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HDAC8 mutations in Cornelia de Lange syndrome affect the cohesin acetylation cycle

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Cornelia de Lange syndrome (CdLS) is a dominantly inherited congenital malformation disorder, caused by mutations in the cohesin-loading protein NIPBL[1,2] for nearly 60% of individuals with classical CdLS[3-5], and by mutations in the core cohesin components SMC1A (~5%) and SMC3 (<1%) for a smaller fraction of probands[6,7]. In humans, the multisubunit complex cohesin is made up of SMC1, SMC3, RAD21 and a STAG protein. These form a ring structure that is proposed to encircle sister chromatids to mediate sister chromatid cohesion[8] and also has key roles in gene regulation[9]. SMC3 is acetylated during S-phase to establish cohesiveness of chromatin-loaded cohesin[10-13], and in yeast, the class I histone deacetylase Hos1 deacetylates SMC3 during anaphase[14-16]. Here we identify HDAC8 as the vertebrate SMC3 deacetylase, as well as loss-of-function HDAC8 mutations in six CdLS probands. Loss of HDAC8 activity results in increased SMC3 acetylation and inefficient dissolution of the `used' cohesin complex released from chromatin in both prophase and anaphase. SMC3 with retained acetylation is loaded onto chromatin, and chromatin immunoprecipitation sequencing analysis demonstrates decreased occupancy of cohesin localization sites that results in a consistent pattern of altered transcription seen in CdLS cell lines with either NIPBL or HDAC8 mutations.