Persistent tachypnoea of infancy (PTI/NEHI) and obesity in *SRRM2*-related developmental disorder

Received: 6 Oct 2025
Accepted: 13 Nov 2025

To the Editor:

Within the chILD-EU register, we are longitudinally following 221 individuals with persistent tachypnoea of infancy (PTI, also referred to as neuroendocrine cell hyperplasia of infancy (NEHI)) diagnosed by a multidisciplinary team specialised in childhood interstitial lung disease (chILD) [1]. Since its description in 2022, *SRRM2*-haploinsufficiency has been associated with neurodevelopmental delay (NDD), obesity [2–6] and, in at least one case, the PTI/NEHI phenotype [3]. We performed trio-exome sequencing among 80 PTI/NEHI patients, as previously described [7], and identified four unrelated individuals harbouring novel *SRRM2* loss-of-function (LoF) variants (gnomAD v.4.1.0; ClinVar; October 2025): one premature stop (NM_016333.4:P2:c.559C>T, p.(Gln187Ter)) and three frameshifts (P1:c.3232_3233del, p.(Gln1078GlufsTer17), P3:c.4583_4584del, p.(Val1528GlyfsTer18), P4:c.5645del, p.(Leu1882ArgfsTer2)) (figure 1a; red). All were classified as pathogenic according to American College of Medical Genetics and Genomics criteria [8] and predicted to trigger nonsense-mediated RNA-decay, abolishing functional SRRM2 protein production on the affected allele. At a median age of 6 months symptoms started and at 12 months PTI/NEHI was diagnosed.

While we were searching for evidence to link PTI/NEHI to *SRRM2*-haploinsufficiency, we read with interest the manuscript by Louvrier *et al.* [9], describing *SRRM2* LoF variants in four of their 71 PTI/NEHI patients. Here we contribute some novel, important observations:

1) Expansion of the *SRRM2* variant spectrum (figure 1a): among 32 published LoF variants [2–6, 9] and 31 additionally collected (likely) pathogenic LoF variants in ClinVar (October 2025), 73.0% (46 of 63) were located within exon 11. Exon 11 constitutes approximately 80% of the *SRRM2* coding sequence and is rich in arginine and serine residues, increasing the likelihood of nonsense variant generation [10] and contributing to disease through established *SRRM2*-haploinsufficiency. These data argue against a mutational hotspot of exon 11.
2) Highlighting the risk of obesity (figure 1b): of great importance appears the observation of the development of overweight, even in PTI/NEHI patients who most commonly struggle with failure to thrive and undernutrition in infancy [1, 11], as also observed in our four patients at time of PTI/NEHI diagnosis. Long-term weight trajectories reveal the development of obesity eventually beyond the 95th percentile at median age of 7.2 years (range 1.9 to 10.7 years). Hyperphagia was reported in all as a clinically significant problem. Louvrier *et al.* [9] reported hyperphagia in two of four cases, although the children were not obese at the time of their report. Hyperphagia was presented in 14 of 40 published cases and overweight in 22 [2–5, 9]. Notably, *SRRM2* was identified in three of 521 patients as a monogenic cause of obesity [12].
3) Long-term need for supplemental oxygen (figure 1c): all eight PTI/NEHI cases with *SRRM2*-haploinsufficiency required long-term nocturnal oxygen supplementation. Conversely, the majority of the remaining cohort, PTI/NEHI patients without SRRM2 LoF variant, had lost their need for oxygen above the age of 5 years (87.5%, 35 of 40), consistent with previously reported data [13]. Patients 1 and 4 had persistent ground-glass opacities on high-resolution computed tomography at the average age of 12 years, suggesting a more severe form of PTI/NEHI. In patients 1, 2 and 3, persistent oxygen requirement was attributable to sleep-disordered breathing with a mixed pattern of central and obstructive hypoventilation or apnoea, the latter most likely related to excessive overweight. Oxygen supplementation was sufficient

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In children diagnosed with persistent tachypnoea of infancy (PTI/NEHI) consider *SRRM2*-haploinsufficiency, in particular when obesity or neurodevelopmental symptoms develop or hypoxaemia persists longer than usual https://bit.ly/486qDvc

Cite this article as: Rapp CK, Rodler J, Mauss-Schwarzer K, *et al.* Persistent tachypnoea of infancy (PTI/NEHI) and obesity in *SRRM2*-related developmental disorder. *Eur Respir J* 2026; 67: 2502135 [DOI: 10.1183/13993003.02135-2025].

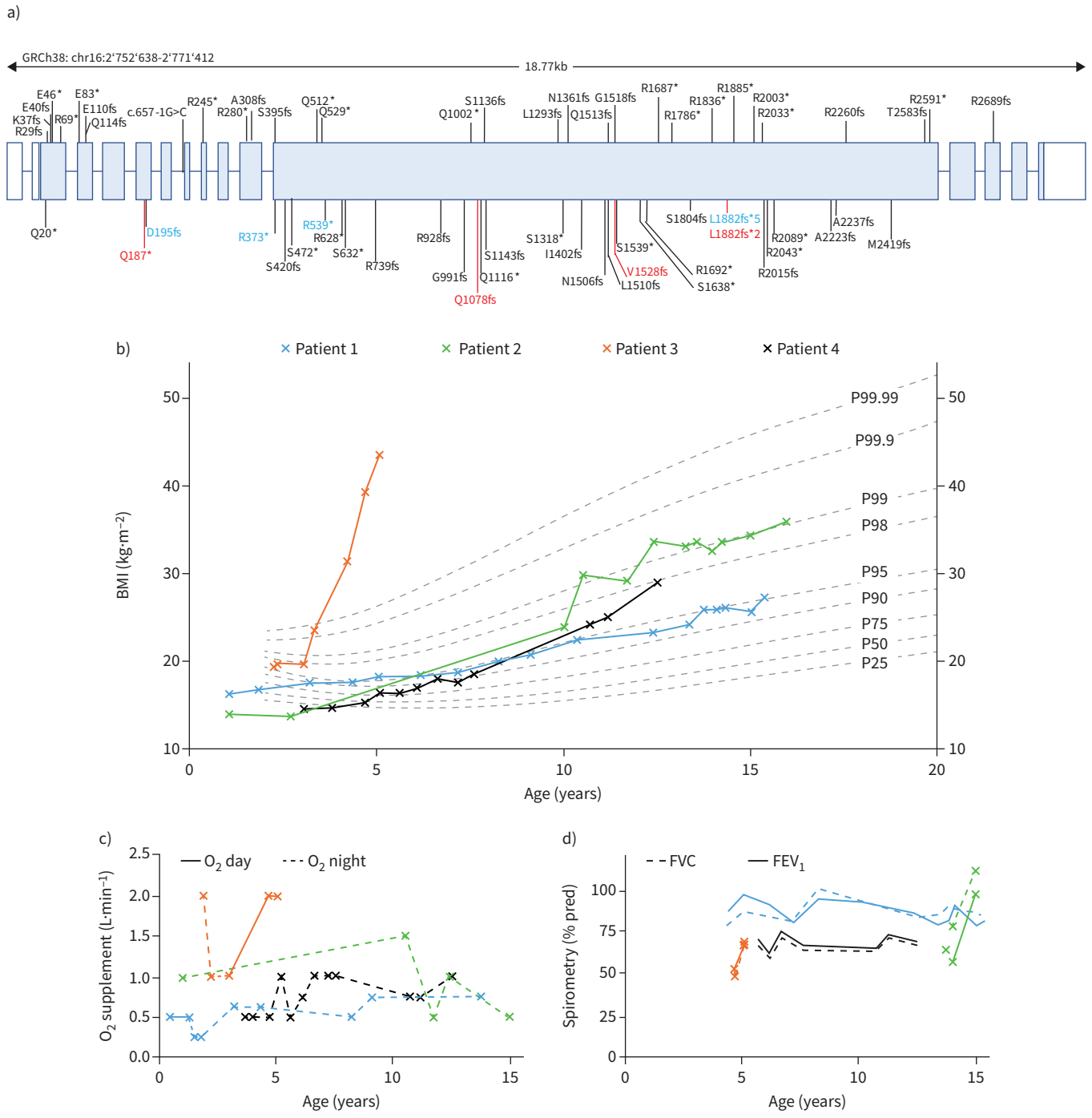

FIGURE 1 a) Single nucleotide variants with loss-of-function mechanism in *SRRM2*. Top: Reported as likely pathogenic or pathogenic in clinical database ClinVar (October 2025). Bottom: Published studies (Cuinat *et al.* [2], Regan-Fendt *et al.* [3], Pagnamenta *et al.* [4], Louvrier *et al.* [9], and our four cases (marked in red)). Previously published cases with persistent tachypnoea of infancy/neuroendocrine cell hyperplasia of infancy (PTI/NEHI) are marked in blue. b) Body mass index (BMI) of all four patients plotted along percentile curves, illustrating individual BMI trajectories in relation to standard reference values. Note that percentiles were asymmetrically plotted above P75, to accommodate the pronounced weight gains (https://www.cdc.gov/growthcharts/). Time course of c) oxygen supplementation (daily oxygen: solid line; and nocturnal oxygen: dotted line) and d) lung function (forced vital capacity (FVC): dotted line; and forced expiration volume in 1 s (FEV_1): solid line).

as treatment. Of interest, increased prevalence of obstructive sleep apnoea syndrome in PTI/NEHI has been previously described [1, 14].

4) Abnormal pulmonary function tests (figure 1d): long-term follow-up revealed a restrictive pattern in two patients, with forced vital capacity (FVC) values between 60% and 75% of predicted. One patient

had normal FVC and forced expiratory volume in 1 s but reduced maximal expiratory flow at 25% of FVC (39% of predicted), suggesting small airway obstruction.

5) Neurodevelopmental involvement: all four patients exhibited NDD, with first appearance around 3.6 years (range 1.1 to 4.3 years). Additionally, patient 1 presented with hypotonia, muscle weakness, motor incoordination, seizures, and persistent motor delay; patients 3 and 4 had mild language impairment. Patients 2 and 4 had short attention spans, and patient 4 fulfilled criteria for autism spectrum disorder. Neurological comorbidity was observed in 23.7% (18 out of 76) of the remaining PTI/NEHI cohort, including 12 cases with NDD, consistent with previously reported increased prevalence [11].
6) Combining our cohort and the data of Louvrier *et al*. [9], eight patients with *SRRM2*-haploinsufficiency were identified among the 151 PTI/NEHI subjects, yielding a diagnostic rate of 4.7%. Considering only PTI/NEHI patients with NDD (n=19) the likelihood of *SRRM2*-haploinsufficiency (n=8) was substantially increased with a diagnostic rate of 42% (Fisher's exact test, $p<0.0001$).
7) Among 40 published patients with *SRRM2*-haploinsufficiency, nine patients exhibited a PTI/NEHI phenotype (22.5%), demonstrating an overall enrichment of the rare PTI/NEHI manifestation in even less frequent *SRRM2*-haploinsuffciency [3, 9].

These data suggest that *SRRM2*-haploinsufficiency may initially manifest as a respiratory phenotype resembling PTI/NEHI, followed by subtle NDD and obesity. This knowledge is of interest for neurologists evaluating tachypnoea and hypoxaemia, and for pneumologists monitoring early signs of obesity or NDD. *SRRM2* should be included in the molecular workup for PTI/NEHI. Although our analysis did not include copy number variant (CNV) detection, the identification of seven microdeletions among 40 cases [2, 4, 9] highlights the importance of high-quality exome or genome sequencing with integrated CNV analysis as a preferred diagnostic strategy.

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Acknowledgements: We thank all probands and families for their kind contributions and participation in the study.

Ethics statement: The parents gave their written informed consent and the children assented to participate in the chILD-EU register study. The study was approved by the ethics committees of the University of Munich, Germany (EK111-13, EK20-329).

Author contributions: C.K. Rapp collected and visualised the data, carried out the initial analyses, conceptualised and designed the study, and drafted the initial manuscript. M. Griese conceptualised and designed the study, coordinated and supervised data collection, funded the study, drafted the initial manuscript, and critically reviewed and revised the manuscript. S. Reu-Hoefer interpreted and visualised the data from the histopathological tissue sample. J. Rodler, F. Gothe, D. Aschmann-Mühlhans, F. Prenzel, E. Eber and M. Egger collected data through the chILD-EU registry and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects

Conflict of interest: F. Prenzel reports payment or honoraria for lectures, presentations, manuscript writing or educational events from Sanofi, ALK-Abelló, Vertex Pharmaceuticals, BioCryst and Takeda Pharma, support for attending meetings from BioCryst, and participation on a data safety monitoring board or advisory board with Takeda Pharma. M. Griese reports support for the present study from Deutsche Forschungsgemeinschaft and Boehringer Ingelheim, payment or honoraria for lectures, presentations, manuscript writing or educational events from Boehringer Ingelheim, and participation on a data safety monitoring board or advisory board with Boehringer Ingelheim. The remaining authors have no potential conflicts of interest to disclose.

Support statement: The chILD-EU register is a collaborative study (trial registration number: NCT02852928) initiated by the FP7 project 305653-chILD-EU (www.childeu.net) and kept up by participating institutions, which may be supported by funders. Of relevance for this study were grants from the Deutsche Forschungsgemeinschaft (DFG, Gr970/9-1 and 9-2), Bonn, Germany. The funders had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the manuscript for publication. Funding information for this article has been deposited with the Open Funder Registry.

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