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Human diseases related with leucine rich repeats

Norio Matsushima
Sapporo Medical University, Japan

Leucine rich repeats (LRRs) are unusually rich in the hydrophobic, amino acid leucine. LRRs have been reported in over 100,000 proteins from viruses to eukaryotes. The LRRs are composed of 20-30 residues stretches and repeat in tandem. The repeat numbers range from two to ninety-seven. LRR units are divided into a highly conserved segment (HCS) and a variable segment (VS). Twenty-three types of LRRs including eight classes well recognized have been proposed. The HCS part consists of an eleven or twelve residue stretch, LxxLxLxx(N/C)(x/-)L, in which "L" is Leu, Ile, Val, or Phe, "N" is Asn, Thr, Ser, or Cys, "C" is Cys, Ser or Asn, "x" is any amino acid, and "-" is a deletion. Three residues at positions 3 to 5 in the HCS part form a short β-strand. These β-strands stack parallel; they have the pattern of H-bonding (N-H → O=C), and then tandem repeats of LRRs assume their super helical arrangements called a solenoid structure. Structural data of LRR proteins have increased. Meanwhile, a number of human diseases have been shown to be associated with mutation in the genes encoding LRR proteins which count over forty. The LRR proteins include opticin, lumican, fibromodulin, FLRT3, F-box/LRR-repeat protein 4, LGI1, Trk-A, nyctalopin, FSHR, LH/CGR, TSHR, keratocan, GPIb□, GPIb□, GPIX, LRRK2, CIAS1, CIITA, and Nod2. The mutations of these proteins are associated with high myopia, congenital hypogonadotropic hypogonadism, mitochondrial encephalomyopathy, ADLTE/ADPEAF, CIPA, CSNB1/XLCSNB, ODG1, LCH, Graves disease, thyrotropin resistance, FGH, papillary cancer, hyperthyroidism, CNA2, BSS, PT-vWD, Parkinson's disease, CINCA/NOMID, BLS II, and Crohn's disease. The mutations occur frequently within the LRR domains as well as in their neighboring domains at the N- and C-termini. Here, we review the adverse effects of different sequence variants based on the sequence analysis of the LRR domains and the known structures of LRR proteins.

e: norio_irreko@outlook.jp