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PRESS RELEASE (2026/11/09)

Small histone differences help shape gene regulation during sperm development

Researchers show that H3mm15, a histone differing from H3.3 at just three amino acids, has distinct chromatin properties and supports normal sperm development in mice

Fukuoka, Japan— Researchers from Kyushu University have found that H3mm15, a histone H3.3 subvariant, contributes to normal sperm development in mice by helping regulate gene expression during spermatogenesis. The findings show that H3mm15 cannot be interchanged with conventional H3.3; although the proteins differ at only three amino acids, they behave differently in chromatin and the DNA-protein structure that packages genetic material.

Histones act like molecular spools around which DNA is wrapped, helping organize the genome and regulate gene activity. H3.3, a histone H3 variant, is incorporated into chromatin independently of DNA replication and is associated with active genomic regions.

The researchers previously identified several closely related H3.3 subvariants in mice. Among them, H3mm15 differs from conventional H3.3 at just three amino acids, and RNA analyses showed that the gene encoding H3mm15 is predominantly expressed in the testis. These observations raised a broader question: can such small differences in histone amino acid sequence lead to distinct biological functions?

In the present study, a research team led by Professor Akihito Harada of the Faculty of Medical Sciences, in collaboration with Qianmei Wu, Distinguished Professor Yasuyuki Ohkawa of Kyushu University's Medical Institute of Bioregulation, and Professor Tatsuya Takemoto of Tokushima University, investigated the function of H3mm15. They generated H3mm15-deficient mice and assessed their testis structure, sperm motility, and gene expression. The study was published online in the journal *Nucleic Acids Research* on November 9, 2026.

The team found that mice lacking H3mm15 showed disorganized seminiferous tubules—the structures in which sperm develop—as well as reduced sperm motility. In addition, there was altered expression of spermatogenesis-related genes, particularly those associated with transition into meiosis. In cultured cells, H3mm15 was incorporated into chromatin less efficiently than H3.3 but showed relative enrichment near promoters, where gene transcription begins. Analysis of transgenic mouse testes also detected H3mm15-EGFP enrichment around transcription start sites.

Structural and biochemical analyses revealed that H3mm15 forms less stable nucleosomes, the basic units of chromatin, than H3.3. Live-cell measurements showed more dynamic chromatin association, with glutamine at position 100 contributing strongly to this behavior. However, H3mm15-containing nucleosomes did not enhance RNA polymerase II transcription in vitro under the conditions tested, suggesting that reduced nucleosome stability alone does

not explain its effects on gene regulation.

“Our findings show that histone variants that look almost identical can still have distinct structural and cellular properties and biological roles. The three amino acid differences in H3mm15 are associated with changes in chromatin behavior, and these differences may contribute to the maintenance of normal spermatogenesis in mice,” says Harada.

The findings support a “histone sub-barcode” model in which closely related H3.3 subvariants contribute distinct chromatin properties through differences in genomic localization, stability, and dynamics.

“Understanding why cells retain closely related histone subvariants may reveal how specialized chromatin environments are established during development. The findings provide a framework for investigating whether other tissue-expressed histone variants contribute to normal development or disease,” says Harada.

“Since H3mm15 is a mouse H3.3 subvariant, additional studies are required before considering applications to humans. In the long term, understanding how specialized histone variants regulate gene expression may help researchers interpret epigenetic abnormalities associated with impaired spermatogenesis and sperm quality,” concludes Harada.

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For more information about this research, see "Histone H3.3 subvariant H3mm15 is required for normal spermatogenesis by regulating gene expression,” Qianmei Wu, Akihito Harada, Cheng-Han Ho, Eisho Tanida, Kaori Tanaka, Kazumitsu Maehara, Bing Wang, Ryuki Shimada, Kei-ichiro Ishiguro, Haruhiko Ehara, Shun-ichi Sekine, Shinya Oki, Yuma Ito, Hitoshi Kurumizaka, Tatsuya Takemoto, and Yasuyuki Ohkawa, *Nucleic Acids Research*, https://doi.org/10.1093/nar/gkag994

About Kyushu University

Founded in 1911, Kyushu University is one of Japan's leading research-oriented institutions of higher education, consistently ranking as one of the top ten Japanese universities in the Times Higher Education World University Rankings and the QS World University Rankings. Located in Fukuoka, on the island of Kyushu—the most southwestern of Japan’s four main islands—Kyushu U sits in a coastal metropolis frequently ranked among the world’s most livable cities and historically known as Japan’s gateway to Asia. Its multiple campuses are home to around 19,000 students and 8,000 faculty and staff. Through its VISION 2030, Kyushu U will “drive social change with integrative knowledge.” By fusing the spectrum of knowledge, from the humanities and arts to engineering and medical sciences, Kyushu U will strengthen its research in the key areas of decarbonization, medicine and health, and environment and food, to tackle society’s most pressing issues.

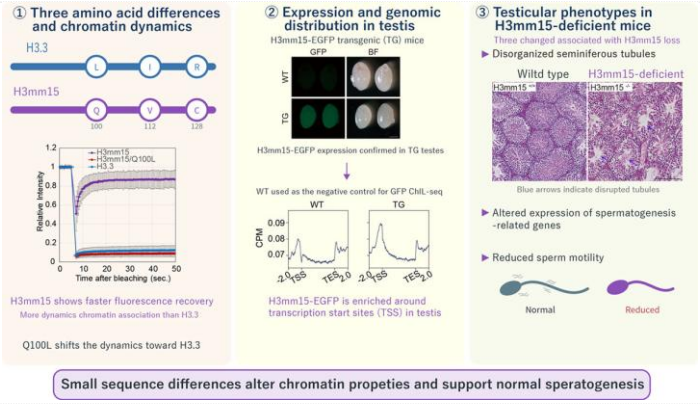


FIG.1 H3mm15: A distinct histone H3.3 subvariant supporting normal spermatogenesis. H3mm15 is predominantly expressed in the testis and differs from conventional H3.3 at amino acids 100, 112, and 128. Live-cell FRAP analysis showed that H3mm15 associates more dynamically with chromatin than H3.3, while replacing glutamine 100 with the corresponding H3.3 residue shifted its behavior toward that of H3.3. Mice lacking H3mm15 exhibited seminiferous tubule disorganization, altered expression of spermatogenesis-related genes, and reduced sperm motility. Together, these findings indicate that small differences in histone amino acid sequence can alter chromatin properties and contribute to normal spermatogenesis. (Akihito Harada and co-authors/Kyushu University)

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