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MEETING ABSTRACT

A2.8

The role of methyl transferase PRDM12 in nociceptor function in development and adulthood

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Background: Congenital insensitivity to pain (CIP) syndromes are a group of rare genetic disorders of the peripheral nervous system (PNS) marked by the inability to perceive painful stimuli due to dysfunctional or absent sensory neurons within dorsal root ganglia (DRG). We, and others, have recently reported mutations in methyl transferase PR-domain containing member 12 (PRDM12) to cause a novel type of autosomal recessive CIP syndrome [1, 2]. We showed that PRDM12 is a key regulator of sensory neuronal specification in *Xenopus leavis* and necessary for nocifensive behavior of *Drosophila melanogaster*. Mutations in PRDM12 cause structural instability to the protein resulting in large aggregates in the nucleus. Subsequently, we reported that PRDM12 is expressed in the PNS early during development in mice and is required for directing nociceptor specification by regulating TrkA expression [3]. Early developmental ablation of PRDM12 expression leads to a marked reduction of DRG volume, and a complete absence of TrkA+ sensory neurons.

Methods: Well-established cellular, molecular, behavioral and electrophysiological assays were employed in temporal and spatially restricted developmental (*PRDM12*$^{fl/fl}$, *Avil-Cre*) and inducible (*PRDM12*$^{fl/fl}$, *Brn3a-CreER*^{T2} or *PRDM12*$^{fl/fl}$, *R26-CreER*^{T2}) genetic mouse models to delineate the function of PRDM12 in pain perception.

Results: We find that PRDM12 is expressed in a specific subtype of nociceptors within the DRG. In both developmental and adult PRDM12-deficient mice, electrophysiological and behavioral assays reveal a complete absence of pain perception. Furthermore, we report evolutionary conserved downstream targets of PRDM12 in human patient fibroblasts, and validate them in *D. melanogaster* and mouse models of nociception.

Discussion: We conclude that PRDM12 is required for nociceptor outgrowth and function during development, and for pain perception in adulthood. PRDM12-dependent transcriptional program and function differs during development and adulthood, making it an attractive therapeutic pain target.

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