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Sommario	Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterized by degeneration of motorneurons leading to progressive paralysis and eventually death due to respiratory failure. So far, no effective treatments are available for this devastating disease. Interestingly, genetic forms of ALS show the same pathological alterations observed in the most frequent sporadic cases. For this reason, studying the role of single disease causing mutations is important to gain insight into the pathophysiological events that lead to disease development. Ten years ago a mutation in the gene encoding for VAPB was associated with a dominantly inherited form of ALS (termed ALS8). Moreover, sporadic ALS patients have reduced levels of the endogenous protein. VAPB belongs, along with its homologue VAPA, to the VAP protein family: ER resident tail anchored proteins that, thanks to their binding partners, are involved in several cellular functions like lipid transport, ER stress and membrane contact site formation. The ALS-associated mutation P56S dramatically alters VAPB structure, thus preventing the binding to its physiological interactors and causing its aggregation. The cellular and molecular mechanisms underlying pathogenicity of mutant VAPB are still poorly understood. It is still

	unclear whether P56S-VAPB-generated inclusions exert a direct toxic function or whether reduced levels of the wt protein are sufficient to trigger the disease. An intermediate situation, where both mechanisms contribute to ALS development, could also be possible. The aim of my thesis is to analyze the contribution of mutant VAPB gain or loss of function in the development of ALS. To reach this goal, I used two complementary approaches: I analyzed cellular models that either express moderate levels of P56S-VAPB or have reduced levels of the endogenous protein. Our findings would be relevant not only to understand the pathogenesis of ALS8, but also for forms of sporadic ALS, in which VAPB levels are reduced.
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