The Nucleoporin 358 I585M Mutant Displays Non-Canonical Orientations in the C-Terminal Alpha Helices of the Alpha Helical Domain: Determining the Structure of Acute Necrotizing Encephalopathy 1 Associated Mutant via X-Ray Crystallography

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Acute Necrotizing Encephalopathy (ANE) is a severe neurologic complication manifested primarily in young Asian children in the form of encephalopathy, seizures, coma, and symmetric brain lesions within days of common febrile infection. ANE1 refers to ANE caused by one of many possible missense mutations in nucleoporin 358 (nup358), a massive protein belonging to the nuclear pore complex and responsible for a wide variety of functions in upper eukaryotes. To determine if an ANE1-causing missense mutation in nup358 alters its structure, part of the alpha helical domain of the nup358 isoleucine to methionine (I585M) mutant was successfully expressed in E. coli B121 cells, purified via Ni-NTA affinity, ion exchange, and size exclusion purification, and crystallized via hanging drop methods for x-ray diffraction analysis. Here we present its structure to 7.2Å and provide the first evidence that the physiologically relevant I585M nup358 ANE1 mutant, caused by a heterozygous 1880C-->T mutation, displays deviations in the c-terminal alpha helices of the alpha helical domain when compared to wild type nup358. This structural change may impede function(s) of nup358, thus contributing to ANE1.

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