Multiple alignment of RNF213 orthologs. Sequences were retrieved from NCBI non redundant protein database or from UniProt reference proteomes with the following accessions: Mus musculus (NCBI: ref|NP_001035094.2 ), Homo sapiens (UniProt: sp|Q63HN8), Gallus gallus (NCBI: ref|XP_015151083.1), Xenopus laevis (UniProt: tr|A0A1LBETH7), Danio rerio (UniProt: sp|A0A0R4IBK5); sequences were aligned with MAFFT version 7.427 (28), and visualized with Jalview (27). Alpha helices (grey) and beta strands (black) are derived from the cryo-EM structure and shown on top. Residues with no structural data are indicated by a dashed line. At the bottom, positions with MMD mutations are marked by polygons, where green represents a low (<15), magenta an intermediate (< 20) and red a high CADD score (>= 20). Arrows indicate domain borders. Within the AAA+ domains, functional residues for nucleotide binding and hydrolysis are indicated by letters (A, Walker A; B, Walker B; S1, sensor I; S2, sensor II; RF, arginine finger). Regions IR3, IR5, and the E3-RING are enframed.