Structural insights into calcineurin in complex with its inhibitor, RCAN-1 in the context of Down syndrome and Alzheimer's disease

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INTRODUCTION

A progressive disease that destroys memory and other important mental functions called **Alzheimer's disease** Alzheimer's disease is a clinical illness with long preclinical phases (20 years) and an average clinical duration of 8-10 years.Memory loss and confusion are the main symptoms people may also experience mental decline , difficulty in thinking and understanding etc… Alzheimer's disease destroys nerves connections in the brain, making it progressively more difficult to do ordinary things like move around, swallow and feed yourself. While the disease devastates the brain , it does not kill you. Complications in brain may lead to death. The disease has an estimated prevalence of 10%-30% in the population>65 years age with an incidence of 1-3% . In 2015 , dementia affected some 10.5 million citizens aged between 30 and 90+ people in europe.There is no treatment for alzheimer's but has medications to slow down the process. A genetic chromosome21 disorder causing developmental and intellectual delays called **Down syndrome.** It causes a indistinct facial appearence , intellectual disability . it may also associated with heart and thyroid diseases.There are no particular drugs for treating down syndrome but early intervention programmes with a team of therapists and special educators who can treat each child's specific situation are helpful in managing down syndrome.The incidence of the down syndrome is estimated to be about one in every 1000 births.Approximately 25-30% of patients with Down syndrome die in the first year of life. RCAN 1 inhibits CN via multiple routes first by blocking substrate recruitment sites and secondly by blocking the active site or it also converts CN1 into weak inhibiter which gets reversed by the process phosphyrylation

6UUQ is the protein structure of calcineurin that is bound to the RCAN1. Regulator of calcineurin (RCAN1) was first discovered as the gene present on the human chromosome 21.It is generally expressed in humans and excessive expression leads to Down syndrome

Various forms of cellular stress such as oxygen species and hyperglycemia leads to increase in RCAN1 species Regulator of calcineurin (RCAN1) , an endogenous inhibitor of ser/Thr phosphatase calcineurin(CN) which shows excessive inhibition of CN is a critical factor for down syndrome and Alzheimer's disease.

EXPERIMENTAL DESIGN

The 3 dimensional analysis of the structure (6UUQ) was analysed using computational biology tool . The structure was downloaded from Protein Data Bank (PDB). The quality of the structure will be determined by two tests. First, For the good quality of the structure the difference between R-free and R-Work should be less or equal to 0.05 (5%). Second , The R-Work value should be roughly equal to 1/10th of the resolution. The analysis includes evaluation of the secondary structure , α-helices and **β-**strands followed by hydrogen bonds.

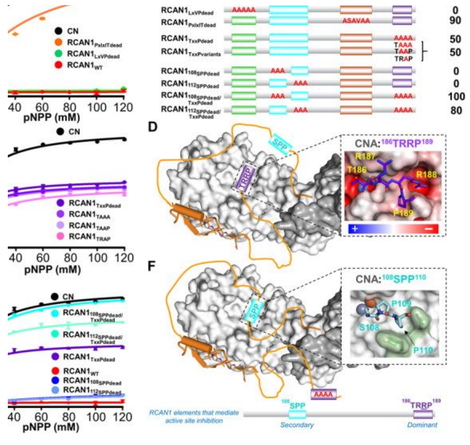

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Figure 1: RCAN1 inhibits CN by binding and blocking the active site(A) .

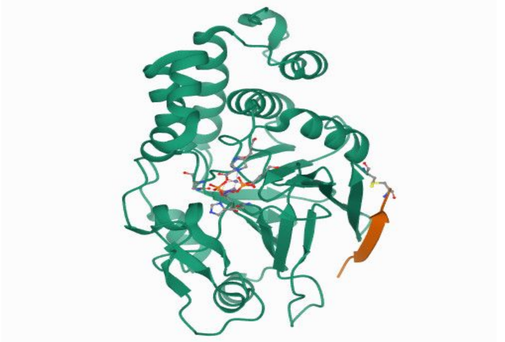

Figure 2: structure of Calcineurin bound to RCAN1

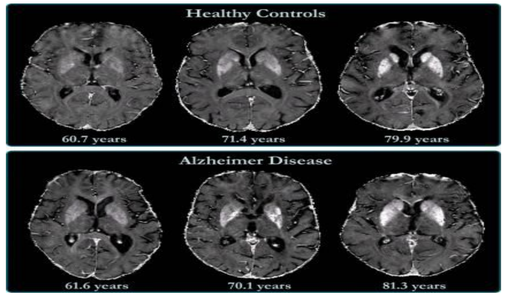

Figure 3: Differences in iron concentration in basal ganglia are too small to allow visual separation between patients with Alzheimer disease and control participants, and iron levels strongly depend on anatomic structure and subject age

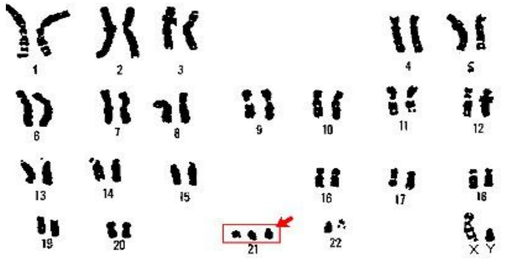

Figure 4: Translocation at chromosome 21

RESULTS & DISCUSSION

The structure 6UUQ has three small molcules (PO4 , Zn , Fe) where PO4 has multiple hydrogen bonds and Zn , Fe ligands doesn't form any hydrogen bonds with any atom . The difference between R-Free and R-Work is 0.205-0.164= 0.041 (4.1%) . Since the difference is less than 0.05 (5%) the quality of the structure is good . The R-Work value (0.164) should be roughly equal to 1/10th of the resolution(1.85) i.e 1.85*1/10= 0.185 and the R-work value is 0.164 the difference between them is small(0.02) so the R-Work value is roughly equal to 1/10th of the resolution . These two test's result show that the quality of the structure is good .The total number of α-helices is 09 and β-strands is 17 . When the colour of the chain is changed (colour>chain>by chain) two colours are observed cyan and green . Where Cyan chain has 01 α- helices and 0 β-strands and green chain has 09 α- helices and 16 β-strands .

REFERENCES

Colin L masters *et al* 2015 , nature reviews . Disease Primers , 15 oct 2015 . The florey Institue of neuroscience and medical health , Melbourne , 30 Royal parade , parkville , Australia.

Peter T *et al* , Research and Innovation Centre Bioinformatics , slovaika .12 dec 2018, Article ID : 8137464.

Yang yi *et al* , Department of Chemistry and Biochemistry , University of Arizona Tucson , USA . PMID: 329367

Heshan Peiris , College of Medicine and Public Health and Centre for Neurosciences ,Flinders university , Adelaide , SA, Australia. PMID: 29094385.

B Rothermel , Department of Internal Medicine and Molecular Biology , University of Texas south western Medical Center , Dallas , Texas , USA. PMID:10722714

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