Parkinson´s disease

Parkinson’s disease (PD) is a gradually worsening brain disease accompanied by stiffness, shaking, fatigue, memory difficulties, behavioural changes, problematic walking, coordination, and balance. Movement problems typical for this disease are caused by the death of neurons producing dopamine. Other health issues, such as fatigue, sudden drop in blood pressure, or decreased function of digestive system might be caused by the nerve endings loss of neurons producing norepinephrine. Parkinson´s disorder can be hereditary or occur randomly [1]. Hereditary form of this disease is usually inherited in autosomal dominant pattern [2].

LRRK2

This multidomain protein called LRRK2 or dardarin is a product of *LRRK2* gene. Its abbreviation stands for leucine rich repeat kinase 2 and it belongs to ROCO protein family. Although its precise function is unknown, it is proposed that LRRK2 interacts with microtubules, phosphorylates Rab GTPase which marks membranous cargos moving along the microtubules, phosphorylates β-tubulin, moesin, FoxO1, tau, and others [3]. The cargo might be implicated in pathology of Parkinson´s disease [4].

LRRK2 is 2527 amino acids long protein in which we can distinguish N-terminus with scaffold domains such as armadillo, ankyrin, and leucin-rich repeats interaction motifs, and C-terminus with Ras-like GTPase (ROC domain controlling kinase activity of LRRK2), MAPKKK-like kinase domain, COR domain important for dimerization, and scaffold WD40 domain (see Figure 1) [5]. LRRK2 has both GTPase and kinase activity, mediated by ROC domain and kinase domain, respectively, and the kinase activity is regulated by the ROC domain [6].

COR domain represents a central part in head-to-head orientation when LRRK2 folds into predominant form of globular dimer, where kinase-WD40 module folds back to domains of N-terminus and thus allows these parts to interact and create autophosphorylation sites [7].

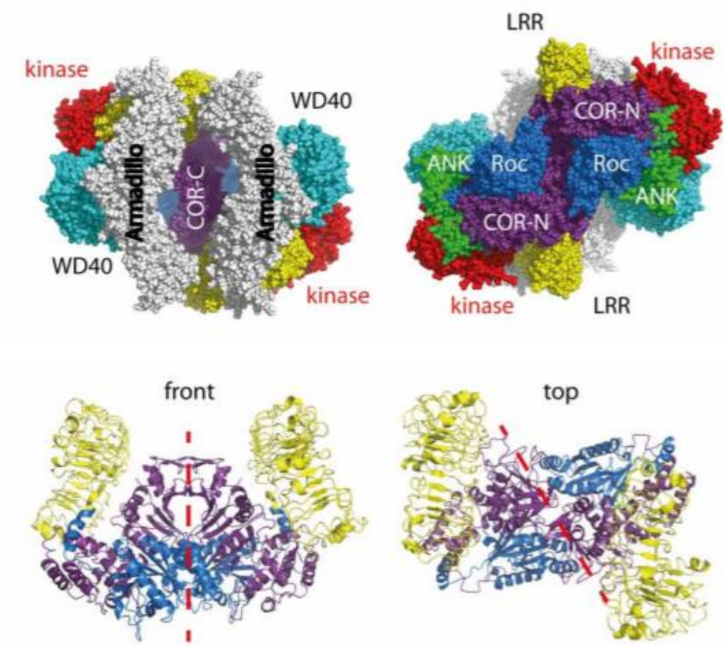

Figure 1: Top and bottom view of dimeric full-length LRRK2 model with domains indicated in color (Armadillo, white; Ankyrin [ANK], green; LRR, yellow; Roc, blue; COR, violet; kinase, red; WD40, cyan.) Bottom pictures: LRR, yellow; Roc, blue; N-/C-terminal COR subdomains, violet [5].

LRRK2 and Parkinson’s disease

Mutations in LRRK2 are accompanied by cell loss and α-synuclein aggregates in the form of Lewy bodies and neurite [8]. Mutation in the position R1441C in LRRK2 is considered pathogenic for PD [9]. With other mutations such as R1441G, and Y1699C occurring in ROC and COR domains, it decreases GTPase activity and induces neuronal toxicity [10], [11]. Among LRRK2 mutations that are proven to cause PD, the R1441 is the second most common, and it was found to be substituted by different amino acids [12].

Mechanism of action of R1441C mutation

It was shown that R1441C mutation leads to decrease in the GTPase activity of LRRK2 [13], [14] which results in increase in phosphorylation by this kinase [6]. The R1441C mutation interferes with ROC domain’s GTP-hydrolysing function. Generally, binding of either GDP or GTP stabilizes the protein, the former nucleotide being more effective in this regard. The R1441C mutation affects the stability of the ROC domain as demonstrated by a decrease of melting temperature in comparison to the wild-type protein [15]. This destabilization is less profound with GDP bound than with GTP.

The LRRK2 was proposed to act in the form of a homodimer [16]. The position of R1441C residue was predicted to be at the interface between two monomers in a protein dimeric structure, distal to the active site of the protein – see Figure 2 [17]. Mutation in R1441C could therefore destabilize the interaction between monomers and interrupt their enzymatic function [15]. R1441 plays a role in stabilizing the formation of dimer and any mutation at the position R1441 with shorter side chain disrupts both the exquisite hydrogen bonding and stacking interactions provided by the arginine side chain [17]. The interaction between a wild-type ROC domain and ROC mutated at R1441C was shown to be decreased experimentally, simulating the mutation in heterozygous constitution[15].

On top of that, the R1441C mutation has also been shown to improve binding of LRRK2 to neuronal microtubules [18].

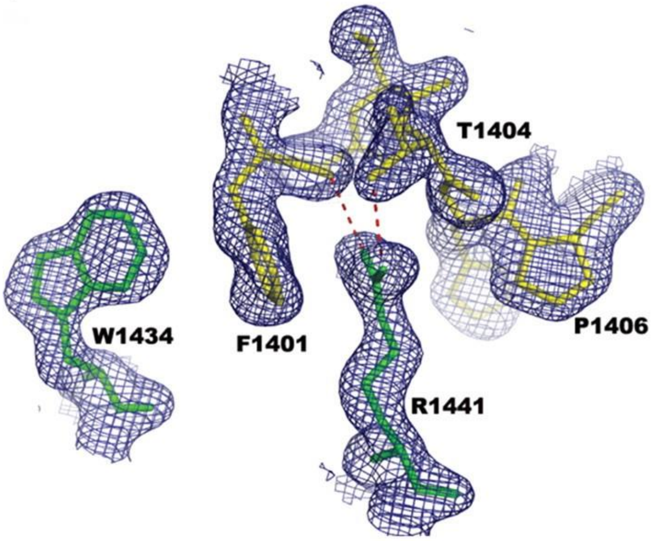

Figure 2: The residue R1441 is located at the end of helix α3 and interacts with helix α2 from the other paired monomer peptide chain at the dimer interface [17].

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