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CSNK2B Mutation: A Rare Cause of IGHD

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Keywords: CSNK2B | epilepsy | growth hormone deficiency | intellectual disability | Poirier–Bienvenu Syndrome

ABSTRACT

Objective: Poirier-Bienvenu neurodevelopmental syndrome (POBINDS) is a rare neurodevelopmental syndrome, resulting from germline heterozygous *CSNKB2* pathogenic variants. The main presentations are severe epilepsy, delayed psychomotor development, and/or profound intellectual disability. More recently, *CSNK2B* pathogenic variants have been reported in patients with mild intellectual disability and no history of epileptic symptoms. Short stature is present in 66% of patients, in half of these cases due to proven growth hormone deficiency.

Methods: Whole genome sequencing (WGS) was performed through a French genomic program for a patient with isolated growth hormone deficiency after negative next generation sequencing (NGS) results. NGS panel analysis of *CSNK2B* and genes involved in isolated growth hormone deficiency (IGHD) was performed in 44 patients from the Genhypopit network ($n = 2144$) with growth hormone deficiency (GHD) and intellectual disability (ID) or epilepsy and in a convenience cohort of 68 GHD patients.

Results: We present the first case of POBINDS presenting mainly as growth delay due to GHD. Genome analysis revealed a de novo pathogenic variant in the translation initiation codon of *CSNK2B* (c.1 A > G, p.(Met1?)). The patient had mild intellectual disability and subsequent analysis of the patient's clinical history revealed that he had had febrile convulsions, compatible with POBINDS. No *CSNK2B* pathogenic variants were identified among the 44 selected patients with GHD and ID or epilepsy, or in a convenience cohort of 68 patients with GHD.

Conclusion: Although rare, pediatricians should be aware that POIBNDS syndrome may present as IGHD with mild ID.

1 | Introduction

In 2017, Poirier et al. described a new syndrome, termed Poirier–Bienvenu neurodevelopmental syndrome (POBINDS), which was found to be associated with mutations in *CSNK2B* [1]. Two *CSNK2B* splicing variants were identified by whole exome sequencing (WES) in two patients, one with isolated intellectual disability (ID), and the other one with ID and epilepsy. The *CSNK2B* gene, located on chromosome 6 at position p21.33, encodes the beta subunit of casein kinase 2, a ubiquitous protein predominantly expressed in the brain [2]. CSNK2B, which acts as a regulator, seems to be essential for cerebral development, as homozygous knockout is embryonic lethal in mice [3, 4]. Nevertheless, the underlying mechanism involved in seizures

(epilepsy) and ID remains incompletely understood. Since its first description, over 80 cases of POBINDS have been reported, with mainly neurological symptoms, primarily epilepsy and/or delayed psychomotor development [5]. However, patients with mild ID due to *CSNK2B* pathogenic variants have been described without any history of epileptic symptoms [6], and additional clinical features such as behavioral disorders, microcephaly, dysmorphia and endocrine abnormalities have been described suggesting that POBINDS would be better referred to as CNSK2B related disorders [6–8]. Roughly 50%–65% of patients with POBINDS have short stature [9–11]. Roughly 50%–65% of patients with POBINDS have short stature, and although the underlying cause is rarely investigated, growth hormone (GH) stimulation tests have shown that approximately half of the tested patients have GH deficiency (GHD), and GH treatment has been reported to be effective regardless of the presence or absence of GHD [12]. Short stature (with or without GHD) is the third most common clinical feature of POBINDS but diagnosis is usually based on neurological symptoms in early infancy.

In France, patients with congenital pituitary deficits without identified genetic causes have access to whole genome analyses (Plan France Médecine Génomique 2025). We present the case of a patient with isolated GHD (IGHD) who was found to have a de novo pathogenic variant in *CSNK2B*. To investigate whether pathogenic variations in this gene might be identified in other patients with similar clinical presentations, we retrospectively analyzed *CSNK2B* in a group of patients with GHD associated with ID and/or a history of seizures from the Genhypopit network, and in a cohort of GHD patients.

2 | Materials and Methods

2.1 | Case Report

Index case: All medical data were collected from the medical records.

2.2 | Selection of Patients

Patients with GHD and ID or epilepsy were selected from the Genhypopit network of patients with pituitary deficiency ($n = 2144$ [13]). Patients were included if they had either IGHD and ID or GHD (either IGHD or combined pituitary hormone deficiency (CPHD)) and epilepsy (seizures), as described by the physician in charge of hypopituitarism treatment.

The convenience sample of patients with GHD consisted of all patients with pituitary deficiency who underwent genetic testing in the molecular laboratory of La Timone Hospital, Marseille, France, between December 2023 and March 2024, regardless of whether they had CPHD or IGHD, with or without ID, but no epilepsy.

2.3 | Genetic Analysis

All participants provided written consent for genetic testing. The study was registered with the French Data Protection Agency (CNIL-France, 1991429v0).

Targeted next-generation sequencing (NGS) was performed using a QIAseq targeted DNA custom panel kit (Qiagen) on a NextSeq. 1000 Illumina sequencing system. Targeted sequences included the coding sequences of the following panel of genes associated with IGHD or CPHD: *ARNT2* (NM_014862), *FGF8* (NM_033163), *FGFR1* (NM_023110), *GH1* (NM_000515), *GHRHR* (NM_000823), *GHSR* (NM_1984087), *GLI2* (NM_005270), *HESX1* (NM_003865), *IGSF1* (NM_001555), *LHX3* (NM_014564), *LHX4* (NM_033343), *OTX2* (NM_021728), *PAX6* (NM_000280), *POU1F1* (NM_000306), *PROKR2* (NM_144773), *PROP1* (NM_006261), *RNPC3* (NM_017619), *SOX2* (NM_003106), *SOX3* (NM_005634), *TBX19* (NM_005149). *CSKN2B* (NM_001320) was subsequently added to this panel. Alignment and variant calling were performed with CLC Genomics software (Qiagen, Hilden, Germany). All targeted regions of interest were sequenced with a coverage depth greater than 30×.

For the index case, whole genome sequencing (WGS) was performed according to the recommendations of the France Genomic Medicine program. Whole-blood-extracted genomic DNA was sequenced according to standard procedures for PCR-free sequencing on a NovaSeq. 6000 instrument (Illumina). Sequencing data were aligned to the reference genome assembly (GRCh38p13) using bwa 0.7+. Variants were called using the algorithms GATK4+, Bcftools1.10+, Manta1.6+, and CNVnator0.4+, and annotated using Variant Effect Predictor. Detected variants were prioritized using in-house procedures. Further details are available on request at http://www.auragen.fr.

2.3.1 | Variant Classification

Variants were classified according to the ACMG/AMP (American College of Medical Genetics and Association for Molecular Pathology) guidelines for the interpretation of sequence variants [14] as benign (B), likely benign (LB), a variant of uncertain significance (VUS), likely pathogenic (LP), and pathogenic (P).

The *CSKN2B* variant was confirmed by Sanger sequencing (primer sequences and details of sequencing method available on request).

3 | Results

3.1 | Case Report

3.1.1 | Growth Delay

After an uneventful pregnancy and delivery, the patient was born at term with normal birth weight from non-consanguineous parents. After growing at −1 SDS, in keeping with his target height, he presented growth delay (− 2 SDS) at the age of 6 years. He was then referred to a pediatric endocrinologist for growth monitoring. The initial biological work-up revealed no abnormalities and simple growth monitoring was initiated. At the age of 12 years, his growth rate decreased slightly despite Tanner 2 pubertal development. A growth hormone secretion test was performed, which

revealed complete GH deficiency (GH peak during hypoglycemia at 0.18 ng/mL). Cerebral and pituitary MRI findings were normal. Growth hormone therapy (0.2 mg/kg/week) was initiated at the age of 12 years. The patient's growth velocity increased (Supporting Information S1: data 1) and his final height was −1.5 SDS, consistent with the midparental height.

3.1.2 | Neurological Presentation

The patient had a psychomotor delay. Walking was acquired at 18–20 months and language delay required early speech therapy support. Learning difficulties appeared after beginning school. A neuropsychological assessment was conducted at the age of 7 years, with a homogenously low WISC IV score of 60. The child was educated in a school for children with disabilities until the age of 14 and then attended a medico-social institute for teenagers and young adults with disabilities. The patient had three seizure episodes in early childhood, the latest at the age of 5 years, which were considered febrile seizures. At the age of 19 years, pending the results of genomic analysis, the patient had an epileptic seizure, with no identifiable triggering factor (trauma, toxic effect, ionic imbalance, infection). An EEG performed 24 h after the seizure showed no paroxysmal abnormalities.

3.1.3 | Other Clinical Features

The patient also had ophthalmological abnormalities, including myopia, astigmatism, and megalocornea. His father similarly had a nonspecific corneal abnormality. A varicocele was discovered at the age of 12 years, in the pre-pubertal period. No pubertal abnormalities or thyroid dysfunction were observed during follow-up.

3.1.4 | Genetic Testing

Initial genetic analysis was performed in 2017 upon diagnosis of IGHD. Targeted NGS analysis did not identify any variants of interest (VUS, LP, or P) in the analyzed genes (see material and methods section). WGS was then indicated in 2020 for the patient and his parents, which revealed a de novo (PM6) variant in *CSNK2B* (c.1 A > G) affecting the initiation codon (ACMG-AMP criterion PVS1), absent from databases in healthy populations (GnomAD v.4) (PM2), and classified as P/LP in the literature in several patients (PP5). The patient's phenotype is compatible with POBINDS (PP4). The variant was thus classified as pathogenic, according to the ACMG classification (Supporting Information S1: data 2). The variant was subsequently confirmed by Sanger sequencing (Figure 1).

3.2 | Intellectual Disability and/or Epilepsy in Patients With IGHD and CPHD from the Genhypopit Network

Among the 2144 patients in the Genhypopit network, 178 had ID in addition to pituitary deficiency. Of these, seven patients have a genetic explanation for their pituitary deficiency, either

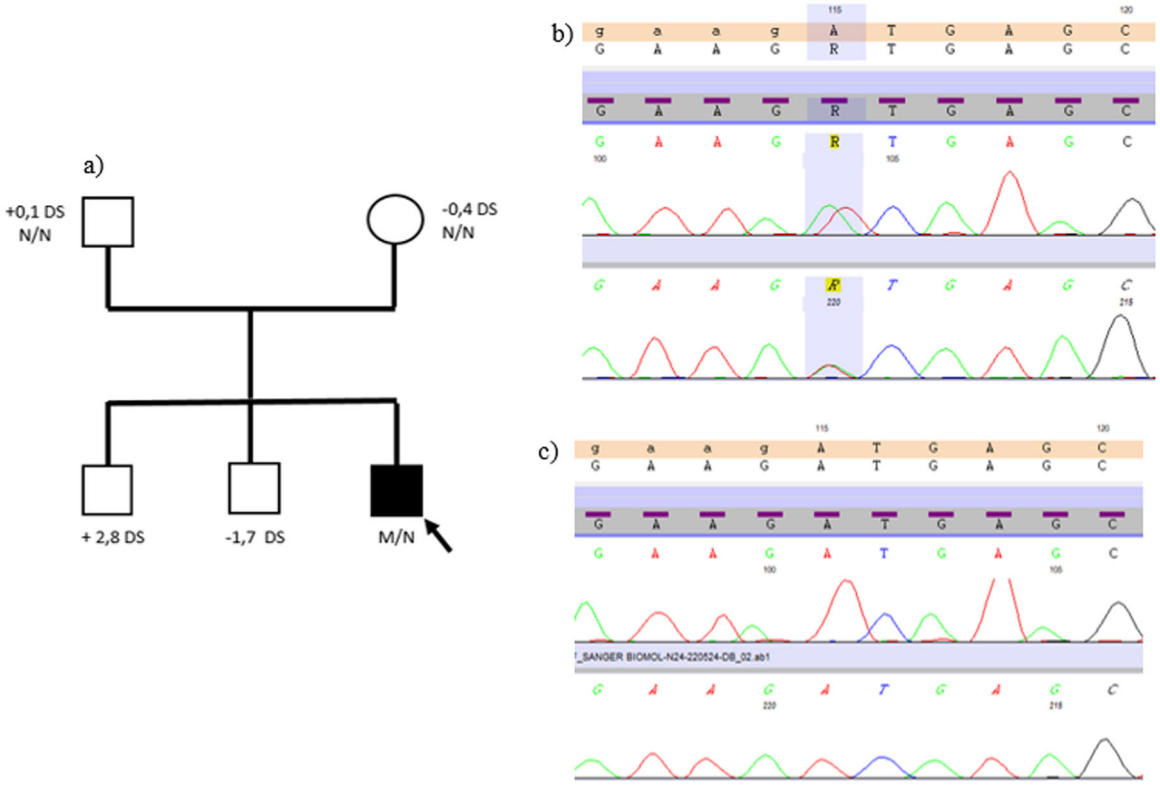

FIGURE 1 | (a) Family pedigree of the patient (squares, male family members; circles, female family members; filled black symbols, affected; Genotypes: M/M, homozygous; N/M, heterozygous; N/N, normal; SDS at final height or at the age of index case diagnosis) (b, c) Sanger sequencing results (b) with the *CSNK2B* variant NM_001320.7:c.1 A > G (c) without the variant.

IGHD or CPHD (three *PROP1* variants, three *POU1F1* variants and one *GLI2* variant). Among the 171 patients with no identified genetic cause, 41 had IGHD. Patients with IGHD and ID had MRI abnormalities in 74% of cases (29/41), of which 24/41 had pituitary hypoplasia, 14/41 had pituitary stalk interruption syndrome (PSIS), 5/41 had a corpus callosum abnormality, 1/41 a Chiari malformation and 1/41 a septal defect.

Overall in the Genhypopit network, seven patients had epilepsy in addition to pituitary deficiency, including four who also had ID. Among these seven patients, four had IGHD and three CPHD (2/7 had pituitary hypoplasia and 3/7 had PSIS). None had a genetic explanation for their pituitary phenotype. Age at epilepsy was available for 4/7 patients and was respectively 1, 2, 3, and 4 years. NGS with a gene panel including *CSNK2B* was performed for the 44 patients with GHD and ID or epilepsy (41 with IGHD and 3 with CPHD). No P/LP variants or VUS were identified. Analysis of the *CSNK2B* coding sequence in the convenience cohort of 68 patients with pituitary deficiency (30 with IGHD and 38 with CPHD) likewise found no *CSNK2B* P/LP variants or VUS.

4 | Discussion

We report an unusual case of a patient with a pathogenic *CSNK2B* variant, identified by genomic analysis following prepubertal IGHD, in whom POBINS was subsequently confirmed by a generalized seizure after puberty. A retrospective investigation of this clinical history revealed nonspecific symptoms compatible with POBINDS, such as mild ID beginning in infancy and febrile seizures. Although POBINDS was initially described as epilepsy and ID, growth delay has emerged as the third most commonly reported clinical feature [10]. Although GHD has rarely been investigated in POBINDS patients, it has been diagnosed in several cases and GH treatment has been found to be effective [9, 10]. Our case is different, however, because genetic analyses were performed to identify the cause of endocrine (IGHD) rather than neurological manifestations.

Casein kinase 2 (CK2) is a serine/threonine-selective protein organized as a tetramer with two catalytic subunits (alpha and alpha') and two regulatory subunits (beta) [15, 16]. As mentioned above, CK2 is a ubiquitously expressed protein, primarily located in the brain, but present in multiple cellular compartments and involved in numerous signaling pathways and biological processes. Its full range of activities remains unclear, but it is established that CK2 is a "master regulator" [17]. The action of CK2 on the Wnt/beta-catenin, PI3K/Akt [16] and HH [18] pathways are potential links to pituitary development. Moreover, the beta subunit of CK2 (CK2B) plays a significant role in osteogenic, myogenic and neurological development [19]. CK2B plays a key role in the phosphorylation of beta-catenin in the Wnt/beta-catenin pathway [20], which is essential for the proper development of the pituitary gland [21]. Furthermore, cancer research has shown that CK2 is involved in the SHH pathway [18], which is also known to be an important pathway for pituitary organization [22]. CK2 has also been implicated in the modulation of transcription factor LHX3 activity in pituitary development [23], and *LHX3* mutations are a known cause of pituitary deficiency [13]. These results suggest that CK2 may profoundly influence early pituitary development, potentially explaining GHD in patients with POBINDS. Although some variants in genes involved in early pituitary development are known to cause IGHD [24], it is noteworthy that no cases of CPHD and no morphological abnormalities of the pituitary gland have been reported in POBINDS patients. In light of these findings, it is reasonable to suggest that assessment of the somatotropic axis may be beneficial in patients with POBINDS and growth delay. Confirmation of GHD would allow these patients to benefit from effective treatment. Nevertheless, the involvement of *CSNK2B* in growth may result from both pituitary and peripheral roles. Indeed, some children with POBINDS have growth delay without clear GHD [9], raising the question of a downstream defect in GH receptor (GHR) pathways. CK2 has indeed been shown to act on the JAK/STAT pathway [16], the major pathway of GH action [25], and another study has reported the possible involvement of CK2 in GHR activation and endocytosis [26]. However, the fact that GH treatment is effective even in the absence of a clearly identified GHD, suggests that alteration of CK2 does not lead to total GHR inactivity [9, 10].

The alpha subunit of CK2 also appears to have an impact on growth, with *CSNK2A1* pathogenic variants causing Okur-Chung syndrome (OCS) [27], which like POBINDS, is a neurodevelopmental syndrome sometimes (but more rarely than POBINDS) associated with short stature [28, 29]. As for *CSNK2B*, *CSNK2A1* mutations are associated with GHD in some patients [30, 31]. In their comparison of OCS and POBINDS, Ballardin et al. found that while clinical presentations overlapped, the more severe phenotypes of POBINDS patients could be explained by the more specific role of CK2B in cells [11].

Most of the 81 recently reviewed patients with POBINDS [5] had generalized tonic-clonic seizures before the age of 3 years, with or without MRI or EEG abnormalities. Nevertheless, like our patient, at least 6 others only had febrile seizures [32, 33]. The fact that our patient later had a generalized seizure at the age of 19 years raises the question of the follow-up of patients with pathogenic *CSNK2B* variants and mild neurological involvement in POBINDS. The same variability is observed in the degree of ID, which varies from severe to mild [7], with no clear correlation between genotype and phenotype. Moreover, loss of function (LOF) variants [10, 34] do not seem to be associated with more severe phenotypes. Our patient with a pathogenic variant in the initiation codon of CSNK2B has a mild phenotype. Ballardin et al. [11] suggest that patients with initiation codon variants, either in *CSNK2B* or *CSNK2A*, have milder phenotypes. However, the three patients with initiation codon variants whose phenotype has been described [6, 10] have highly variable seizure, ID and growth delay severity (Supporting Information S1: Table S3). This variability can be explained by the fact that the consequences of initiation codon variants can range from complete LOF to just an N-terminal deletion due to an alternative ATG codon. The next in-phase ATG codon in *CSNK2B* does not seem to correspond to a natural transcript and is predicted to code for a protein missing 51 N-terminal amino acids. Moreover, Clinvar lists 25 other P or LP variants in this N-terminal region, suggesting that even if the protein is synthetized, it is not functional. Further studies are

required to gain further insights into the effects of *CSNK2B* initiation codon variants.

Our patient had a varicocele in the pre-pubertal period. Lymphatic and blood vessel anomalies have already been reported in one patient with POBINDS [7], and are possibly related to CK2's ubiquitous activity [17, 35]. CK2 upregulation and downregulation have indeed been associated with numerous other pathologies, such as schizophrenia and cancer [16].

The high phenotypic variability of POBINDS also raises the question of whether the *CSNK2B* variants alone are pathological, or whether the different manifestations are the consequences of cumulative, possibly oligogenic effects. Indeed, at least three patients with POBINDS and severe epilepsy were found to have another *de novo* pathogenic variant in *KCNQ2* or *SCN1A*, two genes classically associated pediatric epilepsy/seizures [7, 33, 36]. The question of oligogenicity may also be relevant for *CSNK2B*-associated IGHD. In our patient, genomic analyses did not identify other P/LP variants or VUS in genes known to be involved in pituitary deficiency but it would be interesting to investigate these genes in other patients with pathogenic *CSNK2B* variants and IGHD.

Our cohort analysis suggests that IGHD associated with ID or seizures is rarely due to a *CSNK2B* variant, moreover, no pathogenic *CSNK2B* variants were identified in our larger cohort of patients with GHD. Larger studies are required to evaluate the value of including *CSNK2B* in GHD gene panels. Until further evidence emerges, it is prudent to consider *CSNK2B* and *CSNK2A* genes of unknown significance in IGHD [37].

5 | Conclusion

Further investigations are required to ascertain the role of *CSNK2B* in GHD. Patients with *CSNK2B* mutations (POBINDS) undoubtedly require a detailed characterization of the growth hormone axis. Growth hormone treatment should be considered in most cases. Conversely, pediatric endocrinologists should look out for the association of GHD with even mild ID or a history of febrile convulsions, as an indication for genetic analysis of *CSNK2B* on suspicion of POBINDS. These measures would help improve our knowledge of the spectrum of genetic causes of GHD.

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Ethics Statement

All participants provided written consent for genetic testing. The study was registered with the French Data Protection Agency (CNIL-France, 1991429v0).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.