Cotranslational degradation of mutant sacsin explains lack of genotype-phenotype correlation in ARSACS patients

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Longo et al. demonstrated that the clinical variability in ARSACS does not depend on the type/position of the *SACS* mutations. They indeed demonstrated that sacsin is almost absent in a large panel of ARSACS patients regardless of the nature of the mutation. Sacsin is not detectable when it carries null mutations, but even when it carries different kinds of missense mutations. They indeed discovered that mutant sacsin undergoes a preemptive cotranslational degradation, which prevents the production of a mature protein thus causing ARSACS. They propose that sacsin levels should be evaluated to unambiguously define ARSACS diagnosis.