Glutamate transporter loss-of-function mutations cause human dicarboxylic aminoaciduria

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Excitatory amino acid transporter 3 (EAAT3) has been shown to be the major epithelial transporter of glutamate and aspartate in the kidney and intestine in rodents. EAAT3 is also found in the brain where it is responsible for clearing the major excitatory neurotransmitter glutamate from the extracellular space. In this study we describe two mutations in EAAT3 that cause human dicarboxylic aminoaciduria, an autosomal recessive disorder of urinary glutamate and aspartate transport that has been associated with mental retardation. The single point mutation R445W causes an increase in substrate affinity and a significant reduction in transport and cell-surface expression. The non-functional deletion mutation, I395del, exhibits negligable cell surface expression. Our study provides definitive evidence that EAAT3 is the major renal transporter of glutamate and aspartate in humans and implicates EAAT3 in the pathogenesis of neurological disorders.