Letter to the Editor: Focus on progressive myoclonic epilepsy in Berardinelli-Seip syndrome

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We have read the report of congenital generalized lipodystrophy (CGL) type 2 by Ferranti et al. [1] with interest. The authors report the case of two sisters with progressive myoclonic epilepsy (PME) associated to type 2 CGL due to the biallelic variant c. 1048C>T (rs763070770, NM_001122955.3: p.Arg350Ter) in exon 8 of the *BSCL2* gene. Apparently both patients presented an overlapping clinical phenotype suggestive of Berardinelli-Seip syndrome and progressive myoclonic epilepsy. The older sister died at the age of 18 due to the neurodegenerative nature of this disease. Strikingly, and despite the title of the report and a comment in the Abstract, the authors do not speak at all of lipodystrophy in the description of the cases, focusing mainly on the neurological features. Therefore, in addition to the lipodystrophic phenotype, it would have been essential for the authors to complete the clinical descriptions indicating if the patients presented acanthosis nigricans, hypertriglyceridemia, hepatomegaly, or phlebomegaly, and if so, from what age. We might hypothesize that the patients exhibited generalized lipoatrophy, but if this were not the case, it would suggest that the variant c.1048C>T does not impair the lipid droplet biogenesis.

Except for the progression rate of the disease, the clinical features described by the authors are superimposable to those we reported years ago in the case of PELD (Progressive Encephalopathy with or without Lipodystrophy or Celia's Encephalopathy, MIM: #615924) [2], caused by the variant c.985C>T in *BSCL2*. The PELD variant (rs587777606, NM_001122955.3: c.985C>T, p.(Arg329Ter) produces a cryptic splicing site, causing skipping of exon 7 in *BSCL2*, and giving rise to the truncated seipin p. (Tyr289Leufs*64). This leads to much higher brain expression of the shortest *BSCL2*-201 transcript (which is hardly expressed in a normal brain, <1%) [2], and which is harmful to neurons in homozygosity or compound heterozygosity [3]. PELD is an extremely rare neurodegenerative childhood disease with a fatal prognosis before the age of 9. Most, but not all affected patients exhibit some signs of lipodystrophy (which is actually variable in homozygous PELD, with no acanthosis nigricans or muscular hypertrophy). The children who eventually died had developed progressive encephalopathy with psychomotor regression, cognitive deterioration, spasticity, loss of speech, and seizures between the ages of 2 and 3 [2].

In 2016, Opri et al. [4] described 3 patients with PME and recessively inherited CGL type 2 associated with known seipin variants. We have recently discovered that one of the variants (c.974dupG) in fact gave rise to the skipping of exon 7 of *BSCL2* [5], as is also the case in PELD, but the progression of neurodegeneration was more prolonged. When comparing the evolution of the onset of symptoms in Ferranti's patients (the beginning of psychomotor delay, neurological deterioration, seizures, and subsequently, death), it is obvious that the progression rate of the disease remained much slower than in the PELD cases we reported previously. That might be explained by the consequences of the c.1048C>T variant for the three seipin isoforms encoded by the *BSCL2* gene under natural conditions. We observed that it results in a premature stop codon for both the longest NM_001122955.3 transcript (*BSCL2*-203, ENST00000360796.9; CCDS44627), which encodes the 462 amino acids seipin isoform: c.1048C>T, p.Arg350Ter, R [CGA] > * [TGA], and for the NM_032667.6 (*BSCL2*-205/207/210, ENST00000403550.5; ENST00000407022.7; ENST00000421906.5; CCDS8031) tran-

script, which encodes the 398 amino acids seipin isoform: c.856C>T, p.Arg286Ter, R [CGA] > * [TGA]. However, for the shortest NM_001130702.2 transcript (*BSCL2*-201, ENST00000278893.11; CCDS55769), which encodes the 287 amino acids seipin isoform, the variant (c.714C>T, p.Asn238=, N [AAC] > N [AAT]) caused no resulting change to the encoded amino acid. Therefore, our hypothesis is that the longest and medium isoforms of seipin with premature stop codons caused by the c.1048C>T variant, are probably subject to nonsense-mediated mRNA decay, and that the shortest seipin isoform, which remains intact, is probably more expressed in the brain albeit not as much as in the classic form of PELD. This would explain the differences observed in the evolution rate of both described patterns. Nonetheless, this would need to be quantified in brain samples from the deceased patient if available. Furthermore, it would be of interest to perform cDNA studies, for example using the *in silico* program HSF (https://www.genomnis.com/access-hsf), which predicts the effects of the variant on splicing, detecting significant alterations of the ESE/ESS auxiliary sequences which may modify the exon recognition by the spliceosome.

References

1. Ferranti S. et al. (2020) Focus on progressive myoclonic epilepsy in Berardinelli-Seip syndrome. Neurol Sci, doi: 10.1007/s10072-020-04418-1. Online ahead of print.
2. Guillén-Navarro E. et al. (2013) A new seipin-associated neurodegenerative syndrome. J Med Genet, 50: 401-409.
3. Ruiz-Riquelme A. et al. (2015) Larger aggregates of mutant seipin in Celia's Encephalopathy, a new protein misfolding neurodegenerative disease. Neurobiol Dis, 83: 44-53.
4. Opri et al. (2016) Progressive myoclonus epilepsy in congenital generalized lipodystrophy type 2: Report of 3 cases and literature review. Seizure, 42: 16.
5. Sánchez-Iglesias S. et al. (2019) Celia's encephalopathy and c.974dupG in BSCL2 gene: a hidden change in a known variant. Neurogenetics, 20(2): 73-82.