



HAL
open science

RNA methyltransferase holoenzymes: implications in mRNA maturation and translation and in neurodevelopmental disorders

Marc Graille

► **To cite this version:**

Marc Graille. RNA methyltransferase holoenzymes: implications in mRNA maturation and translation and in neurodevelopmental disorders. RNA modification and Processing, Sep 2024, Mayence, Germany. hal-04908412

HAL Id: hal-04908412

<https://cnrs.hal.science/hal-04908412v1>

Submitted on 23 Jan 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

RNA methyltransferase holoenzymes : implications in mRNA maturation and translation and in neurodevelopmental disorders

Modified nucleotides in non-coding RNAs, such as rRNAs, tRNAs and snRNAs, represent an important layer of gene expression regulation through their ability to fine-tune mRNA maturation and translation. Dysregulation of such modifications and the enzymes installing them have been linked to various human pathologies including neurodevelopmental disorders and cancers.

Several methyltransferases (MTases) are regulated allosterically by human TRMT112. The complete interactome of this regulator and the substrates of its interacting MTases have been only recently characterized, confirming that all these TRMT112-MTase complexes modify factors (snRNAs, tRNAs, rRNAs and proteins) involved in the mRNA maturation and translation processes. Indeed, the TRMT112-BUD23 and TRMT112-METTTL5 complexes catalyze the formation of N7-methylguanosine (m⁷G) and N6-methyladenosine (m⁶A) on the 18S rRNA and participate in 40S ribosomal subunit biogenesis pathway. The TRMT112-HEMK2 complex modifies the translation termination factor eRF1, which is a tRNA mimicry critical for the release of the newly synthesized proteins. The TRMT112-ALKBH8, TRMT112-TRMT11 and TRMT112-THUMPD3 complexes contribute to translation elongation by modifying tRNAs. Finally, the TRMT112-THUMPD2 complex methylates U6 snRNA, the core component of the major catalytic spliceosome and hence is important for optimal splicing of weak splice sites.

Recent results obtained on the functional characterization of eight homozygous METTTL5 missense mutants identified in patients suffering from intellectual disability and microcephaly with varying degrees of penetrance will be presented. This work brings decisive information on the importance of this 18S rRNA m⁶A methylation, in normal brain development. Considering that the modification is adjacent to the ribosomal decoding site, it suggests that its absence rewires translation with important consequences in maturing neurons.