Dear Editor,

We thank de Boer *et al.* for their valuable comments to our article and for drawing attention to the early manifestations and pre-manifest subjects in retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S)[1]. In our article, we reported phenotypic variability in three related cases and analyzed their large genealogy. The genetic testing identified 15 additional *TREX1* gene mutation carriers, who in the neurological evaluation conducted at that time did not show evident clinical symptoms of RVCL-S, including Raynaud's phenomenon (authors' Fig. 1). The mean age of these pre-manifest relatives was 27.2±7.0 years (median = 25; range = 18-40 years, and 60% aged 18-27 years) thus, most of them had not reached the typical age of onset. Due to financial constraints, no neuroimaging or neuro-ophthalmological clinical studies were performed; therefore, we could not ascertain the absence of vascular retinopathy or subclinical brain signs in some of the older pre-manifest carriers. Vascular retinopathy in RVCL-S becomes apparent in the fourth or fifth decade of life, soon followed by clinical manifestations of progressive focal and global brain disease[1], and according to Stam et al., the mean age at diagnosis is 42.9±8.3 years[2]. Regarding the follow-up of pre-manifest carriers, we agree with de Boer et al., and medical care was offered to all of them at our institution. Since a brain biopsy should only be considered in cases with uncertain imaging findings and negative family history, the molecular test is definitely the gold standard for RVCL-S diagnosis. Finally, in relation to withholding a diagnosis to pre-manifest mutation carriers, the pre-symptomatic diagnosis was offered to at-risk persons, although only 11 relatives accepted. Until now, merely one out of three pre-manifest carriers returned to our hospital to receive his genetic results; in the remaining carriers, delivery of their results was postponed due to depression, highlighting that few people wish to know their genetic status. Since this is a personal decision, we considered ethical to respect the subjects' autonomy, and their right to not to know[3].

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