IDH2 gene mutation

Isocitrate dehydrogenase [NADP], mitochondrial is an enzyme that in humans is encoded by the IDH2 gene.

Isocitrate dehydrogenases are enzymes that catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate. These enzymes belong to two distinct subclasses, one of which utilizes NAD(+) as the electron acceptor and the other as NADP(+). Five isocitrate dehydrogenases have been reported: three NAD(+)-dependent isocitrate dehydrogenases, which localize to the mitochondrial matrix, and two NADP(+)-dependent isocitrate dehydrogenases, one of which is mitochondrial and the other predominantly cytosolic. Each NADP(+)-dependent isozyme is a homodimer. The protein encoded by the IDH2 gene is the NADP(+)-dependent isocitrate dehydrogenase found in the mitochondria. It plays a role in intermediary metabolism and energy production. This protein may tightly associate or interact with the pyruvate dehydrogenase complex.

Somatic mosaic mutations of this gene have also been found associated to Ollier disease and Maffucci syndrome.

IDH1 Arg132 mutations and IDH2 Arg140 and Arg172 mutations accounting for >90% of aberrations [1] [2]. IDH1 and IDH2 mutations reduce the enzymatic capacity of these proteins to bind isocitrate, their substrate, and convert it into alpha-ketoglutaric acid (α-KG), generating carbon dioxide and replenishing NADH and NADPH as side products [3]. This is one of the irreversible steps in the tricarboxylic acid cycle important for cellular respiration. Mutant IDH1 (cytoplasmic) and IDH2 (mitochondrial) enzymes also show a modified enzymatic capacity to convert α-KG into 2-hydroxyglutarate (2-HG), a small oncometabolite. Equally important, IDH1 and IDH2 mutations stratify individuals into molecular subtypes with distinct clinical outcomes – the mutations are associated with lower-grade astrocytomas, oligodendrogliomas (grade II/III) and secondary gliomas with better overall survival, progression-free survival and chemosensitivity than glioblastomas that are wild type for both genes [4] [5] [6].

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