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ALADIN and its Protein Interactions with the Nucleoproteins: An Insilico Analysis

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Abstract

The nuclear pore complex (NPCs) are big, protein complexes made up of multiple units that traverse the nuclear envelope (NE), establishing a discerning channel between the cytoplasm and nucleus for the nucleocytoplasmic transport. It has different roles in cellular processes, like cell-cycle progression, control of gene expression, and signal transduction. NPC is a vast and complex structure, compiled from almost 30 proteins, termed nucleoporins. Earlier studies have shown that each nucleoporins has an exclusive role in controlling NPC function and the nucleocytoplasmic transport of proteins and RNAs. ALADIN also referred to as adracalin is a nucleoporin is associated with a genetically heritable human disease known as Triple A syndrome. But many mutant ALADIN studies have showed that defect is functional rather than structural, so further suggesting an intricate protein interaction network among several hundred individual components of this ordered assembly of huge complex. In this study, insilico tools have been used to predict the protein-protein interactions of ALADIN protein with other nucleoporins.

Keywords: *Nucleoporin, mutant, signal transduction, protein interactions, WD-repeats*

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INTRODUCTION

Nuclear pore complexes (NPCs) are the gateways for nucleocytoplasmic exchange. These are large, multiprotein complexes that span the nuclear envelope (NE), form a selective channel between the cytoplasm and nucleus [1]. As the sole sites of nucleocytoplasmic transport, NPCs play a role in a variety of cellular processes, including cell-cycle progression, control of gene expression, and signal transduction. Being the seat of highly specific and tightly regulated processes specifically nucleocytoplasmic trafficking, the NPC is an immense and intricate structure, assembled from approximately 30 proteins [2], termed nucleoporins (NUPs). termed nucleoporins (NUPs). There is a lot of information available about this huge complex from different experimental techniques, but its big size has made critical study is problematic. The complete human NPC has an approximate molecular mass of ~125 MDa [2, 3], one of the biggest protein assemblies in the cell. Although the NPC is very huge in terms of size, it is created from a small number of NUPs (~30) that exist in several copies. (Figure 1).

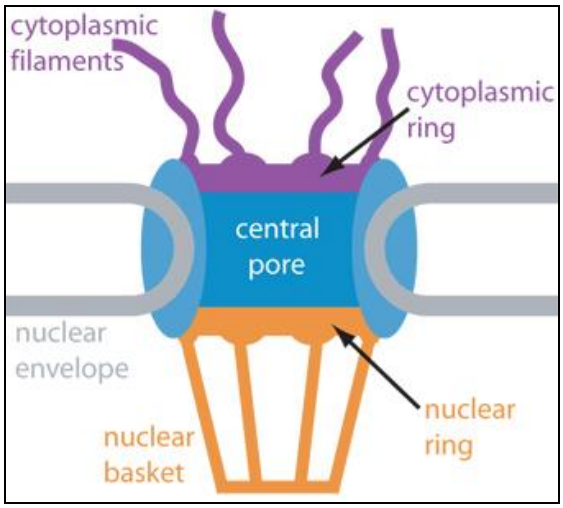

Fig. 1: *Nuclear Pore Complex.*

Among the various NUPs, ALADIN had been added as a new member of the NPC. Much is not known about its structure but studies have shown that mutations in ALADIN are known to cause triple A syndrome, a rare autosomal recessive disorder characterized by adrenal insufficiency, alacrima, and achalasia [4]. In

fact it is the first nucleoporin that was linked to a human genetic disorder, the Triple A syndrome, also called Allgrove syndrome. ALADIN is encoded by the AAAS gene and is 546 amino acid protein of 60 Kda, which belongs to the WD-repeat family of protein [5]. The central 170-aa domain composed of four WD repeats, the flanking N and C termini, of 150 and 230 residues, respectively, contain no obvious structural domains. ALADIN is conserved in higher eukaryotes with apparently no related homologue in lower counterparts like *Saccharomyces cerevisiae* [6]. WD-repeat domains are likely to be responsible for assembly of macromolecular complexes [7], showing that ALADIN might be acting as a scaffold for multiprotein assemblies. However, as WD-repeat proteins are involved in a many cellular pathways, the unique function of ALADIN is unknown. Sequencing of the *ALADIN* gene from several Triple A patients has shown numerous mutations placed throughout the gene [8]. Most of these mutations include nonsense, frameshift, or splice-site mutations that are thought to truncate the C terminus of ALADIN, hinting that this domain is significant for the function of ALADIN. There is no definite proportionality between diverse ALADIN mutations and disease phenotype. Patients with the same mutation, even belonging to the same family, mostly show a high degree of variability in clinical seriousness and age of display of their symptoms [9]. Studies have shown that mutations linked with Triple A syndrome cause a change in the localization of ALADIN from NPCs to the cytoplasm [10]. Categorization of an ALADIN mutant cell line shows that the non-appearance of a functional ALADIN does not cause in shape related anomalies in nuclei, NPCs, or NEs, suggesting that the resulting deficiency in the protein complex is in function rather than in structure [11]. This suggests that other features play a significant role in the pathogenesis of triple A syndrome.

Research has shown the presence of WD-repeats (producing a β-propeller structure) predicting that ALADIN is probably responsible for protein-protein interactions and may help in the assembly of multi molecular complexes [7]. So, an attempt has been made to know the functional interactions of ALADIN with other proteins by using *insilico* approaches. We have used protein- protein interaction tool STRING to predict interactions of ALADIN protein with other nuclear proteins.

MATERIALS AND METHODS

Protein Sequence: Protein sequences of ALADIN protein was retrieved from NCBI database http://www.ncbi.nlm.nih.gov/protein.

Protein-Protein Interactions – The interactions network of the ALADIN protein with other proteins were found using STRING database http://string-db.org/. The sequence used as a query was the human ALADIN protein and the results were analysed.

RESULTS AND DISCUSSION

ALADIN also known as adracalin is a protein encoded by the *AAAS* gene. ALADIN is a 60-kDa protein. ALADIN belongs to the WD-repeat family of regulatory proteins with a central 170-aa domain composed of four WD repeats. The flanking N and C termini, of 150 and 230 residues, respectively, contain no obvious structural domains. ALADIN protein belongs to nuclear pore complex which consist of roughly 30 different proteins and furnish the only platforms for macromolecular transport between cytoplasm and nucleus. ALADIN might be a scaffold for multiprotein assemblies. But, because WD repeats proteins aid in a various cellular processes, the unique function of ALADIN is unknown.

Numerous mutations such as nonsense, frameshift, or splice-site mutations are suggested to truncate the C terminus of ALADIN, showing that this domain is significant for the activity of ALADIN. In addition, there are four point mutations, three of which (H160R, S263P, and V313A) are within the WD-repeat domain, whereas the fourth (Q15K) is close to the N terminus. Mutations in ALADIN are responsible for triple A syndrome or Allgrove syndrome a rare autosomal recessive disorder with symptoms of adrenal insufficiency, alacrima, and achalasia. The AAAS gene is present on long arm of the 12 chromosome 12q13.

The protein interactions of human ALADIN protein with other proteins was studied using STRING database (Figure 2). The human ALADIN protein sequence was used as a query. The results showed the human ALADIN protein interacts with ten different proteins namely ubiquitin (UBC) and the nucleoporins NUP43, NUP37, NUP85, NUP107, NUP50, NUP62, NUP35, NUP155, NUP160 as shown in Table 1.

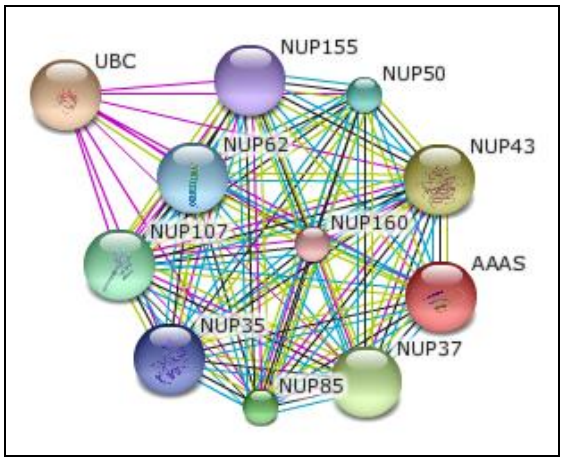

Fig. 2: *STRING Database Results Showing the Interactions of Human ALADIN Protein (AAAS).*

Table 1: *A List of the Interacting Protein Partners of Human ALADIN As Shown by STRING Database.*

S. No	Name of the Interacting Protein	Description	Size (Amino Acids)
1	UBC	Ubiquitin	685
2	NUP43	Nucleoporin	380
3	NUP37	Nucleoporin	326
4	NUP85	Nucleoporin	656
5	NUP107	Nucleoporin	925
6	NUP50	Nucleoporin	468
7	NUP62	Nucleoporin	522
8	NUP35	Nucleoporin	326
9	NUP155	Nucleoporin	1391
10	NUP160	Nucleoporin	1436

CONCLUSIONS

Numerous mutations like nonsense, frame-shift, or splice-site mutations lead to truncation of the C terminus of ALADIN, showing that this domain is significance for the activity of ALADIN. Further, there exists four point mutations, three of them (H160R, S263P, and V313A) lying in the WD-repeat domain, but the fourth (Q15K) is near the N terminus [12]. Mutations in ALADIN are responsible for triple a syndrome. In this study, STRING database have been used to predict the protein-protein interactions of ALADIN protein with other nucleoporins. The results show the human ALADIN protein interacts with ubiquitin and nine nucleoporins NUP43, NUP37, NUP85, NUP107, NUP50, NUP62, NUP35, NUP155, NUP160 which further corroborates the previous findings that ALADIN is a part of the intricate protein interaction network and that the mutations in ALADIN cause a defect in its function rather than structure as shown by previous mutant studies [10].

REFERENCES

1. Allen TD, Cronshaw JM, Bagley S, Kiseleva E, Goldberg MW. The nuclear pore complex: mediator of translocation between nucleus and cytoplasm. *J. Cell Sci*. 2000; 113: 1651–1659p.
2. Cronshaw JM, Krutchinsky AN, Zhang W, Chait BT, Matunis MJ. Proteomic analysis of the mammalian nuclear pore complex. *J Cell Biol*. 2002; 158(5): 915–927p.
3. Reichelt R, Holzenburg A, Buhle EL, Jarnik M, Engel A, Aebi U. Correlation between structure and mass distribution of the nuclear pore complex and of distinct pore complex components. *J. Cell Biol.* 1990; 110: 883–894p.
4. Allgrove J, Clayden GS, Grant DB, Macaulay JC. Fa-milial glucocorticoid deficiency with achalasia of the cardia and deficient tear production. *Lancet.* 1978; 1284–1286p.
5. Dickmanns A, Kehlenbach RH, Fahrenkrog B. Nuclear pore complex and nucleocytoplasmic transport : From structure to function to disease. in Ed. Book.;Jeon, K.W. international review of cell and molecular biology 1st Edn: Elsiever Inc:USA, 2015; 320
6. Tullio-Pelet A, Salomon R, Hadj-Rabia S, Mugnier C, de Laet MH, Chaouachi B, Bakiri F, Brottier P, Cattolico L, Penet C, Bégeot M, Naville D, Nicolino M, Chaussain JL, Weissenbach J, Munnich A, Lyonnet S. Mutant WD-repeat protein in triple-A syndrome. *Nat Genet.* 2000; 26; 332–335p.

7. Smith TF, Gaitatzes C, Saxena K, Neer E. The WD repeat: a common architecture for diverse functions. *J.Trends Biochem. Sci*. 1999. *24*, 181–185.
8. Huebner, A.; Kaindl, AM, Knobeloch KP, Petzold H, Mann P, Koehler K. The Triple A syndrome is due to mutations in ALADIN, a novel member of the nuclear pore complex. *Endocr Res*. 2004; 30(4): 891–9p.
9. Huebner A, Kaindl AM, Braun R, Handschug K. New insights into the molecular basis of the triple A syndrome. *Endocrine Research.* 2002; 28(4): 733–739p.
10. Cronshaw JM, Matunis MJ. The nuclear pore complex protein ALADIN is mislocalized in Triple A syndrome. *Proc Natl Acad Sci USA.* 2003; 100(10): 5823–7p.
11. Janet M, Cronshaw JM, Matunis MJ. The nuclear pore complex protein ALADIN is mislocalized in Triple A syndrome. PNAS. 2003; 100(10): 5823–5827p.
12. Zamanfar D , Shokri E , Shadani S , Shahmohammadi S. Allgrove's Syndrome: Two Case Reports and Review of Literature. *Journal of Pediatrics Review*. 2015; 3(2): 2653–58p.

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