DOCK3

The DOCK3 (dedicator of cytokinesis 3) gene is located on chromosome 3 in the region 3p21.2 and encodes a 2,030-aa protein and member of the DOCK family of proteins. The DOCK family of proteins are guanine nucleotide exchange factors (GEFs). GEFs help to facilitate the cycling between active and inactive states of small GTPase proteins in the cell1. GTPases are important for transmitting various cellular signals and are active or "on" when bound to guanosine triphosphate (GTP) and inactive or "off" when bound to guanosine diphosphate (GDP). GEFs like DOCK3 facilitate GTP binding to GTPases, thereby activating these proteins2. DOCK3 specifically binds and activates a small Rho GTPase called Rac1. Rho GTPases, including Rac1, are best known for their role in cell motility and polarity and actin cytoskeleton dynamics, and are therefore important for controlling the shape and movement of cells3. DOCK3 is an atypical GEF; unlike typical GEFs, DOCK3 does not have a conventional Dbl homology domain (DH) but rather contains the two homology domains DHR-1 (Dock homology region-1) and DHR-21, 4. The DHR-2 domain is the catalytic domain that contains the GEF activity. DHR-1 binds phosphatidylinositol-3,4,5-triphosphate (PIP3) in the plasma membrane, which means this protein is located at the cell surface. Rac1 is also primarily located at the plasma membrane5. DOCK3 also has an SH3 domain near the N-terminus which can bind to the DHR-2 domain for autoinhibition or may bind to ELMO (Engulfment and Cell Motility) proteins which exposes the DHR-2 domain and enables GEF activity. The proline rich region near the C-terminus mediates protein-protein interactions.

The identified mutation is a point mutation in which Guanine (G) is replaced by an Adenine (A) in an intron after codon 30 of DOCK3. This substitution disrupts a highly conserved splice donor region and introduces a stop codon after exon 30. This nonsense mutation is predicted to eliminate the DHR-2 domain and thus GEF activity of DOCK3 and is likely to be pathogenic.

There is substantial evidence establishing DOCK3's role in regulating neuronal cell morphology6-9. DOCK3 is unique among other DOCK family proteins in that it is expressed almost exclusively in the central nervous system (CNS). DOCK3 is predominantly expressed by neurons, with some glial cell types including oligodendrocytes also showing robust expression. At the tissue level, DOCK3 expression is considered highest in the cerebral cortex, basal ganglia and hippocampus (https://www.proteinatlas.org/ENSG00000088538-DOCK3/tissue). Specifically, Dock3 controls neurite outgrowth by regulating both actin polymerization and microtubule assembly via GEF-dependent Rac1 mediated cytoskeletal organization and GEF-independent mechanisms that target glycogen synthase kinase-3b7, 8, 10. Dock3's GEF-

dependent mechanism of actin rearrangement involves its interaction with WASP family verprolin-homologous (WAVE) proteins through the DHR-1 domain7. In this process, brain-derived neurotrophic factor (BDNF)-TrkB signaling recruits Dock3 and WAVE complex to the plasma membrane due to increased PIP3. At the membrane, Rac1 and the WAVE complex become activated, thus promoting Arp2/3-mediated actin polymerization and axonal sprouting.

In studies with Dock3 knockout mice, the loss of Dock3 led to axonal degeneration, abnormal protein aggregates, and sensorimotor impairments including limb weakness and ataxia6. In a separate study, adult Dock3 KO mice have also been shown to have impaired muscle function and defective myoblasts11. In mouse models of glaucoma, overexpressing Dock3 in transgenic mice protected retinal cells from oxidative stress and prevented retinal degeneration12. In 2003, A 10-year-old male patient harboring a balanced chromosomal inversion affecting genes DOCK3 and SLC9A9 was reported to show features of ADHD and intellectual disability13, 14. Additional reports of a sibling pair with biallelic loss-of-function variants in DOCK3 also showed symptoms of intellectual disability, as well as muscle hypotonia and ataxia15. These findings are consistent with the phenotypes observed in Dock3 knockout mouse models showing sensorimotor impairments.16

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