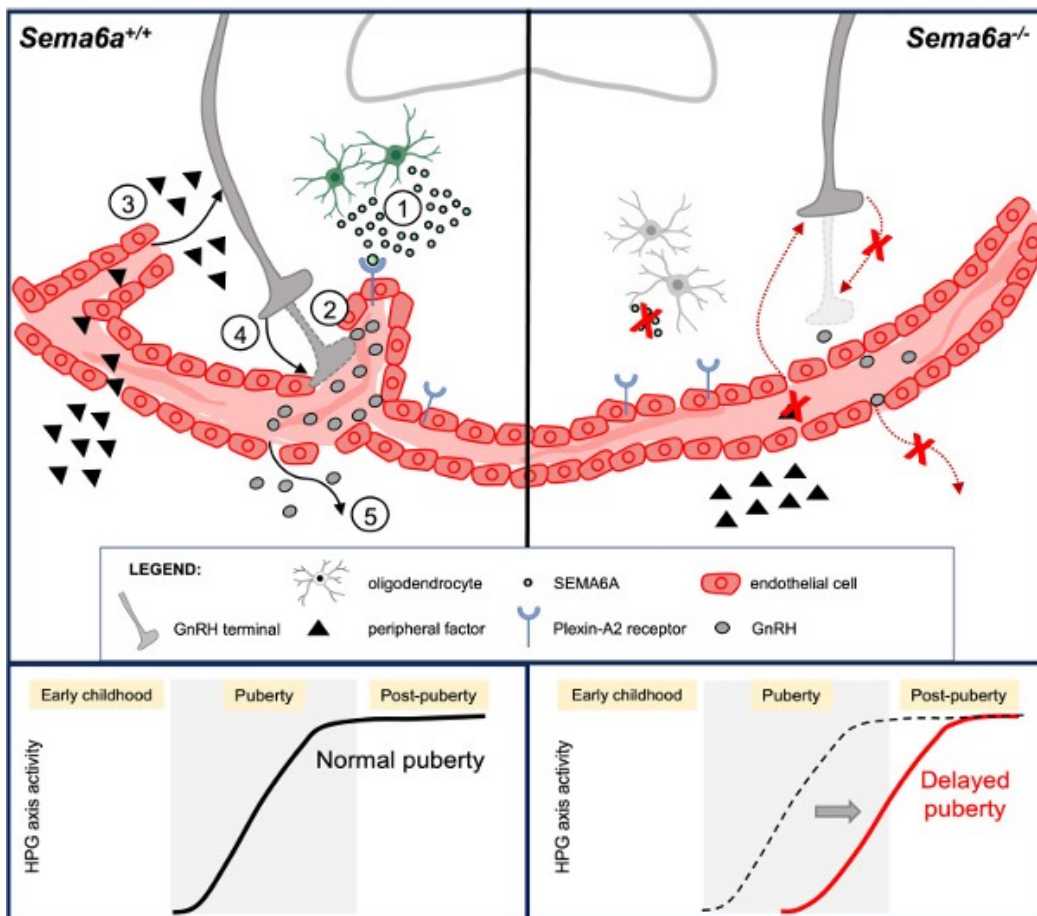


SEMA6A drives GnRH neuron-dependent puberty onset by tuning median eminence vascular permeability.



Gonadotropin-Releasing Hormone (GnRH) neurons control reproduction in most vertebrates and, during embryogenesis, migrate from the nose to the hypothalamus. There, the innervation of the median eminence (ME) by GnRH+ axons is vital to ensure puberty onset. However, molecular and cellular mechanisms underlying ME development and genetic determinants of pubertal timing are incompletely understood. Here, we found a novel *SEMA6A* variant in a 6 proband from 3 unrelated families presenting delayed puberty. First, we demonstrated that the identified variant is pathogenic by *in silico* analyses and affects protein synthesis and localization upon overexpression in COS-7 cells. Then, by analyzing wildtype and *Sema6a*-null embryos, we showed that SEMA6A is expressed during GnRH neuron embryonic development, but is dispensable for their migration. Yet, SEMA6A expression in the ME raised the possibility of SEMA6A additional roles on GnRH neuron within the postnatal brain. In agreement with this hypothesis, we found that SEMA6A is expressed by ME-resident oligodendrocytes (1) and its loss significantly impairs GnRH axon innervation of the ME (2); consequently, puberty onset was significantly delayed in male and female *Sema6a*-null mice. Finally, we investigated cellular and molecular mechanisms through which SEMA6A control these processes. First, we found that SEMA6A receptor PLXNA2 is expressed by fenestrated endothelial cells lining the ME, suggesting a possible involvement of SEMA6A in regulating neurovascular interactions. Then, we demonstrated that SEMA6A is able to enhance the permeability of endothelial cells in a 2D *in vitro* assay by coupling with PLXNA2 receptor. Further, we confirmed that SEMA6A loss *in vivo* reduces vascular permeability and the number of fenestrated loops in the ME. In all, our data revealed a hitherto undescribed role for SEMA6A in tuning the ME vascular barrier and for proper puberty onset, possibly modulating the exchange of molecules (3) key for GnRH neuron patterning (4-5).