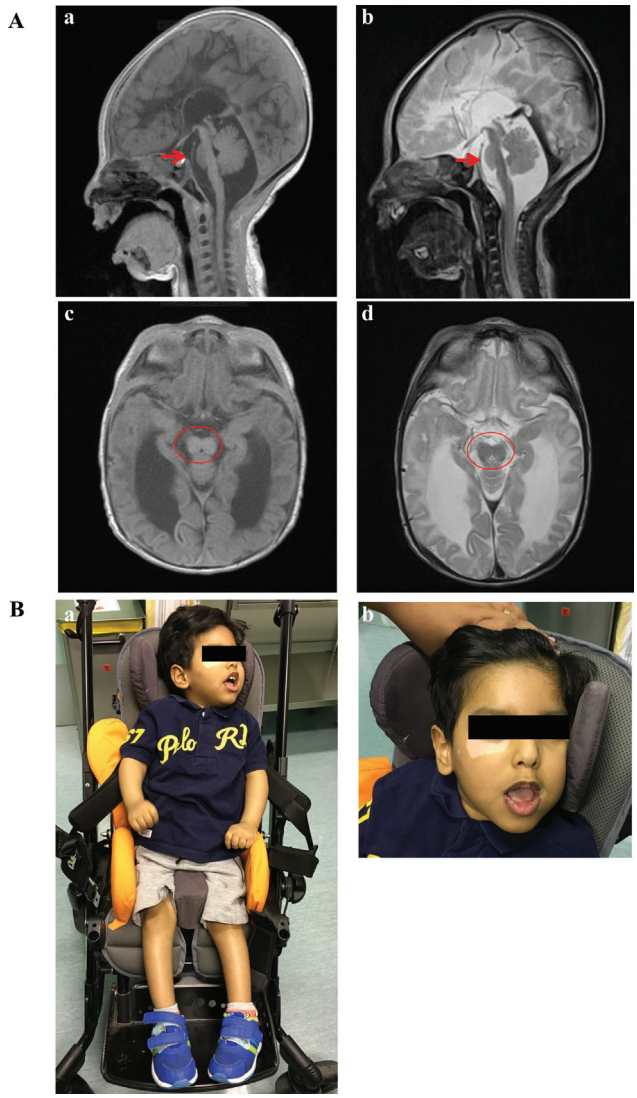

Fig. 2 Clinical presentation of patient. (**A**) Brain magnetic resonance imaging of the proband at 1 day old. Midline sagittal (**a, b**) and axial (**c, d**) images showing hypoplasia/atrophy of the brain stem and cerebellar hemispheres (**a, b**, indicated by the red arrows), note the "figure of 8" appearance in the axial images (**c, d**; encircled in red). The corpus callosum is not visualized, consistent with complete agenesis. (**B**) Patient photo showing some of the clinical phenotype of our patient. Note the spastic posture (**a**), bitemporal narrowing and vitiligo (**b**).

(mean ± SD) was 0.002 ± 0.0008nmol/hr/10^6 cells in the patient sample, significantly lower than in the control 0.01 ± 0.0003 nmol/hr/106 cells. A significant ~82% decrease in enzymatic activity was detected in patient's versus control (mean ± SD= 0.009 nmol/hr/106 cells; 95% CI: 0.008–0.01nmol/hr/106 cells (73.3–91.7%; $p = 0.029$) (►**Fig. 4B**).

Discussion

Using exome sequencing, segregation analysis, and *in vitro* functional analysis, we identified a novel pathogenic mutation in *AMPD2*, causing PCH-9. This mutation was found to significantly decrease the enzyme activity by 82% in the patient sample compared with his mother. Therefore, we confirmed the pathogenicity of the mutation and the

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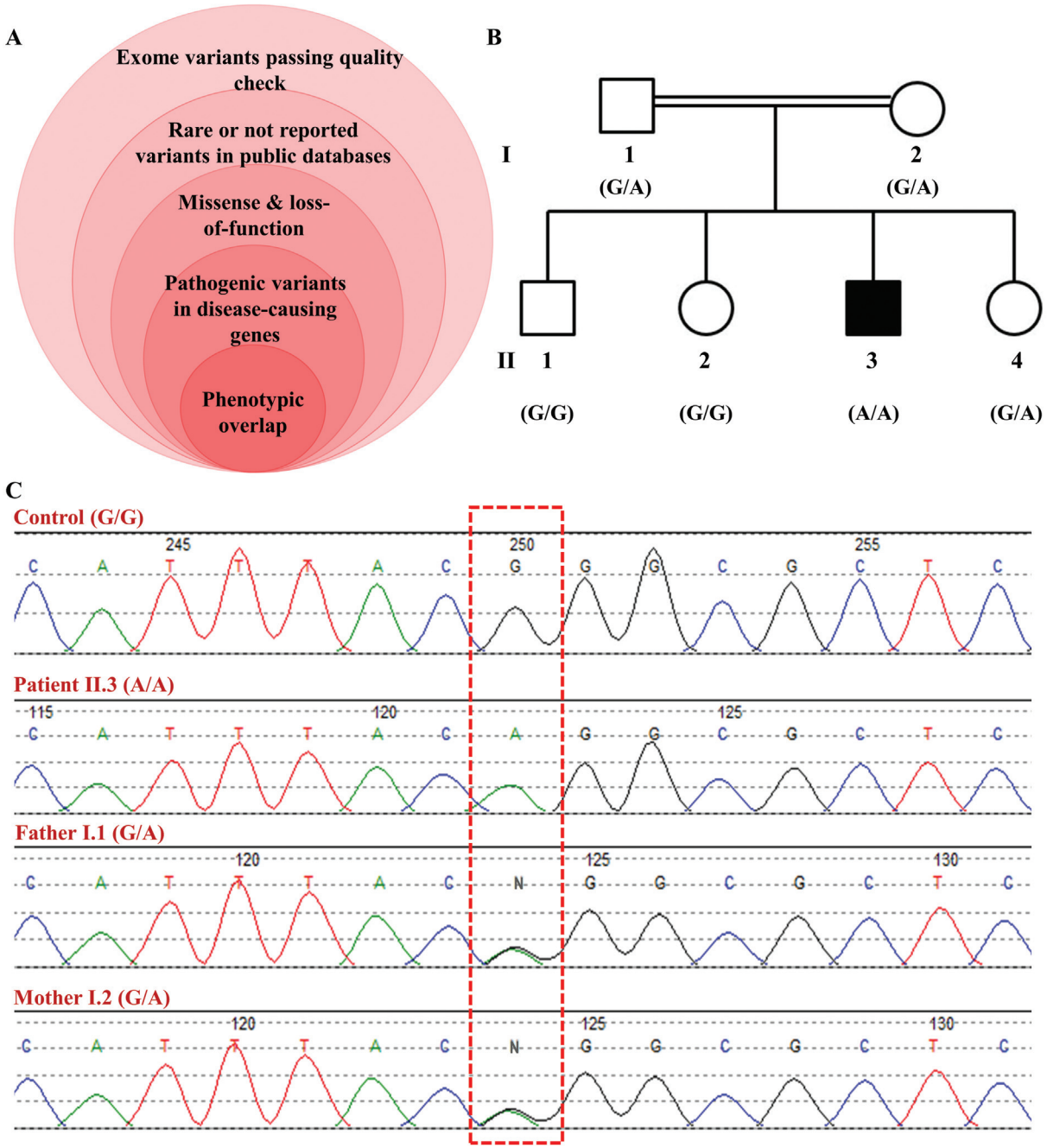

Fig. 3 *AMPD2* novel variant detected is the causative variant. (**A**) A summary of exome sequencing analysis and variant filtering results. (**B**) The family pedigree of the patient. Both parents and a healthy sibling are heterozygous for the mutation. Our proband is the only family member with a homozygous mutated genotype (A/A) and the only symptomatic. (**C**) Sequencing chromatogram of the detected variant region in AMPD2 gene. The genotype of the proband is A/A and for his parents G/A as compared with the wild type sequence of a healthy control (G/G).

diagnosis of PCH-9 in the proband, and document the first case in the Emirati population.

AMDP2 is a highly conserved enzyme in all eukaryotes. AMD1 is the enzyme functional ortholog in *Saccharomyces cerevisiae* and has similarity of 69% (623 AA) to the human AMPD2 enzyme.[8] AMP deaminase catalyzes a critical step in purine *de novo* biosynthesis.[9] It is also necessary for guanine nucleotide biosynthesis and protein synthesis. Its expression is crucial during neurogenesis and neuronal differentiation.[2] Pathogenic mutations in *AMPD2* are associated with two syndromes: spastic paraplegia 63 (MIM: 615686) and PCH-9 (MIM: 615809). Spastic paraplegia 63 has been described by Novarino et al[10] in two siblings from a consanguineous family with spastic paraplegia and normal cognition. PCH-9 is a severe neurodegenerative disorder with a prenatal onset. All patients present in early infancy with progressive spasticity, microcephaly, and global developmental delay. For such patients, the treatment is mainly of manifestations including early intervention program, special education programs, and vocational training addressing developmental disabilities programs such as speech/language, physical, occupational, and feeding therapies. Neurological evaluation

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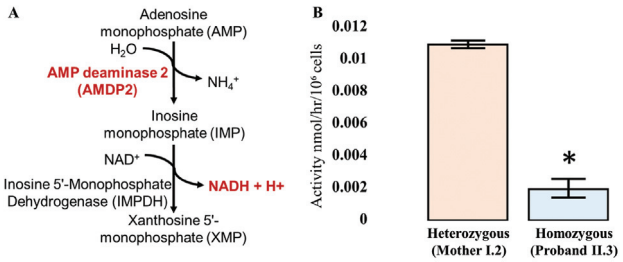

Fig. 4 The impact of Gly491Arg on AMPD2 enzymatic activity. (**A**) The principle of the AMPD2 enzymatic activity assay. This enzymatic assay is based on a reaction involving AMP deaminase enzyme (AMPD) and inosine monophosphate dehydrogenase (IMPDH) enzymes. In the presence of AMP, AMPD enzyme catalyzes the formation of IMP. Then IMP is immediately oxidized by a highly active IMPDH in the presence of NAD with simultaneous formation of $NADH^+H^+$ directly monitored spectrophotometrically at 340 nm. (**B**) Enzyme activity in patient's peripheral blood mononuclear cells (PBMCs) is significantly reduced compared with healthy control in nmol/hr/10^6cells. (*: independent *t*-test *p*-value = 0.029).

and treatment provide personalized medications, especially for plasticity and seizures, if any.

Several disease-causing variants have been reported so far mainly in patients from Middle-Eastern origins. The first reported patients were from five families in a study that recruited 30 families with PCH with undefined genetic causes.[2] Using Whole Exome Sequencing (WES), they detected five mutations in *AMPD2* in five probands and identified *AMPD2* as a causative gene for a new subtype—PCH-9.[2] Farwell et al[11] detected two pathogenic variants in *AMPD2* in a study that recruited 500 families with undiagnosed genetic disorders and reported in a patient with compound heterozygous mutations and described it as *AMPD2*-related brainstem disorder. The first detailed description of the PCH-9 phenotype was published by Marsh et al.[12] They recruited a consanguineous Middle-Eastern family with five affected siblings three of them died before reaching their third year, mostly of sepsis or pneumonia; the other two were followed to the age of 17 and 22 years at the time of reporting. All five siblings were born with normal head circumference and presented in their first year with progressive microcephaly, spasticity, and global developmental delay. The distinctive dysmorphic features reported in these patients, summarized in ►**Table 1**, were not detected in the patient described in a following report by the same authors, nor in our proband described in this report. Another feature that we did not detect in our patient was the axonal neuropathy. Marsh et al[12] performed nerve conduction studies at the age of 10 and 20 years in the surviving siblings and found signs consistent with axonal neuropathy. Our patient was approaching his fourth year, and no signs of axonal neuropathy were recorded so far. Marsh et al[13] reported another pathogenic variant p.Arg251Trp causing PCH-9 in another Middle-Eastern consanguineous family. The infant who was diagnosed at 1 month of age with cerebral palsy had progressive microcephaly and spasticity. His spasticity deteriorated and due to his feeding difficulties percutaneous gastrostomy was done and palliative care was provided, but the patient unfortunately died at 26 months of age due to pneumonia complications. Accogli et al[14] also reported three affected siblings from a consanguineous Middle-Eastern family with the typical MRI features and dysmorphism. In addition, whole-exome sequencing study of 83 Arab families revealed a novel mutation in *AMPD2* p.Gln166Argfs*21 in three patients exhibiting severe psychomotor retardation, PCH, and microcephaly.[15] Likewise, herein we present another patient with pontocerebellar hypoplasia caused by a loss-of-function variant in *AMPD2* gene.

Knowledge of the effect of AMPD2 deficiency in the various tissues will help to better describe the phenotype of the disease and consequently the clinical diagnosis and management in the current and future cases.

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Conflict of Interest
None declared.

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