METTL23 mutation alters histone H3R17 methylation in normal-tension glaucoma

Yang Pan (1) , Akiko Suga (1) , Itaru Kimura (2) , Chojiro Kimura (3) , Yuriko Minegishi (1) , Mao Nakayama (1) , Kazutoshi Yoshitake (1) , Daisuke Iejima (1) , Naoko Minematsu (1) , Megumi Yamamoto (1) , Fumihiko Mabuchi (4) , Mitsuko Takamoto (5) , Yukihiro Shiga (6) , Makoto Araie (5) , Kenji Kashiwagi (4) , Makoto Aihara (5) , Toru Nakazawa (6) , Takeshi Iwata (1)

1 National Institute of Sensory Organs, National Hospital Organization Tokyo Medical Center, Tokyo, Japan.
2 Department of Ophthalmology, Tokai University Hachioji Hospital, Tokyo, Japan.
3 Department of Ophthalmology, Kimura Eye Clinic, Fukushima, Japan.
4 Department of Ophthalmology, University of Yamanashi, Yamanashi, Japan.
5 Department of Ophthalmology, University of Tokyo, Tokyo, Japan.
6 Department of Ophthalmology, Tohoku University Graduate School of Medicine, Sendai, Japan.

Normal-tension glaucoma (NTG) is a heterogeneous disease characterized by retinal ganglion cell (RGC) death leading to cupping of the optic nerve head and visual field loss at normal intraocular pressure (IOP) . The pathogenesis of NTG remains unclear. Here, we described a single nucleotide mutation in exon 2 of the methyltransferase like 23 (METTL23) gene identified in a three-generation Japanese NTG family. This mutation caused METTL23 mRNA aberrant splicing, which abolished normal protein production and altered subcellular localization. Mettl23 knock-in (Mettl23+/G & Mettl23G/G) and knockout (Mettl23+/- & Mettl23-/-) mice developed a glaucoma phenotype without elevated IOP. METTL23 is a histone arginine methyltransferase expressed in murine and macaque RGCs. However, the novel mutation reduced Mettl23 expression in RGCs of Mettl23G/G mice, which recapitulated both clinical and biological phenotypes. Moreover, our findings demonstrated that Mettl23 catalyzed the dimethylation of H3R17 in the retina, and was required for the transcription of pS2, an estrogen receptor ? target gene that was critical to RGC homeostasis th

J Clin Invest. 2022 Sep 13;e153589. doi: 10.1172/JCI153589.
PMID: 36099048 DOI: 10.1172/JCI153589