Structural analysis of kinase domain from the Tau-Tubulin Kinase-2 that is involved in frontotemporal dementia

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INTRODUCTION

Frontotemporal dementia (FTD) is a disorder caused by dementia. It occurs when nerve cells in the frontal and temporal lobes of the brain are lost. This causes the lobes to shrink. Its symptoms include behaviour/ dramatic personality changes such as swearing, stealing and deterioration in personal hygiene habits, impaired judgment, lack of empathy, coordination and balance, decreased self awareness, agitation, increasing dependence,loss of energy and motivation. Some people have physical symptoms such as tremors, muscle spasms, poor coordination balance, difficulty in swallowing, psychiatric symptoms such as hallucinations. There is no single test that can diagnose FTD. If they suspect dementia they evaluate neurological status health including reflexes, muscle strength, muscle tone, sense of touch and sight, coordination and balance. Assess neuropsychological status such as memory, problem solving ability, counting skills and language abilities. Order magnetic resource imaging (MRI) (or) computed tomography (CT) scan for the brain(Fig.1). Some 25% are late-life onset cases. Population studies show nearly equal distribution by gender, which contrasts with myriad clinical and neuropathology reports. FTD is frequently familial and hereditary; five genetic loci for causal mutations have been identified, all showing 100% penetrance. Non-genetic risk factors for are yet to be identified. FTD shows poor life expectancy but with survival. Recent progress includes the formulation of up-to-date diagnostic criteria for the behavioral and language variants, and the development of new and urgently needed instruments for monitoring and staging the illness. There is still need for descriptive populations studies, to fill gaps in our knowledge about minority groups and developing regions.

Tau-tubulin kinase-2 is a protein in humans that is encoded by the TTBK2 gene. This gene encodes a serine-threonine kinase that phosphorylates Tau and tubulin proteins. Mutations in this gene cause spinocerebellar ataxia type 11 (SCA11); a neurodegenerative disease characterized by progressive ataxia and atrophy of the cerebellum and brainstem(Fig.2).

EXPERIMENTALS

We must run two tests with the provided experimental data i.e., by doing x-ray diffraction with resolution is 1.5-2.0, R-value free 0.209 and R- value work -0.174. The first one is the difference between R-free and R-work must be less than 5% and we obtained 3.5% and the second test is the r-work which must be □ of resolution and we obtained 0.15. As it passed two tests the structure is in good quality for further analysis (Pubmed id :32424773). Tau-tubulin kinase-2 and has five ligands (ADP, PO 4, GOL, MG, NA). In PyMOL we can see two chains as secondary structures which are same and consists of 8 alpha(RED) and 10 beta(YELLOW) strands using PyMOL software(Fig.3). The tau protein can undergo a variety of phosphorylation events at its many serine, threonine and tyrosine residues. Some or more possible phosphorylation sites are found in every tau isoform. These phosphorylations can control the normal biological functions of tau, such as its role in microtubule stability and pathological functions, such as its ability to self-assemble into neuronal filaments found in neurodegenerative diseases(Fig.4).

Fig.3. The 3-D structure of Tau-Tubulin Kinase-2 showing the ligands showing alpha helices and beta helices.

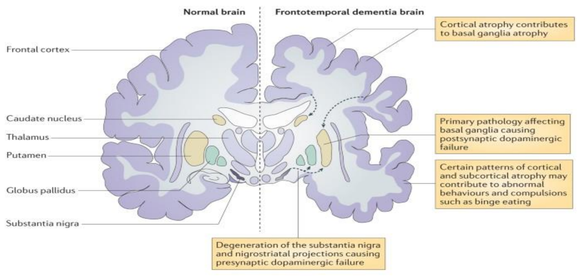

Fig.1. Frontotemporal dementia (FTD)

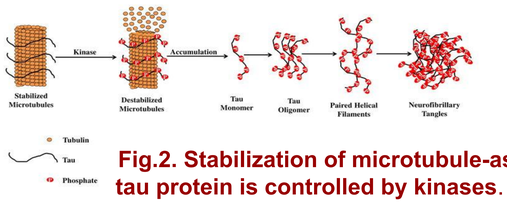

Fig.2. Stabilization of microtubule-associated tau protein is controlled by kinases.

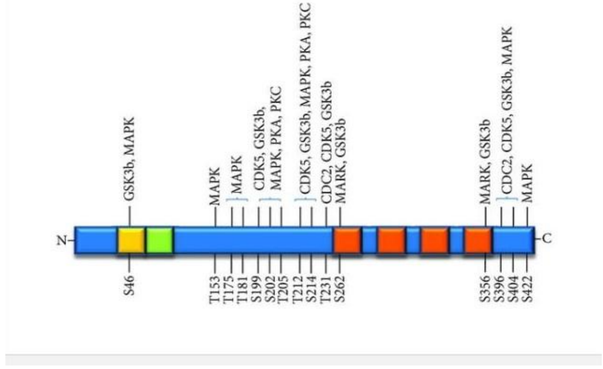

Fig.4. Sites of phosphorylation in tau and the kinases implicated.

RESULTS & DISCUSSION

The structure of Tau tubulin kinase 2 (TTBK2) CONTAINS 8 alpha helices and 10 beta strands followed by the structural analysis a ubiquitin molecule expressing kinase , genetically linked to the diseases like frontotemporal dementia(FTD) and spinocerebellar ataxia type -11 (SCA-11).

REFERENCES

1. BAO, C., Bajarami, B., Macrotte, D.J., (Mechanism of regulation and diverse activities of Tau-Tubulin Kinase-2).
2. Pubmed id :32424773 (2020-24)

e-poster presented online at the ABFR-2020.