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CASE REPORT

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A pigmentary manifestation associated with *PPP2R5D*-related neurodevelopmental disorder: a case report and review of literature

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Abstract

Background The protein phosphatase 2 (PP2A) is one of the major serine/threonine phosphatases in humans. The most frequently reported pathogenic PP2A variants have been identified in *PPP2R5D*, encoding the regulatory subunit B′ delta, and are known to cause intellectual developmental disorder autosomal dominant 35 (MRD35).

Case presentation Herein, we describe a unique case of a patient with a heterozygous pathogenic variant, c.592G>A/p.(Glu198Lys) in the *PPP2R5D* gene which was associated with hyperpigmented skin lesions arising from increased melanin production, known as Café-au-lait macules (CALMs). To our knowledge, this is the first reported case of a *PPP2R5D*-related neurodevelopmental disorder associated with CALMs.

Conclusions Our findings suggest that the documentation and reporting of CALMs when associated with one or more physical and/or neurodevelopmental findings are of utmost importance as they could be indicative of an underreported phenotype and may extend the phenotypic spectrum of MRD35.

Keywords *PPP2R5D*, Neurodevelopmental disorder, PP2A, Intellectual disability, Café-au-lait macules, MRD35, Ras/MAPK, Case report

Background

The identification of de novo pathogenic variants in genes encoding subunits of the protein phosphatase 2 (PP2A) has often been linked to neurodevelopmental disorders (Lenaerts et al. 2021; Houge et al. 2015; Loveday et al. 2015; Reynhout et al. 2019a). PP2A is one of the major serine/threonine phosphatases in humans and has been shown to balance most kinase-regulated signaling pathways, thus regulating cell metabolism, cell cycle, cell proliferation, cell mobility, as well as apoptosis (Seshacharyulu et al. 2013; Alberts et al. 1993; Glenn and Eckhart 1993). PP2A is structurally complex as it forms over 100 different holoenzymes with various tissue and substrate specificity (Yu et al. 2014; Lechward et al. 2001; Biswas et al. 2020). Trimeric PP2A holoenzymes are composed of a scaffold (PP2A-A), a catalytic (PP2A-C) and a regulatory subunit (PP2A-B) (Lenaerts et al. 2021;

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Kamibayashi et al. 1994). The latter is thought to be the master regulator of PP2A holoenzymes; it is encoded by 15 different genes including 26 distinct splice variants which determine substrate specificity (Seshacharyulu et al. 2013; Zolnierowicz et al. 1994).

The most frequently reported de novo pathogenic PP2A variants have been identified in *PPP2R5D*, encoding the regulatory subunit B' delta (B'56δ) (Lenaerts et al. 2021; Shang et al. 2016)**.** *PPP2R5D*-related neurodevelopmental disorder (NDD), also known as intellectual developmental disorder autosomal dominant 35 (MRD35) and Jordan's syndrome, is characterized by a broad phenotypic spectrum of mild to severe neurodevelopmental delay (Biswas et al. 2020). Despite a growing number of documented cases, *PPP2R5D*-related NDD has been linked to a rather limited mutational spectrum (Biswas et al. 2020). In fact, only 17 pathogenic variants have been identified until now (ClinVar [cited 2023]), 9 of which have been extensively documented within 30 cases (Table 1). The first four cases were identified in 2014 after sequencing of 1133 children with undiagnosed severe developmental disorders (Study DDD 2015). These four cases were later well-described along with seven additional cases (Houge et al. 2015). Since then, nine other peer-reviewed publications have reported and described an additional 23 cases for a total of 30 cases (Loveday et al. 2015; Shang et al. 2016; Yeung et al. 2017; Kim et al. 2020; Hetzelt et al. 2021; Madaan et al. 2022; Maines et al. 2021; Walker et al. 2021; Yan et al. 2021). Most cases present with global developmental delay, intellectual disability, hypotonia, and facial dysmorphism with overgrowth (Table 1). Surprisingly, although PP2A holoenzymes modulate the Ras-mitogen-activated protein kinase (Ras/MAPK) signaling pathway, which is associated with physiological and pathological skin pigmentation such as Café-au-lait macules (CALM) (Carvalho et al. 2021; Rzepka et al. 2016; Oiso et al. 2013; Picardo and Cardinali 2011; Zhang et al. 2016), no PP2A-*PPP2R5D* variants have ever been associated with such skin pigmentary abnormalities. However, two cases associated with CALMs have been described for variants affecting the PP2A-C, specifically in the catalytic Cα subunit gene (*PPP2CA*) (Reynhout et al. 2019b).

Herein, we report the first case of *PPP2R5D*-related NDD associated with CALMs in a young girl. This finding suggests that CALMs could be associated with MDR35 and may be indicative of an underreported clinical feature.

Case presentation

The patient is a 2-year-old female born prematurely at 33 weeks and 6 days. She presented with global developmental delay, delayed gross motor development, dysmorphic facial features, feeding difficulties, and muscular hypotonia. Her physical examination revealed macrocephaly, tall stature, and the presence of well-delineated CALMs were identified on the right ankle (1 cm × 1.5 cm) and the right flank of the abdomen (1 cm × 2 cm) (Fig. 1A, B). Electroencephalogram, comparative genomic hybridization, fragile-x testing, screening for congenital defect of glycosylation, and metabolic workup including plasma amino acids, acylcarnitine profile, very long-chain fatty acids, pipecolic acid, urine mucopolysaccharidosis, oligosaccharides, organic acid, and purines/pyrimidines were all without significance, thus, not in favor of chromosomal anomalies, fragile X syndrome, or an inborn error of metabolism. Brain magnetic resonance imaging (MRI) revealed non-specific findings such as mild prominence of the cerebral sulci and ventricles as well as mild-to-moderate white matter atrophy (Fig. 2).

Weaver, Sotos, Banayan-Ruvalcaba syndromes, and in particular, Neurofibromatosis (NF1/NF2) were the primary clinical suspicions due to the presence of CALMs, even though clinical criteria were not fully met. A targeted exome sequencing panel including copy number variants did not reveal any variants in genes associated with the initial suspected genetic disorders. However, the exome sequencing revealed a pathogenic *PPP2R5D* c.592G>A/p.(Glu198Lys) variant, confirming the genetic diagnosis of MRD35. Both parents were also tested, but results came back negative supporting the de novo occurrence of this variant. Due to the presence of CALMs, a re-analysis of genes covering the initial clinical suspicions was performed; however, the results were all negative (Table 2). Also, no family history of neurocutaneous disorders was documented or reported. Surveillance and management of patient, more specifically, monitoring for seizures, vision issues, developmental progress, and education needs were recommended. Furthermore, a follow-up with a speech-language therapist was also recommended.

Discussion

Including this patient, a total of 31 cases of *PPP2R5D*-related NDD have been reported in case reports and 48% (15/31) carry the same c.592G>A/p.(Glu198Lys) variant (Table 1). Interestingly, a new study by Oyama et al. (2022) has recently analyzed clinical data collected from the Simons Searchlight Single Gene Dataset V.7 and have revealed 73 *PPP2R5D*-related NDDs. Unfortunately, detailed growth measurements, clinical photographs, or details on physical examinations were not included, and thus, the presence of CALMs was not assessed. CALMs are hyperpigmented skin lesions arising from increased melanin production by melanocytes in the basal layer of the epidermis (Anderson 2020). While CALMs are usually benign skin hyperpigmentation, careful attention

Table 1 Clinical presentation of patients with *PPP2R5D* variants

Reference	Variants	Neuropsychiatric manifestations	Facies	Other findings
Maines et al. (2021)	**c.592G > A p.(Glu198Lys)**	**Developmental delay, Seizures, Hypotonia**	**Epicanthus and wide forehead, Nystagmus**	**Hypoglycemia, Macrocephaly with wide open anterior fontanel, Two hemangiomas on the lower lip and the back, Vomiting**
Yan et al. (2021)	c.620G > T p.(Trp207Leu)	GDD, ID, Hypotonia, speech impairment, and behavioral abnormality	Prominent forehead, Open mouth	Macrocephaly, Hypoplastic corpus callosum, Temporal lobe parenchymal atrophy, Enlargement of the ventricular system, Retardation of myelination of white matter
Madaan et al. (2022)	**c.592G > A p.(Glu198Lys)**	**GDD, Epileptic encephalopathy, Frequent myoclonic seizures, Central hypotonia**	**Elongated facies, Temporal hollowing, Open mouth**	**Macrocephaly, Enlarged Virchow–Robin spaces, Delay in social, adaptive, and language, Poor eye contact, communicative abilities, and motor stereotypes**
Walker et al. (2021)	c.748G > A p.(Glu250Lys)	GDD, Moderate ID, ADHD, Early-onset parkinsonism, Left rest tremor, and bradykinesia Latter—left rest tremor and bradykinesia that led to the diagnosis of Parkinson's disease (PD)		Macrocephaly, Hydrocephalus, Aqueductal stenosis, Auditory disorder
Hetzelt et al. (2021)	**c.592G > A p.(Glu198Lys)**	**ID, muscular hypotonia and dystonia, seizures, progressive motor decline, and early-onset levodopa-responsive parkinsonism**	**Long face and a tent-shape upper lip**	**Macrocephaly**
Kim et al. (2020) (Duplicate case here reported in Loveday et al. (2015))	c.598G > A p.(Glu200Lys)	Mild developmental motor and language delay, Mild ID, Gait difficulty and bradykinesia, Levodopa-responsive early-onset parkinsonism		White matter hyperintensities, Hypertension, and diabetes mellitus
	c.598G > A p.(Glu200Lys)	ID, Rest tremor and myoclonus, Akinetic rigid parkinsonism. Early-onset non-motor features of Levodopa-responsive parkinsonism		Relative paucity of white matter signal abnormality
	c.598G > A p.(Glu200Lys)	Motor developmental delay and language acquisition, Mild ID, Rest tremor and incoordination, Early-onset Levodopa-responsive parkinsonism, Dyskinesia		Overgrowth
Yeung et al. (2017)	**c.592G > A p.(Glu198Lys)**	**Moderate GDD, Mild ID, Autism, Epilepsy, Hypotonia**	**Hypertelorism, Frontal bossing**	**Megalencephaly**
	c.592G > A p.(Glu198Lys)	**Moderate GDD, Mild ID, Suspected autism, Epilepsy**	**Hypertelorism, Frontal bossing**	**Megalencephaly**

Table 1 (continued)

Reference	Variants	Neuropsychiatric manifestations	Facies	Other findings
Shang et al. (2016)	**c.592G > A p.(Glu198Lys)**	**GDD, ID, Autism, Anxiety**	**Downslanting palpebral fissures, Dolichocephaly**	**Scoliosis, Myopia, Macrocephaly**
	c.592G > A p.(Glu198Lys)	**GDD, ID, Autism, Seizures, Hypotonia, Non-verbal**	**Prominent forehead, Large anterior fontanelle, Mild midface hypoplasia**	**Failure to thrive, Possible short stature, Macrocephaly, Bilateral small arachnoid cysts, Cavum septum pellucidum**
	c.598G > A p.(Glu200Lys)	GDD, ID, Autism, Hypotonia, Water fascination, Licks items, Excitable, Nystagmus	Plagiocephaly, Triangular face, Long philtrum, Short nose, Thin upper lip, Midface hypoplasia, Slightly low set ears, Cleft palate	Torticollis, Pectus carinatum, Clinodactyly and malformation of toes, Rotational delayed visual maturation, Atrial and ventricular septal defects, Bicuspid aortic valve, Short stature, Easy bruising
	c.1258G > A p.(Glu420Lys)	GDD, ID, Autism, Hypotonia, Non-verbal, Aggressive, Stereotypies, Impulse control issues, Ataxia, Wide-based gait, Absent deep tendon reflexes		Alternating esotropia, Macrocephaly, Prominent CSF spaces, Mildly enlarged lateral ventricles, Cavum septum, Cavum verge
	c.1258G > A p.(Glu420Lys)	GDD, Hypotonia	Prominent forehead, Slightly low-set ears, High-arched palate, Small nose	Strabismus, Ventricular septal defect, Patent foramen oval, Sinus tachycardia, Macrocephaly, Moderate dilation of lateral ventricles
	c.1258G > A p.(Glu420Lys)	GDD, ID, Autism, Hypotonia, Tantrums, Perseverative behavior, Wide-based gait	Frontal bossing, Triangular face	Supernumerary nipple, Hypoplastic fifth toenails Astigmatism, Macrocephaly, White matter dysgenesis, Dysmorphic corpus callosum
	c.589G > A p.(Glu197Lys)	GDD, Moderate ID, Hypotonia, Non-verbal	Mild facial asymmetry	Congenital scoliosis, Difficulty chewing, Macrocephaly
Loveday et al. (2015)	**c.592G > A p.(Glu198Lys)**	**ID**		**Hypospadias, Increased height, macrocephaly**
	c.598G > A p.(Glu200Lys)	ID		Increased height, macrocephaly
	c.598G > A p.(Glu200Lys)	ID, Parkinsonism		Increased height, macrocephaly

Table 1 (continued)

Reference	Variants	Neuropsychiatric manifestations	Facies	Other findings
Houge et al. (2015)	c.157C > T p.(Pro53Ser)	Severe ID, Non-verbal		Cataract
	c.592G > A p.(Glu198Lys)	**Severe ID, Hypotonia, Ataxia**		**Pseudo-hydrocephalus, macrocephaly**
	c.592G > A p.(Glu198Lys)	**Severe ID, Hypotonia, Non-verbal, Ataxia**		**NA**
	c.592G > A p.(Glu198Lys)	**Severe ID, Hypotonia**	**Narrow palate**	**Increased weight, Fatigue, Hypoglycemia, Abnormal fat oxidation, Bilateral 6th nerve palsy, Hydrocephalus, macrocephaly**
	c.592G > A p.(Glu198Lys)	**Severe ID, Epilepsy, Hypotonia, Non-verbal**		**Mild syndactyly, Mild ventricular dilatation**
	c.592G > A p.(Glu198Lys)	**Severe ID, Epilepsy, Hypotonia, Non-verbal, Ataxia**		**Increased weight, Scoliosis, Mild ventricular dilatation, Small corpus callosum, macrocephaly**
	c.592G > A p.(Glu198Lys)	**Severe ID, Hypotonia, Non-verbal**		**Increased height macrocephaly**
	c.598G > A p.(Glu200Lys)	Mild ID, Hypotonia		Increased weight, Fatigue, Ptosis macrocephaly
	c.598G > A p.(Glu200Lys)	Mild ID, Hypotonia, Ataxia		Fatigue, Strabismus macrocephaly
	c.602C > G p.(Pro201Arg)	Moderate ID, Epilepsy, Hypotonia, Ataxia		Hip dysplasia, Gastric reflux
	c.619 T > A p.(Trp207Arg)	Moderate ID, Hypotonia		Scoliosis, Hip dysplasia, Fatigue, Mild mitochondrial dysplasia, Macrocephaly

Bold indicates the same pathogenic variant described in this Case Report; c.592G > A p.(Glu198Lys)

GDD Global development delay, *ID* Intellectual disability, *ADHD* Attention-deficit/hyperactivity disorder

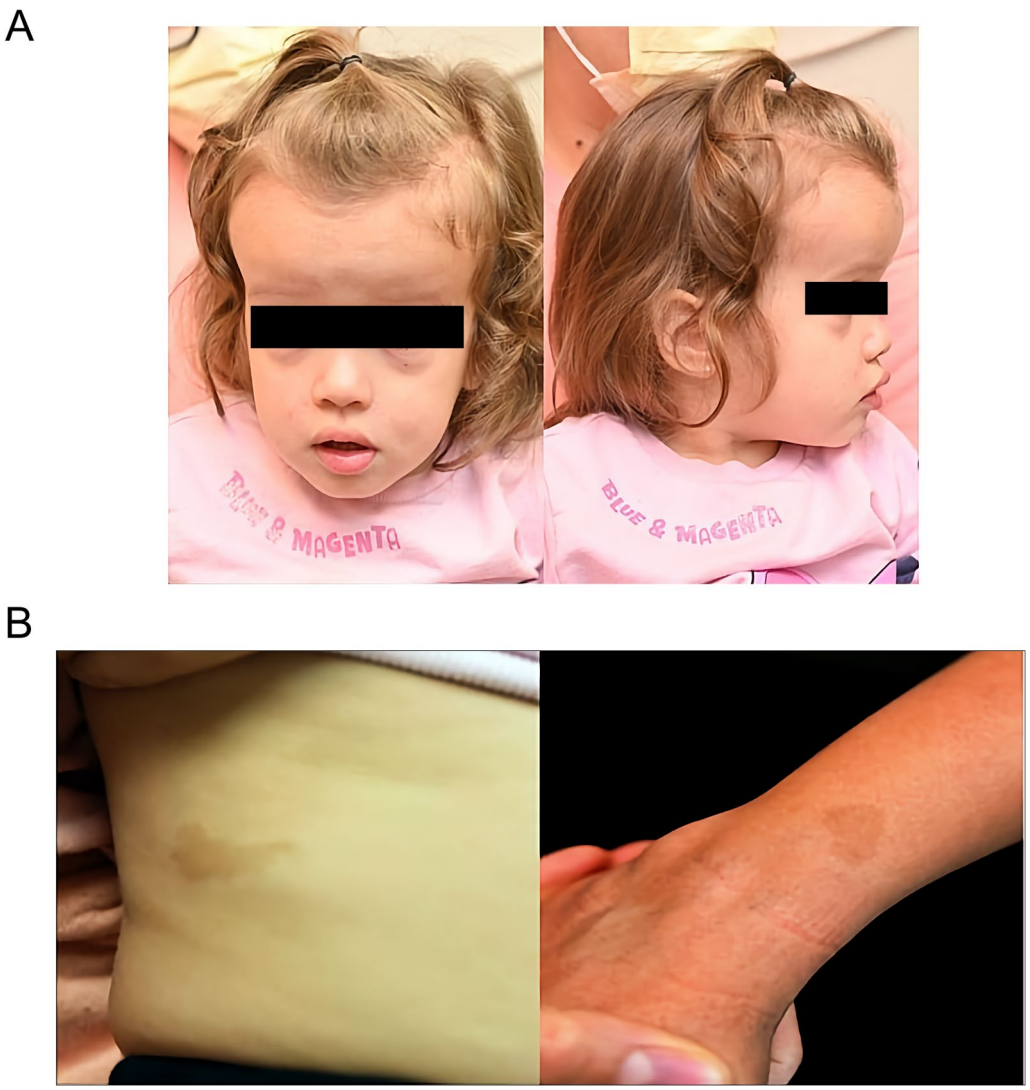

Fig. 1 Clinical photographs of the patient showing: **A** frontal bossing, bi-temporal narrowing, large depressed nasal bridge, low-set ears, hypertelorism, and mild prognathism. **B** Images of well-defined Café-au-lait macules on the right thorax (1by 2 cm) and ankle (1 by 1.5 cm)

should always be given when they are associated with one or more physical and/or neurodevelopmental findings as they have been found to be associated with rare genetic conditions (Carvalho et al. 2021; Zhang et al. 2016; Anderson 2020). In fact, a recent study that aimed at identifying documented diseases that may be present simultaneously with CALMs (Carvalho et al. 2021) was able to identify 60 rare genetic diseases where CALMs were reported in the clinical presentation. For most cases in this list, CALMs were an occasional or unexpected finding, similarly to our case, with an insufficient number of affected patients to establish a clear association with the disease in question (Carvalho et al. 2021). Furthermore, apart from Neurofibromatosis type 1, a disease where CALMs are very well characterized, no clear guidelines seem to exist regarding their number or size except that their presence could highlight a potential genetic disease (Ponti et al. 2012). Thus, it is of great importance to document CALMs or other skin pigmentary abnormalities when they are associated with NDD or other rare diseases as they might be underreported or missed in physical examinations. Systematically reporting CALMs when they are present with other phenotypic characteristics or when a genetic disease is suspected/diagnosed could help in establishing if they underlie a specific disease and request appropriate genetic testing since current neurofibromatosis multigene panels do not include *PPP2R5D* gene.

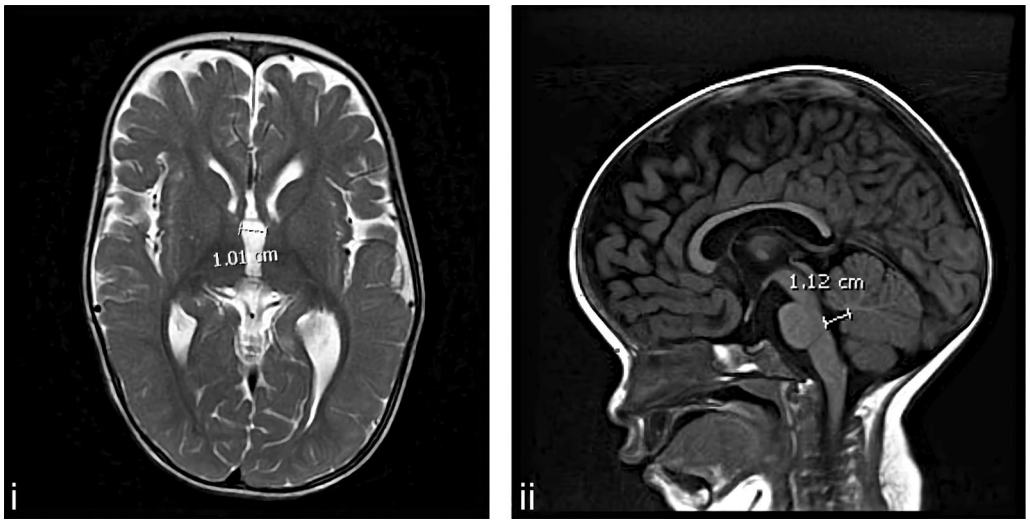

Fig. 2 (i) Axial T2 prop. (ii) Sagittal T1 Flair brain MRI: macrocephaly with slight ventricular extra-axial CSF prominence with prominent cerebral sulci and mild-to-moderate white matter atrophy at 12 months of age

Table 2 Genes re-analyzed by sequencing

Panels	Genes
Weaver, Sotos, and Banayan-Ruvalcaba syndromes a	EZH2, NSD1, NFIX, APC2, PIK3CA, KLLN, PTEN, AKT1, SEC23B
Neurofibromatosis	NF1, NF2, SMARCB1, SPRED1
Congenital glycosylation disease	ALG1, ALG11, ALG12, ALG13, ALG2, ALG3, ALG6, ALG8, ALG9, ATP6V0A2, B4GALT1, COG1, COG4, COG5, COG6, COG7, COG8, DDOST, DHDDS, DOLK, DPM1, DPM2, DPM3, GMPPA, GNE, LARGE, MAN1B1, MGAT2, MOGS, MPDU1, MPI, NGLY1, PGM1, PMM2, RFT1, SLC35A1, SLC35A2, SLC35C1, SRD5A3, SSR4, STT3A, STT3B, TMEM165, TUSC3

Diseases that are known to be associated with CALMs or other skin pigmentary abnormalities often present with mutations in genes implicated in the modulation of the Ras/MAPK pathway (Carvalho et al. 2021; Tajan et al. 2018; Silverstein et al. 2002). PP2A holoenzymes have clearly been shown to regulate this pathway (Silverstein et al. 2002; Letourneux et al. 2006; Ory et al. 2003; Ciccone et al. 2015; Adams et al. 2005; Sieburth et al. 1999; Walter 2003); however, some have shown PP2A to be a key negative regulator of MAPK signaling (Silverstein et al. 2002; Zhou et al. 2002; Alessi et al. 1995; Sonoda et al. 1997; Sontag et al. 1993), while others seem to indicate that it functions as a positive regulator of this kinase cascade (Ory et al. 2003; Adams et al. 2005; Abraham et al. 2000; Kubicek et al. 2002; Jaumot and Hancock 2001; Strack 2002; Dougherty et al. 2005). These discrepancies seem to be due to the complexity of the PP2A holoenzymes' structure, their tissue dependence, and the regulatory subunits involved. In fact, specific PP2A holoenzymes seem to be able to target multiple steps in the Ras-MAPK signal transduction cascade and appear to do so in a cell type-specific manner (Walter 2003). It is unclear whether PP2A holoenzymes simultaneously play opposing roles at different sites in the MAPK signaling, both positive and negative regulations, or if these occur in a cell type-dependent manner or in response to different external stimuli (Walter 2003). These knowledge gaps highlight a crucial need for mechanistic studies in the roles of specific PP2A holoenzymes, such as PP2A-*PPP2R5D* in Ras-MAPK signaling which could lead to a better understanding of P*PPP2R5D*-related NDD and associated CALMs. Some studies have also demonstrated that additionally to the convoluted roles of specific PP2A-holoenzymes in Ras-MAPK regulation, some PP2A complexes seem to have direct roles in melanin synthesis (Reilein et al. 1998; Kim et al. 2005). Reilein et al. (1998) showed that melanosome aggregation could be mediated by PP2A as overexpression of PP2A inhibited pigment dispersion by α-melanocyte-stimulating hormone. Furthermore, in a murine cell model, Kim et al. (2005) showed that PP2A holoenzymes-mediated melanin synthesis through a mechanism that seemed to be dependent

on ERK regulation. Thus, these results also suggest direct roles for PP2A holoenzymes in melanin synthesis and could explain the presence of CALMs in gene variants affecting specific subunits in PP2A holoenzymes.

It is of note that PP2A-*PPP2R5D* holoenzymes have also been shown to regulate the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway by direct AKT dephosphorylation. It is thought that variants disrupting PP2A holoenzyme lead to loss of PI3K-AKT-mTOR growth regulation and affect intellectual skills (Loveday et al. 2015; Yeung et al. 2017). A functional study showed that a constitutively active AKT-mTOR signaling leads to increased cell size and an uncoordinated cellular growth associated with the *PPP2R5D* c.1258G>A/p.E420K variant generated in HEK-293 cells using CRISPR-cas9 biotechnology (Papke et al. 2021).

To the best of our knowledge, CALMs have never been described with *PPP2R5D* variants. We cannot eliminate the possibility that this occurrence might be coincidental because of the higher incidence of CALMs being reported in the general population; however, we strongly believe that cases of CALMs associated with one or more physical and/or neurodevelopmental findings may be underreported. The systematic dermatological review and documentation of patients with mutations in *PPP2R5D* is clearly difficult in such a rare disorder. The only reported cases of CALMs associated with *PPP2R5D* are of two patients with variants in the *PPP2CA* catalytic subunit (Reynhout et al. 2019a). It is of note that this subunit has also been shown to be a regulator of the Ras/MAPK signaling pathway (Wlodarchak and Xing 2016). Interestingly, the identified *PPP2R5D* c.592G>A/p.(Glu198Lys) variant in our patient is one of the most characterized biochemically and has been shown to affect the catalytic subunits of PP2A (Houge et al. 2015; Loveday et al. 2015; Biswas et al. 2020; Shang et al. 2016). Patients with the *PPP2R5D* c.592G>A/p.(Glu198Lys) variant present with more severe intellectual disability because of the conferred degree of biochemical defect in PP2A activity (Houge et al. 2015; Biswas et al. 2020). Specifically, this variant localizes in a highly conserved acidic loop where the substitution of a negatively charged glutamine for a positively charged lysine significantly affects the binding of the catalytic subunit with the scaffolding subunit (i.e., holoenzyme formation) through what is thought to be a dominant-negative mode of action (Lenaerts et al. 2021; Houge et al. 2015). Because the *PPP2R5D* c.592G>A/p.(Glu198Lys) is known to directly affect the catalytic subunit of PP2A, it is possible that the CALMs identified in this case may be associated with the same defective molecular mechanisms underlying the *PPP2CA* catalytic subunit variant.

Because the regulatory subunit of PP2A is the most structurally diverse, it is challenging to study mechanistically. However, we strongly believe that documenting this PP2A-*PPP2R5D* variant associated with CALMs is of utmost importance. A clear limitation of this study remains the lack of molecular and functional studies linking the *PPP2R5D* pathogenic variant to melanogenesis. Future functional studies will thus be needed to uncover the roles of PP2A-*PPP2R5D* in Ras-MAPK signaling as well as in the various paracrine networks mediating melanogenesis which may lead to a clearer clinical association between CALMs and *PPP2R5D*-associated NDD.

Conclusions

This is the first report of *PPP2R5D*-related NDD associated with CALMs. Encouraging the systematic documentation and reporting of CALMs when associated with one or more physical and/or neurodevelopmental findings is of utmost importance to better characterize the phenotype of specific disorders in order to improve differential diagnosis and consequently request appropriate genetic testing. In fact, for most rare genetic cases, CALMs are an occasional or unexpected finding, similarly to our case, with an insufficient number of affected patients to establish a clear association with the disease in question. Further studies will be needed to characterize the roles of PP2A-*PPP2R5D* holoenzymes in Ras/MAPK and AKT/mTOR pathways and may shed light on the association of CALMs with *PPP2R5D*-related NDD.

Exome sequencing

Buccal swab was performed and sent to LifeLabs Genetics (Toronto, ON) who performed the DNA extraction, sequencing, and data analysis in accordance with their protocol.

Abbreviations

NDD	Neurodevelopmental disorder
CALMS	Café-au-lait macules
Ras/MAPK	Ras-mitogen-activated protein kinase
MDR	Intellectual developmental disorder autosomal dominant 35

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Author contributions
NB and PPR reviewed the literature, wrote, and corrected the manuscript. EG performed a literature review and wrote sections of the manuscript. EB performed the first assessment of the patient, and MBA coordinated the clinical investigations, patient management and interpreted the clinical data. All authors reviewed and approved the final version of the manuscript.

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Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
This study was approved by the Vitalité Health Network Research Ethics Board (Reference number: 101112). Informed consent of the legally authorized representative (Mother) was obtained for the study and publication of medical information and images.

Consent for publication
Informed consent of the legally authorized representative (Mother) was obtained for publication of medical information and images.

Competing interests
The authors declare that they have no competing interests.

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