TIAM1

TIAM1 (TIAM Rac1 Associated GEF 1) is a Protein Coding gene. Diseases associated with TIAM1 include Lymphoma and Colorectal Cancer. Among its related pathways are EPH-Ephrin signaling and p75 NTR receptor-mediated signalling. Gene Ontology (GO) annotations related to this gene include guanyl-nucleotide exchange factor activity and guanyl-nucleotide exchange factor activity. An important paralog of this gene is TIAM2.

TIAM Rac1-associated GEF 1 (TIAM1) regulates RAC1 signaling pathways that affect the control of neuronal morphogenesis and neurite outgrowth by modulating the actin cytoskeleton network. To date, TIAM1 has not been associated with a Mendelian disorder. Lu et al. described five individuals with bi-allelic TIAM1 missense variants who have developmental delay, intellectual disability, speech delay, and seizures. Bioinformatic analyses demonstrate that these variants are rare and likely pathogenic. They found that the Drosophila ortholog of TIAM1, still life (sif), is expressed in larval and adult central nervous system (CNS) and is mainly expressed in a subset of neurons, but not in glia. Loss of sif reduces the survival rate, and the surviving adults exhibit climbing defects, are prone to severe seizures, and have a short lifespan. The TIAM1 reference (Ref) cDNA partially rescues the sif loss-of-function (LoF) phenotypes.They also assessed the function associated with three TIAM1 variants carried by two of the probands and compared them to the TIAM1 Ref cDNA function in vivo. TIAM1 p.Arg23Cys has reduced rescue ability when compared to TIAM1 Ref, suggesting that it is a partial LoF variant. In ectopic expression studies, both wild-type sif and TIAM1 Ref are toxic, whereas the three variants (p.Leu862Phe, p.Arg23Cys, and p.Gly328Val) show reduced toxicity, suggesting that they are partial LoF variants. In summary, they provide evidence that sif is important for appropriate neural function and that TIAM1 variants observed in the probands are disruptive, thus implicating loss of TIAM1 in neurological phenotypes in humans [1)].

1)
Lu S, Hernan R, Marcogliese PC, Huang Y, Gertler TS, Akcaboy M, Liu S, Chung HL, Pan X, Sun X, Oguz MM, Oztoprak U, de Baaij JHF, Ivanisevic J, McGinnis E, Guillen Sacoto MJ, Chung WK, Bellen HJ. Loss-of-function variants in TIAM1 are associated with developmental delay, intellectual disability, and seizures. Am J Hum Genet. 2022 Feb 25:S0002-9297(22)00051-9. doi: 10.1016/j.ajhg.2022.01.020. Epub ahead of print. PMID: 35240055.