



Brief Communication

LMOD3 gene variant in familial periodic hypersomnolence

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ABSTRACT

Introduction: Kleine-Levin syndrome (KLS) is a rare and debilitating disorder presenting with periodic hypersomnolence, cognitive, psychiatric and behavioral disturbances. In the absence of biomarkers it can be difficult to diagnose. Rare *LMOD3* variants in a family and in seven sporadic cases with KLS have been described. Here we report a patient and her family with an unclassified, familial, periodic central disorder of hypersomnolence (CDH) in whom the presence of a *LMOD3* gene variant was assessed.

Case description: The female patient presented since early adulthood with recurrent episodes of hypersomnolence. Over more than 20 years of follow-up the diagnoses of idiopathic hypersomnia, KLS and hypersomnia associated with a psychiatric condition were made. The family history is positive for periodic hypersomnolence and psychiatric conditions.

The patient, her symptomatic mother and her asymptomatic sister carried a Proline for Histidine substitution at codon 552 of the *LMOD3*-gene. This variant was previously reported in two sporadic KLS patients and its frequency in the general population is below 0.02%.

Discussion: We report the association of periodic hypersomnia with a polymorphism of the *LMOD3*-gene in a patient with atypical KLS and a positive family history. Further research is needed to assess the pathological and predictive value of *LMOD3* variants in KLS.

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1. Introduction

Kleine-Levin syndrome (KLS) is a debilitating, relapsing and remitting sleep-wake disorder with a prevalence of 1–2 per million, unknown etiology and without known biomarkers. Diagnosis can be difficult as it bases mainly on the patient's history. The disease is characterized by periodic hypersomnolence and can involve cognitive, psychiatric and behavioral disturbances, disinhibited behavior and eating disorders [1].

Familial cases are rare and seem to share a common clinical picture with sporadic cases [2]. There is evidence for a genetic component, with first degree relatives having 800–4000 fold increased risk to develop KLS [3] and a higher prevalence in Ashkenazi Jews [4]. A genome-wide association study (GWAS) reported an association with a genetic variant in *TRANK1* [5]. Linkage

analysis and exome sequencing in a large Saudi-Arabian family with KLS and a European cohort of KLS patients identified several rare variants in the *LMOD3* gene, some predicted to be pathogenic [6].

2. Material and Methods

The local ethical committee has reviewed the study protocol and ethical approval was exempted. The patient and her relatives underwent genetic counselling by an independent geneticist and gave their written informed consent for genetic testing for scientific purposes and the publication of the results within a case report. We gathered information about the patient, her parents and siblings from medical records and direct interview and information about other family members from indirect reporting.

The coding region of *LMOD3*, except for the last exon encoding the eight terminal amino acids (which does not present any polymorphism), was sequenced in both directions by Sanger sequencing. All subjects were sequenced as previously reported [6] with primers:

Exon 1 forward: 5'- TGCTCAGCAAACCACTGAGG-3', reverse: 5'-CAGAGAGACCTAACAGCCCA-3', Exon 2 forward 1: 5'-

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ATCTCCACTAGCTGATGCTCC-3' Exon2 reverse 1: 5'-TGACCCAA-CATGTGCCTCTG-3', Exon2 forward 2: 5'- GGCCATCATGAGGTGTCTCC-3', Exon2 reverse 2: 5'- CTCAGTCACCATTCTCCCTCC-3'.

3. Case description

3.1. Patient's history

In 2001, a young female patient developed periodically pronounced hypersomnolence. After two years with strong symptoms, symptoms were milder over 15 years, but then worsened again.

The first episode started with muscle weakness leading to a fall during a minor viral infection. Several days later, the patient started sleeping through days and nights, having trouble waking up for meals, leading to a relevant weight loss. After three weeks, hypersomnolence improved spontaneously, but fluctuating excessive daytime sleepiness (EDS) with sleep attacks remained (Epworth sleepiness scale (ESS) 20/24 points in 2002, 8/24 points in 2004). Symptomatic treatments with Modafinil and antidepressants (Paroxetine, Fluoxetine, Reboxetine) were unsuccessful. She dropped out of school due to difficulties with concentration, attention and memory. Neuropsychological examination was considered overall within normal range, some difficulties with verbal memory and slowing on dual task tests were interpreted in the context of a psychological dysfunction. She also reported long and unrefreshing naps, sleep inertia, hypnagogic hallucinations and automatic behaviors (e.g. putting shoes in the fridge), but also intermittent insomnia.

In a period with milder symptoms between 2004 and 2018 (no medical follow up, retrospectively reported), there were two to three episodes of hypersomnolence per year, sometimes associated with menstruation or stress, with a sleep duration up to 21 h over a couple of weeks, EDS, depressed mood and reduced appetite. Between those episodic exacerbations, the patient reported persistent EDS.

During a period with intense psychosocial stress in 2017, symptoms worsened again, with episodic hypersomnolence lasting from two weeks to several months, significant EDS (ESS 17–22/24), fatigue (Fatigue Severity Scale 5–6.8/7 points) and some depressive symptoms. In 2018, she reported automatic behaviors (“bumping into lantern masts”), a feeling of being “slowed” or “in a dreamlike state” and sudden sleep attacks during conversations, persisting between the episodes of worsened hypersomnolence.

Under treatment with Bupropion, she temporarily underwent psychiatric counselling and changed her working place. In 2020, symptoms improved slowly, simultaneously with the stabilization of her psychosocial situation. The ESS was 17/24 in fall 2020 and 12/24 in spring 2021. The patient still reported an excessive need for sleep with 10–11 h per night and sensitivity to sleep restriction, leading to prolonged sleep inertia.

3.2. Family history

The family history was positive for hypersomnolence and psychiatric conditions on the maternal side (Fig. 1). Her mother (IV.3) reported EDS since childhood (ESS 16/24, 6/24 under stimulants) with periods lasting days to months with long sleep duration, and symptom free months in between. She also had intermittent insomnia periods, interpreted in the context of depression. Two multiple sleep latency tests (MSLT) were normal. She had a history of most likely psychogenic transient losses of consciousness, fatigue and chronic pain. ESS was normal (6/24) in a period with pronounced insomnia in 2020.

The family reported about similar symptoms with intermittent long sleeping times in the patient's aunt (IV.2) and her great-grandmother (II.1). The patient's grandfather (III.4) had paranoid schizophrenia. The patient's sister (V.3, ESS 2/24), brother (V.1, ESS 8/24) and father (IV.4, ESS 8/24) did not report signs of a sleep-wake disorder.

3.3. Diagnostic work-up

Sleep-wake examinations were performed in periods with less pronounced sleepiness and showed short to normal total sleep times (Table 1). Cerebral magnetic resonance imaging, blood and cerebrospinal fluid examinations were normal.

The patient was referred to our attention with the suspicion of narcolepsy (initial fall considered as possible cataplexy, long-term electroencephalography (EEG) with short sleep latency and suspected sleep onset REM periods, episodic sleep initiation and maintenance insomnia). Ancillary tests did not confirm the suspicion. The HLA DQB1*06:02 was negative and cerebrospinal fluid hypocretin-1 levels were 595 pg/ml shortly after disease onset. The history of sleep inertia, automatic behaviors and unrefreshing naps

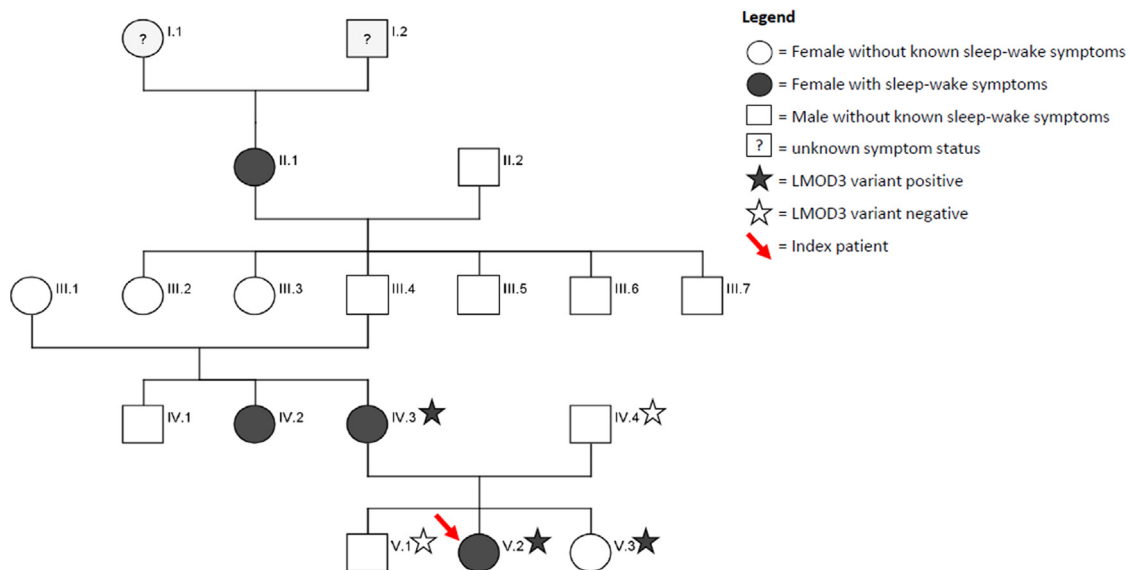


Fig. 1. Patient's family pedigree (Modified from CeGaT Pedigree Chart Designer [7]).

Table 1
Results from multiple electrophysiological examinations.

Parameter [Unit]/Year	Use of medication	ESS	SE _{PSG} [%]	SL _{PSG} [min]	REML _{PSG} [min]	TST _{PSG} [min]	MSL _{MSLT} [min]	STM _{MSLT} /SOREM	IAI _{Acti} [%]
2002	Modafinil 100 mg 3-0-0	20	87	2.00	240.0	440.0	7.0	NREM2	n.a.
2003	17 days after stop Modafinil	21	97	22.5	81.0	439.0	11.0	1 SOREM in first MSLT (latency 8 min)	40
2018	No	22	69	18.5	51.5	264.0	15.0	NREM2	42, control after five months: 33
2019	14 days after stop Bupropion	23	87	7.5	97.0	302.5	7.5	NREM2	47

ESS = Epworth Sleepiness Scale, SE_{PSG} = sleep efficiency during Polysomnography (PSG), SL_{PSG} = sleep latency during PSG, REM = Rapid eye movement sleep, REML_{PSG} = REM-latency during PSG, TST_{PSG} = Total sleep time during PSG, MSL_{MSLT} = mean sleep latency during Multiple Sleep latency test, STM_{MSLT} = maximal sleep stage during MSLT, IAI_{Acti} = Inactivity Index during Actigraphy (indicates percentage of day with low or no activity, not restricted to time spent asleep), n.a. = not available, SOREM = Sleep Onset REM, NREM2 = Non Rapid Eye Movement Sleep stage 2.

in association with high sleep efficiency (97% in 2003) and actigraphy inactivity index (40%) raised the possibility of idiopathic hypersomnia (IH). A sleep diary over 4 weeks indicated 9–13 h of sleep per night. However, the fluctuation of symptoms, with periods of disturbed nocturnal sleep, were considered atypical for IH. During a long-term EEG in 2002, nocturnal sleep duration ranged between 8 and 10 h. An increased daytime sleep propensity was not found, despite an ESS at 17. Discrepancies in the history and between subjective complaints and objective findings, as well as the worsening of symptoms in periods with psychosocial stress, lead to the suspicion of hypersomnia associated with a psychiatric condition. Early evaluations had revealed mild depressive symptoms, immaturity, a tendency towards somatization, unfavorable handling of the situation with overvaluation of symptoms and a high performance demand. A suspicion of imitatorial behavior was also considered, as the symptoms were similar to her mothers'. The patient however never fulfilled the criteria for a psychiatric disorder.

Finally, due to the positive family history and periodicity of symptoms, the diagnoses of atypical KLS and familial periodic hypersomnia, were made. Noteworthy, the patient reported milder hypersomnolence and sleep inertia also between the episodes of hypersomnolence.

3.4. Genetic sequencing

Due to significant diagnostic uncertainty, life impairing symptoms and based on recent findings [6], we sequenced the *LMOD3* gene in all family members. Sequencing revealed a Proline for Histidine substitution at the codon 552 in the patient, her symptomatic mother and her asymptomatic sister. Her father and brother do not carry this variant. We suspect an atypical form of familial KLS, even if diagnostic criteria are not fully met.

4. Discussion

We verified a variant of the *LMOD3* gene in a patient with a long history of unclassified CDH and a positive family history. Her symptomatic mother and asymptomatic sister also carry the variant, a Proline for Histidine substitution at codon 552 (p.P552H), which was previously reported in two sporadic KLS patients [6]. *LMOD3* gene variants seem to be pathogenic for KLS. Other pathogenic *LMOD3* variants were described in patients with nemaline myopathy [8]. Muscle tissue expresses *LMOD3*, but also important areas of the brain regulating wakefulness (cortex, hypothalamus, hippocampus, mesopontine and brainstem), including hypocretin, dopamine, serotonin, noradrenaline and most histamine producing neurons [6]. The finding of *LMOD3*-expression in these sleep-wake-regulating neurons, and particularly in hypocretin neurons is interesting in the context of a Chinese study, which reported reduced CSF hypocretin-1 levels during a relapse of KLS [9].

The variant p.P552H is rare in the general population and further studies are needed to clarify if it is a rare variant without pathological value or a risk factor. A large GWAS did not find any association between *LMOD3* variants and KLS [5]. However, *LMOD3* variants were not systematically assessed, but only in 17 patients and 268 controls and replication was performed by imputation and not by assessing real polymorphisms.

The subacute disease onset following a minor viral infection is typical for KLS [3]. Hypersomnolence periods can last between days and months with large inter- and intra-individual variation [10] [11]. The disease duration of 20 years is rather long, compared to a mean of 8 years [4]. Aggravation of symptoms in 2018 may represent a second peak after a mild course lasting for 15 years [10]. The absence of hyperphagia and disinhibition does not exclude the diagnosis of KLS [4].

This case demonstrates the difficulties diagnosing CDH, when disease course and diagnostic findings are atypical or inconclusive. It underlines the importance and the challenge of accurate timing of sleep examinations, ruling out insufficient sleep and considering inter-individual differences in sleep need. We believe, that intermixed conditions could explain some of the patient's symptoms in between exacerbations. The reported need of sleep between 10 and 11 h in 2021, in a period with less EDS, lead us to suspect a "long sleeping type". In our opinion, intermittent relative sleep insufficiency and some functional component could be an explanation for the lack of decrease in symptoms in between periods.

The verification of the *LMOD3* variant points toward an atypical form of KLS. Nevertheless, this result cannot be used for diagnostic purposes yet. Our results are limited by the small number of participants and the lack of a control group, excluding generalization. We recommend further systematic research on CDH and KLS and the assessment of the *LMOD3* gene variants in a case–control study with patients having a clear KLS diagnosis. There is a strong need for biomarkers allowing an earlier and accurate diagnosis of KLS.

Author contributorship

All authors contributed to the writing of the manuscript.
Elena Wenz: review clinical history, ethical protocol, informed consent procedure.
Mehdi Tafti: molecular genetic analysis.
Claudio L.A. Bassetti: medical care of the patient over more than 20 years.

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Conflict of interest

The authors have no conflicts of interest to declare.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <https://doi.org/10.1016/j.sleep.2022.02.019>

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