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Enzyme mutations may protect against vascular thrombosis and stroke

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(Medical Xpress)—Yale researchers have identified the mechanism behind a molecular variation that reduces risk of stroke in children with sickle cell anemia. The molecular variation was recently identified but not understood due to a limited grasp of the gene's role in hemostasis—the stopping of bleeding. These new findings open a path

for the development of novel drugs that may prevent stroke, particularly in children with sickle cell anemia who are at risk of this devastating complication. The study appears online in the *Journal of Biological Chemistry*.

The researchers demonstrate that an enzyme known as NPP1, encoded by the gene associated with stroke protection, is part of a family of enzymes that encourages the coagulation of blood on vascular surfaces. Too much clotting on the vascular lining can lead to thrombosis and stroke. By demonstrating that NPP1 can induce platelet aggregation at low concentrations (on the vascular lining, for example), the team established a direct role for the enzyme in thrombotic stroke.

"Our findings strongly suggest that NPP1 inhibitors would confer some level of stroke protection to patients at risk for thrombotic stroke, especially to children with sickle cell anemia in whom the NPP1 variation was identified," said senior author Demetrios Braddock, M.D., associate professor of pathology at Yale School of Medicine.

The team also determined the molecular structure of a close relative of NPP1 called NPP4, which revealed the molecular details of the target site for new inhibitors directed against the gene—further enabling the possible design of novel anti-stroke drugs.

More information: Ronald A. Albright, Deborah L. Ornstein, Wenxiang Cao, William C. Chang, Donna Robert, Martin Tehan, Denton Hoyer, Lynn Liu, Paul Stabach, Guangxiao Yang, Enrique M. De La Cruz, and Demetrios T. Braddock. "The Molecular Basis of Purinergic Signal Metabolism by Ecto-Nucleotide Pyrophosphatase/Phosphodiesterases 4 and 1 and Implications in Stroke." *J. Biol. Chem.* jbc.M113.505867. First Published on December 12, 2013, DOI: 10.1074/jbc.M113.505867

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