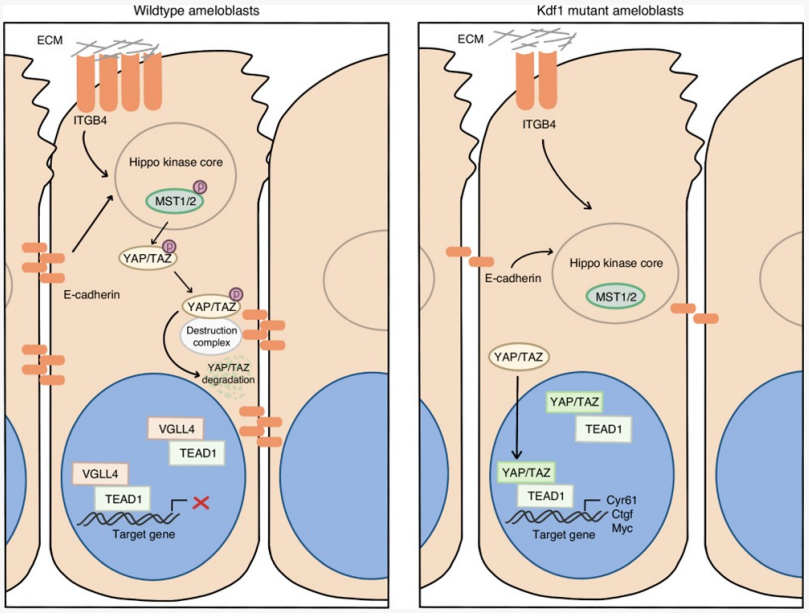
How a Single Genetic Change Derails Enamel Formation in Developing Teeth

Researchers uncover how a patient-derived KDF1 mutation disrupts cell adhesion and Hippo-YAP signaling, impairing enamel-producing cells



Researchers showed that a Kdf1 mutation disrupts cell-adhesion complexes in enamel-forming cells, alters Hippo pathway regulation, and increases nuclear YAP activity, leading to abnormal ameloblast behavior and defective enamel formation.

CHENGDU, CHINA, June 29, 2026 /EINPresswire.com/ -- A patient-derived KDF1 mutation was found to impair enamel formation by disrupting cell adhesion and Hippo-YAP signaling in dental epithelial cells. Using genetically engineered mice and cellular models, the scientists showed that the mutation weakened intercellular connections, increased abnormal YAP activity, and blocked proper ameloblast differentiation. Treatment with a YAP-TEAD1 inhibitor partially restored enamel-forming functions. The findings reveal a new disease mechanism underlying amelogenesis imperfecta and suggest potential therapeutic strategies for patients.

Dental enamel is the hardest substance in the human body, protecting teeth from wear, temperature changes, and decay. However, enamel cannot regenerate once damaged. Inherited disorders, such as amelogenesis imperfecta, disrupt enamel formation during development, leaving affected individuals with fragile, discolored, and decay-prone teeth. Although several genes have been linked to this condition, the mechanisms by which specific mutations impair enamel-forming cells have remained unclear.

Addressing this challenge, a research team was led by Professor Wei Zhao and Professor Dongsheng Yu from the Department of Oral Emergency, Guanghua School of Stomatology, Hospital of Stomatology, Guangdong Provincial Key Laboratory of Stomatology at Sun Yat-sen University, Guangzhou, China. The researchers investigated a patient-derived keratinocyte

differentiation factor 1 (KDF1) mutation, p.R303P, previously associated with inherited enamel defects. Using genetically engineered mice, molecular analyses, imaging techniques, and dental epithelial cell experiments, they explored how the mutation disrupts tooth development. Their findings were published in Volume 18 of the journal International Journal of Oral Science on May 21, 2026.

The team first examined KDF1 activity during tooth development. They found that KDF1 was highly expressed in dental epithelial cells and was closely associated with regions of cell–cell contact, suggesting a role in maintaining epithelial organization. Although the mutation did not reduce KDF1 production, it impaired proper membrane localization, suggesting disruption of cellular interactions essential for enamel formation.

To assess the effects of the mutation, the researchers studied mice carrying one or two mutant copies of KDF1. Both groups developed enamel abnormalities, with the most severe defects observed in homozygous animals. Analyses revealed thinner enamel, reduced mineral density, abnormal enamel prism structure, and delayed tooth eruption. Mutant mice also showed lower levels of key enamel proteins and enzymes, including amelogenin, ameloblastin, and matrix metalloproteinase 20, which are necessary for enamel secretion and maturation.

Further experiments showed that the mutation disrupted adhesive structures that connect ameloblasts, the cells responsible for enamel production. Levels of important adhesion molecules, including E-cadherin and integrin β4, were significantly reduced. As adhesion weakened, Hippo pathway regulation became disrupted, allowing excessive accumulation of YAP in the nucleus. This activated genes that promote cell proliferation. Rather than maturing into enamel-producing cells, mutant ameloblasts remained in a proliferative state and failed to differentiate properly.

“Our findings reveal that KDF1 is much more than a structural protein,” said Prof. Zhao. “It acts as a critical coordinator that links cell adhesion to signaling pathways controlling whether ameloblasts continue dividing or mature to form enamel. When this balance is lost, enamel development is severely compromised.”

The researchers next tested whether correcting this signaling imbalance could improve enamel development. Using verteporfin, a drug that inhibits YAP-TEAD1 interactions, they partially reversed the abnormal cellular behavior. Treated cells showed reduced proliferation and improved differentiation, while mutant mice displayed increased enamel volume. Although enamel mineralization was not completely restored, the findings demonstrated that the disease process can be modified therapeutically.

“This work provides a strong foundation for developing targeted treatments for hereditary enamel disorders,” said Prof. Yu. “By identifying a drug-responsive pathway, we have opened new opportunities for translating fundamental developmental biology into future clinical interventions.”

The implications extend beyond dentistry. Because cell adhesion and Hippo-YAP signaling regulate tissue growth in many organs, the findings may stimulate collaborations in regenerative medicine, stem cell biology, tissue engineering, craniofacial research, and precision medicine. In the short term, the study improves understanding of the genetic basis of enamel disorders and may support earlier diagnosis. Over the longer term, these insights could contribute to therapies that preserve, repair, or regenerate dental tissues, improving oral health outcomes for future generations.

Overall, the study uncovers a previously unknown mechanism linking a disease-causing KDF1 mutation to enamel defects through disrupted cell adhesion and Hippo-YAP signaling. By showing that pharmacological intervention can partially rescue these abnormalities, the researchers provide new insight into tooth development and a promising path toward future treatments for inherited enamel disorders.

Reference
Titles of original paper: Kdf1 missense mutation caused enamel defects by disrupting cell adhesion and Hippo-YAP signaling in dental epithelium
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About Sun Yat-sen University, Guangzhou, China
Founded in 1924 by Dr. Sun Yat-sen, Sun Yat-sen University (SYSU) is one of China's leading public research universities and a key institution under the Ministry of Education. With five campuses across Guangzhou, Zhuhai, and Shenzhen, and ten affiliated hospitals, SYSU offers comprehensive strengths in humanities, social sciences, natural sciences, engineering, and medicine. Renowned for academic excellence, innovation, and global engagement, the university serves as a major center for research, education, and talent development in South China. SYSU is committed to advancing interdisciplinary scholarship and fostering world-class learning and societal impact.
Website: https://www.sysu.edu.cn/sysuen/

About Professor Wei Zhao
Wei Zhao is a professor and doctoral supervisor at the Guanghua School of Stomatology, Sun Yat-sen University, Guangzhou, China. As an overseas high-level talent recruit and vice chairman of the Guangdong Provincial Association for Brain Development and Brain Disease Prevention and Treatment, he specializes in epigenetic regulation within the tumor microenvironment. His research uses single-cell transcriptomic and epigenomic approaches to identify key cellular subpopulations and regulatory mechanisms, including RNA and histone modifications. Prof. Zhao also investigates epigenetic therapeutics for cancer treatment. He has published more than 30 papers in leading journals, including Cell, Science Advances, Cancer Research, and Advanced Science.

About Professor Dongsheng Yu
Dongsheng Yu is a professor in the Department of Oral Emergency at the Guanghua School of Stomatology, Sun Yat-sen University, Guangzhou, China. His research spans signal transduction, postoperative pain, vascularization, dental pulp stem cells, immune checkpoints, phosphatases, biomaterials, and tissue regeneration. He has made significant contributions to understanding the molecular mechanisms underlying oral diseases and regenerative therapies, with particular interest in protein expression, quantitative techniques, and translational dental research. Prof. Yu has authored 59 scientific publications, receiving more than 2,849 citations and achieving an h-index of 31. His work continues to advance innovation in oral health and craniofacial regenerative medicine.

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Yini Bao
Sichuan University
+862885546461 ext.
ijos@scu.edu.cn
