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Presentation preference: oral presentation, poster presentation

The interplay between AUTS2-/FBRSL1-ncPRC1.3 in transcriptional regulation and brain development

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The heterogeneous family of complexes comprising Polycomb Repressive Complex 1 (PRC1) is instrumental to establishing facultative heterochromatin that is repressive to transcription. Yet, two PRC1 species, ncPRC1.3 and ncPRC1.5, are known to comprise novel components, AUTS2, P300, and CK2 that convert this repressive function to that of transcription activation. Here, we report that patients harboring mutations in the HX repeat domain of AUTS2 exhibit defects in AUTS2 and P300 interaction as well as a developmental disorder reflective of Rubinstein-Taybi syndrome, which is mainly associated with a heterozygous pathogenic variant in *CREBBP/EP300*. Moreover, the absence of AUTS2 or mutation in its HX repeat domain gives rise to a mis-regulation of a subset of developmental genes and curtails motor neuron differentiation of mouse embryonic stem cells. Notably, the transcription factor, Nuclear Respiratory Factor 1 (NRF1) exhibits a novel and integral role in this neurodevelopmental process, being required for AUTS2-ncPRC1.3 recruitment to chromatin. Furthermore, AUTS2 and its analogue, FBRSL1 incorporate into ncPRC1.3 in a competitive and developmental stage-specific manner. The selective incorporation of these two components into ncPRC1.3 shifts throughout brain development as well as during ESC to neuronal lineage differentiation. We postulate that this phenomenon reflects a switch in ncPRC1.3 composition from one that represses neuronal genes in ESC (PRC1-FBRSL1) to one that activates specific genes for neuronal differentiation (PRC1-AUTS2).