Original article

Structural insight into mutations at 155 position of valosin containing protein (VCP) linked to inclusion body myopathy with Paget disease of bone and frontotemporal Dementia

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A B S T R A C T

Mutations in Valosin-containing protein (VCP) have been implicated in the pathology linked to inclusion body myopathy, Paget disease of bone and frontotemporal dementia (IBMPFD). VCP is an essential component of AAA-ATPase superfamily involved in various cellular functions. Advanced In-silico analysis was performed using prediction based servers to determine the most deleterious mutation. Molecular dynamics simulation was used to study the protein dynamics at atomic level. Molecular docking was used to study the effect of mutation on ATP/ADP transition in the kinase domain. This ATPase of 806 amino acids has four domains: N-terminal domain, C-terminal domain and two ATPase domains D1 and D2 and each of these domains have a distinct role in its functioning. The mutations in VCP protein are distributed among regions known as hotspots, one such hotspot is codon 155. Three missense mutations reported in this hotspot are R155C, R155H and R155P. Potentiality of the deleteriousness calculated using server based prediction models reveal R155C mutation to be the most deleterious. The atomic insight into the effect of mutation by molecular dynamics simulation revealed major conformational changes in R155C variants ATP binding site in D1 domain. The nucleotide-binding mode at the catalytic pocket of VCP and its three variants at codon 155 showed change in the structure, which affects the ATP–ADP transition kinetics in all the three variants.

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1. Introduction

Frontotemporal Dementia (FTD) formerly known as “Pick’s Disease” is an anomaly of neurodegenerative disorder caused by neuronal loss in frontal and/or temporal lobes of the brain (Lowe and Spillantini, 1998). The disease features gradual and progressive decline in behaviour and/or language, based on these signs FTD is divided into two major clinical syndromes: the behavioural variant and the language variant (Rascovsky et al., 2011). With almost equal incidence has been reported in men and women, the signs and symptoms of FTD become evident more commonly between the age group of 45 and 65 years. This disease is most prevalence like Alzheimer’s disease and limited studies have shown a trend of 20–50% of reported cases younger than 65 years (Ratanavalli et al., 2002). The aetiology of FTD has been associated with mutations. Mutations in MAPT, GRN, TARDBP, CHMP2B and VCP genes are known genetic factors for aetiology of FTD (Lynch et al., 1994; Baker et al., 2006; Van Swieten and Heutink, 2008; Kabashi et al., 2008; Skibinski et al., 2005; Neumann et al., 2007).

Mutations in valosin-containing protein (VCP) gene are associated with inclusion body myopathy and Paget disease of bone and FTD (IBMPFD), which is a rare autosomal-dominant disorder (Neumann et al., 2007; Watts et al., 2004). The disease is characterized by adult-onset proximal and distal muscle weakness, early-onset of Paget disease of bone (PDB) in most cases, and premature FTD (Kovach et al., 2001). PDB involves increased bone turnover, localized enlargement with deformity of the long bones. Early stages FTD in IBMPFD patients is characterized by progressive decline in behaviour by showing traits like dysnomia, paraphasic errors, comprehension deficits, dyscalculia and memory loss. In advanced stage of FTD language disability, alexia, and agraphia become evident. Among individuals who meet diagnostic criteria
for IBMFD, nearly 100% have an identified mutation in the VCP gene, and approximately 80% of individuals have family history and 20% are first time affected by de-novo mutations (Kimonis et al., 2018).

VCP protein is an essential component of AAA-ATPase super-family involved in cell cycle regulation (Hetzer et al., 2001), homotypic membrane fusion (Kondo et al., 1997), postmitotic Golgi reassembly (Rabouille et al., 1998) and ubiquitin–proteasome pathway-mediated endoplasmic reticulum-associated degradation (Watts et al., 2004). The VCP protein is an ATPase constituting of 806 amino-acids, the protein has four domains: N-terminal domain, C-terminal domain and two ATPase domains D1 and D2. The N-terminal domain binds specific ubiquitin substrates through cofactors such as Ufd1, Npl4, and p47 and the C-terminal domain binds multiubiquitination enzyme Ufd2 (Wang et al., 2004). Till date ten VCP missense mutations has been reported and half of which fall in mutation hotspots (Kimonis et al., 2008). One such hotspot is codon 155, where a missense mutation is a cause of IBMFD in more than 50% of reported IBMFD individuals. The three missense mutations reported in this hotspot are R155C (Guyant-Marechal et al., 2006), R155H (Viassolo et al., 2008) and R155P (Haubenberger et al., 2005), among them R155H is the most common.

To understand the effect of single amino acid substitution on protein structure and dynamics, the use of In-silico techniques has become a reliable tool (Mokhdomi et al., 2016). In this study we have used computer aided prediction methods to evaluate the damaging capability of the mutations. VCP protein and its 155 codon variants we observed under virtual microscope of molecular dynamics simulation, the tool is used to observe the conformational changes inflicted by the mutation on protein structure.

2. Material and methods

2.1. Data set preparation

The atomic coordinates of a single monomer VCP protein used in this study were retrieved from PDB entry: 4KLN (Tang and Xia, 2013), the coordinated amino acids alone were used to generate the models using mutate module of Discovery Studio 4.5 (Studio, 2013). The X-ray crystallographic structure was the highest resolved (2.62 Å) structure available for a hexameric assembly. The geometry of the modelled structures was optimized using Swiss PDB viewer, where the structures were searched for missing atoms and energy was minimized. The first structure generated was Wt, and GROMACS 4.6.5 (Pronk et al., 2013) platform was used for energy minimization. The other three structures generated from Wt were Mu1 (R155C), Mu2 (R155H) and Mu3 (R155P). The same nomenclature was used throughout the study. The ATP and ADP structures used for molecular docking analysis were retrieved from PubChem database. All the simulations in this study were carried out using GROMOS 43a1 force field.

2.2. SNP damage prediction

The deleterious effect of the mutations was studied using prediction based models. Three online servers selected were SIFT (Kumar et al., 2009), PolyPhen2 (Adzhubei et al., 2010) and PoPMuSiC (Dehouck et al., 2011).

2.3. Molecular dynamics simulation

Molecular dynamics simulation using GROMACS 4.6.5 platform (Pronk et al., 2013) was used to look into the dynamics of the VCP and its three 155 codon variants. 50 ns simulation of native and mutant proteins was carried out. The proteins were placed in water with simple point charge (SPC) water molecule and ions (Jorgensen et al., 1983). The ions were added using the GENION tool of the GROMACS, the random water molecules were replaced by Na+ or Cl- ions to achieve the simulation under physiological salt concentration (150 mM). Periodic boundary condition were set to maintain constant pressure and temperature, Parrinello-Rahman method and Berendsen temperature coupling method were employed for pressure and temperature, respectively (Berendsen et al., 1984; Martonák et al., 2003). Position restrain simulation was performed at 310 K for 1 ns with a coupling time of 0.2 ps. The bond formation was regulated by SHAKE algorithm, which was used to impose general harmonic constraints after every two frames during molecular simulations (Elber et al., 2011).
A run of 50 ns was performed; the trajectories generated were analysed using GROMACS in-build tool. DSSP program was used to check the secondary structure architecture over time (Hooft et al., 1996). Graphs were plotted using Grace and GNUPLOT programs (Turner, 2005; Racine, 2006). All the visualizations were carried out using pymol and discover studio visualize (DeLano, 2002).

### 2.4. Molecular docking simulation and MM-PBSA calculations

AutoDock 4.2 tool (Goodsell et al., 1996) was used for molecular docking simulations, ATP and ADP were alternatively used to evaluate the nucleotide-binding mode at the catalytic pocket of VCP and its three variants at codon 155.

### 3. Results

#### 3.1. Structure and assembly of VCP protein

Schematic representation of the domains and sub-domains were shown in Fig. 1, the portion of the VCP protein under investigation ranges from 14 to 469 amino acids and can be divided into N-terminal (14–187) and D1-domain (209–460) with N-terminal and D1-domain linker ranging from 188 to 208. The N-terminal region has two sub-domains of Na and Nb required for cofactor and substrate binding. The D1-Domain has two regions D1-ATPase domain (209–370) and D1α domain (370–460). The D1-ATPase domain has three sub-domains Walker A motif (WA), Walker B motif (WB) and second region of homology (SRH).

Fig. 2(A) shows the secondary structure architecture of the domains and the sub-domains, Fig. 2(B) shows the crystallographic structure of the two domains and the 155 codon position and its variant amino acids. The amino acid arginine has its own specific size, charge, hydrophobic value and the three variants differ in these properties. The mu1 has R155C variation, the variant cysteine is smaller in size, neutral in charge and changes the five running hydrophobicity value (Fig. 3). Mu2 R155H variation, the change in five running hydrophobicity value is least, but the change in charge and size at 155 position due to incorporation of histidine. The variation at 155 codon under observation is of R155P, where proline incorporation changes the size and charge of the position, however change in five running hydrophobicity is least. The change in the amino-acid properties is a factor that may alter the phenomenon of asymmetry in hexameric structure of VCP proteins, this change can alter the functioning, particularly the ATP/ADP transition.

#### 3.2. Prediction based mutational analysis

Three in-silico tools were selected for predicting the damaged effect of the mutation, the selection of the servers was done to check both sequence and structure based effect. For SNP damage prediction in-silico tools use algorithms that have been outlined, designed, and developed for predicting whether a mutation is deleterious or neutral. These uses of such tools make studies more feasible and accurate and are less time-consuming. The selected servers for this study looked into and double checked both sequence and structure based effect of the selected mutations. Table 1 shows the result generated, selected servers predicted all the three mutations to be damaging (see Tables 2–5).

For sequence based method to predict the effect of mutations at codon 155, used SIFT server and the three mutations were classified as damaging and tolerated, mu1 was predicted to be damaging among the three. PolyPhen2 (Polymorphism Phenotyping v2) is a tool which predicts possible impact of an amino acid substitution on the structure and function of a human protein using straight forward physical and comparative considerations. In this HumDiv (a preferred model for evaluating rare alleles) predicted all the mutation to be PROBABLY DAMAGING, R155C is the most damag-
ing of the three with a score of 1 (sensitivity: 0.00; specificity: 1.00) as shown in Fig. 4 (A). Other model i.e. HumVar (a preferred model for diagnostic of Medalian Disease) predicted R155C and R155P to be PROBABLY DAMAGING and R155H as BENIGN - with a score of 0.135 (sensitivity: 0.90; specificity: 0.71) as shown in Fig. 4(B). The third tool that was used is PoPMuSiC, a tool for the CAD (computer aided design) of mutant proteins with controlled stability properties. It assess the changes in stability of a given protein or peptide under single-site mutation, on the basis of its structure. In this case single option was used that enabled to predict stability change resulting from a given mutations. The result generated showed R155C to be the most destabilizing with Acc = 75.50% and ΔG = 0.30 kcal/mol. The generated result showed R155C as highly deleterious and least stable.

3.3. Structural and conformational dynamics of VCP and its variants

The changes at 10 ns interval of time were taken and the picturesque representation is shown in Fig. 5. The results give a general outline of the effect of the mutations on protein structure and dynamics. To look into more detail, the average secondary structure layout was observed (Fig. 6). The mutation in the N-terminal region of VCP is changing the secondary structure layout of both N-terminal and D1-domain in all mutant structures. GROMACS inbuilt tools g_rms, g_gyrate, g_sas and g_hbond tool were used to study the structural and conformational dynamics of VCP and its three 155 codon variants. Root mean square deviation (RMSD) was calculated using g_rms tool, Fig. 7(A) shows the value curves

Table 1

| Server  | R155C       | R155H       | R155P       |
|---------|-------------|-------------|-------------|
| SIFT    | DAMAGING    | TOLERATED   | TOLERATED   |
| PolyPhen2 | Probably damaging | TOLERATED | TOLERATED   |
| PoPMuSiC | Destabilizing | Destabilizing | Destabilizing |
The xyz coordinates of the amino acids selected for gauging the distance spanning in the ATP/ADP binding pocket.

| Table 2 | The ATP/ADP binding mode of the wildtype (wt), mutant1 (Mu1), mutant2 (Mu2) and mutant3 (Mu3) valosin-containing protein (VCP). Bold amino acids are common in ATP and ADP binding pockets. |
|---------|---------------------------------------------------------------------------------|
| ATM Binding Mode | ADP Binding Mode |
| Wt | ASN348, PRO247, LYS251, PRO246, THR249, GLY250, THR252, ARG256, VAL201, His384, Ala142 |
| Mu1 | Pro247, PRO246, THR249, LYS251, THR252, LEU409, ALA412, HIS384, GLY248, GLY250, ASN348 |
| Mu2 | PRO247, CYSS209, GLY212, GLY370, ILE371, GLY370, ILE371, ILE369, ASP304, ASN348, THR252, GLY250, ALA409, HIS384, GLY408, PRO372, GLY208 |
| Mu3 | THR252, ALA409, LEU409, GLY248, LYS251, GLY250, ILE383, ILE206, ILE254, GLN212, ASP205, GLY207 |

Comparative Binding energy during ATP-ADP transition.

| Table 3 | Comparative Binding energy during ATP/ADP transition. |
|---------|-----------------------------------------------------|
| WT | R155C | R155H | R155P |
| ΔGATP | 33.077 ± 23.873 | 182.634 ± 32.714 | 236.345 ± 22.743 |
| ΔGADP | -4.21 | -7.31 | -8.32 |
| ΔGATP-ADP | 1.55 | 0.62 | 0.96 |

Table 5

| Table 5 | MM-PBSA calculations. |
|---------|-----------------------|
| Summary | WT | R155C | R155H | R155P |
| ATP Binding energy | -236.345 | -163.901 | -173.543 | -201.154 |
| kJ/mol | ±25.657 | ±32.714 | ±22.743 | ±25.387 |
| ADP Binding energy | -182.634 | -158.654 | -145.567 | -189.675 |
| kJ/mol | ±23.873 | ±34.234 | ±31.565 | ±31.265 |

of wildtype and its mutant systems over time. Mu1 structure showed the maximum deviation, the deviation can be the result of change in secondary structure architecture. The RMSD result at 310 K temperature shows the wild type to converge at 0.5 nm after 50 ns simulation, while mu3 is showing the least SASA (125 nm²) after 50 ns.

The hydrogen bond pattern was studied using g_hbond tool, intra-protein hydrogen bond pattern and protein water hydrogen bond pattern was studied. Fig. 8 shows the results generated the WT VCP domain forms 336 average number of intra hydrogen bond per frame (each frame calculated after 2 ps) and with water the number is 917 hydrogen bond per frame. On comparison all the three mutant structures are showing decrease in average number of intra hydrogen bond per frame, the numbers are 328, 334 and 331 respectively for mu1, mu2 and mu3. The protein-water hydrogen bond pattern is also showing decrease in number as compared to wt.

3.4. Flexibility and compactness in WT and mutants

To look into the flexibility and compactness of VCP N-terminal and D1 domain, g_rmsf tool of GROMACS package was employed. The tool calculates root mean square fluctuation (RMSF), giving an account of standard deviation of c-alpha atoms in the trajectory after fitting to a reference frame. Fig. 9 (A) represents the mobility of c-alpha atoms of the amino-acids, to investigate further the RMSF plot was broken into three, based on the structural domains of the VCP protein segment under investigation, Fig. 9(B) shows the RMSF plot of N-terminal, N-D1 linker and D1-Domain. The ATP binding domain of the D1-ATPase domain was studied for fluctuations. Fig. 9(C) shows the fluctuations. On observing the RMSF pattern it is evident that all the mutations have drastic fluctuation pattern. In r_rmsf tool the option --qv was used to convert the RMSF value into B Factor values and implicit them on the VCP structure.

Table 4

| Table 4 | The xyz coordinates of the amino acids selected for gauging the distance spanning in the ATP/ADP binding pocket. |
|---------|-------------------------------------------------|
| 0 ns | AA | X | Y | Z | Distance S197-G273 | Distance G273-S414 | Distance S416-S197 |
| Wt | SER197 | 34.696 | 53.459 | 43.408 | 23.355 | 27.645 | 21.126 |
| Glu273 | 39.502 | 55.981 | 52.556 | 39.104 | 55.839 | 52.419 | 40.662 | 49.398 | 43.194 |
| SER416 | 40.023 | 43.692 | 46.182 | 38.460 | 56.208 | 49.163 | 39.726 | 53.952 | 41.941 | 40.559 | 44.557 | 46.810 |
| Mu1 | SER197 | 34.719 | 53.264 | 43.459 | 38.413 | 56.208 | 49.163 | 38.460 | 56.208 | 49.163 | 39.726 | 53.952 | 41.941 | 40.559 | 44.557 | 46.810 |
| Glu273 | 37.911 | 55.781 | 52.914 | 32.607 | 27.967 | 21.598 | 37.911 | 55.781 | 52.914 | 24.098 | 26.536 | 18.631 |
| SER416 | 40.077 | 43.404 | 46.164 | 34.413 | 55.861 | 42.914 | 40.559 | 44.557 | 46.810 | 42.341 | 45.935 | 47.850 |
| Mu2 | SER197 | 34.864 | 53.373 | 43.298 | 38.175 | 55.789 | 42.914 | 37.911 | 55.781 | 52.914 | 24.098 | 26.536 | 18.631 |
| Glu273 | 39.528 | 55.992 | 52.727 | 23.475 | 28.096 | 21.497 | 38.761 | 57.868 | 50.328 | 27.693 | 25.432 | 17.591 |
| SER416 | 40.066 | 43.499 | 46.184 | 42.341 | 45.935 | 47.850 | 38.761 | 57.868 | 50.328 | 27.693 | 25.432 | 17.591 |

Table 6

| Table 7 | Summary | WT | R155C | R155H | R155P |
|---------|---------|---------|---------|---------|---------|
| ATP Binding energy | -236.345 | -163.901 | -173.543 | -201.154 |
| kJ/mol | ±25.657 | ±32.714 | ±22.743 | ±25.387 |
| ADP Binding energy | -182.634 | -158.654 | -145.567 | -189.675 |
| kJ/mol | ±23.873 | ±34.234 | ±31.565 | ±31.265 |
Fig. 4. (A) HumDiv (a preferred model for evaluating rare alleles) of PolyPhen2 (Polymorphism Phenotyping v2) predicted all the mutations to be PROBABLY DAMAGING, R155C is the most damaging of the three with a score of 1 (sensitivity: 0.00; specificity: 1.00). (B) HumVar (a preferred model for diagnostic of Medalian Disease) of PolyPhen2 predicted R155C and R155P to be PROBABLY DAMAGING and R155H as BENIGN with a score of 0.135 (sensitivity: 0.90; specificity: 0.71).

Fig. 5. Retrieved snapshots of the tertiary Wt, Mu1, Mu2 and Mu3 structures along 50 ns MDS trajectory, 10 ns gap was kept between each structure from left to right.
Fig. 6. Secondary structure layout of Wt, Mu1, Mu2 and Mu3 structures. Mu1 structure is showing maximum variation in secondary structure elements when compared with that of Wt.

Fig. 7. (A) VCP’s RMSD plot for wt (black) and Mu1 (red), Mu3 (green) and Mu4 (blue) structures at 310 K. The R155C structure is showing maximum deviation. (B) VCP’s Radii of gyration for wt (black) and Mu1 (red), Mu3 (green) and Mu4 (blue) structures at 310 K. The R155C structure is showing maximum decrease over time. (C) VCP’s Solvent Accessible Surface Area for wt (black) and Mu1 (red), Mu3 (green) and Mu4 (blue) structures at 310 K.
under observation (blue representing the most stable and red most fluctuating). Fig. 9(D) shows the B factor projection where blue colour represents rigid and red represents most flexible, the mutant structures are showing significant fluctuations in N-terminal and D1-Domain. The comparative B factor projection primarily indicates fluctuations variations are most in R155C variant (see Figs. 10–12).

4. Discussion

The functional consequence of the three mutations reported at the VCP codon was studied. ATP–ADP transition was calculated, AutoDock tool was used to place the ATP and ADP in ATP/ADP binding domain (Baker et al., 2006). The ATP and ADP structures were docked in the D1-domain of the energy minimised four structures, the binding domain, the ATP/ADP transition were studied. The allosteric effect identified by this method showed that the mutations have a direct effect on ATP-ADP transition, and that the R155C variant was the most affected among three, having the maximum number of unfavourable interactions with ATP and ADP. The ATP/ADP binding mode was also studied in the available X-ray crystallographic structure of codon 155 mutant variant with ATP (4KO8) and ADP (4kod) in their binding pocket. The unfavourable interactions were also observed in their ATP/ADP binding pockets (Hooft et al., 1996). GLY408 appeared to be in all mutant ATP/ADP binding pockets, and was also observed in the ATP/ADP binding pockets of 4k08 and 4kod structure respectively. To study the changes in ATP/ADP binding groove, the distances between D1 ATPase domain, Dα domain and N-terminal were studied. Three amino acids GLU273, SER416 and SER 197 each from D1 ATPase domain, Dα domain and N-terminal respectively were selected for gauging their distance over time (Turner, 2005). The xyz co-ordination of the amino acids and the distance between them was analyzed. The major changes are observed in the distance between SER416 and SER197, where in the starting structures at 0 ns of wt, mu1 mu2, and mu3 the distance is around 21 Angstrom and at 50 ns the wt shows the distance at 33 Angstrom and all the mutants have around 18 Angstrom. This when observed at atomic level shows the conformational change is one of the helix of Dα domain of VCP. This data show that the wt structure at the end of 50 ns simulation shows a relaxed form attains an open confor-
Fig. 9. (A) VCP residue RMSF at 310 K temperature of the four structures. (B) The domain based; N-Terminal, N-D1 liker and D1-domains RMSF profile at residue level of VCP and its 155 codon variants. (C) RMSF variation at the ATP binding domain of VCP, showing fluctuations across all amino acids in this domain. (D) Average Tertiary structures colored according to Bfactor values, Showing Mu1 to be most fluctuating.

Fig. 10. ATP/ADP binding mode in valosin-containing protein (VCP), harbouring R155H mutation, the crystal structures used PDB ID: 4KO8 and 4KOD are co-crystallized with ATP and ADP respectively. The unfavourable interactions and the presence of GLY408 in the binding pocket are a common feature in these crystallized structures and our modelled mutant variants of VCP.
mation, which is favorable for ATP/ADP transition (Dehouck et al., 2011). The data also affirms the movement of GLY 408 into the ATP/ADP binding pocket. The helix (400–425 amino acid) moves laterally relatively closer to the ATP/ADP binding pocket in all the mutant structures, the maximum shown by mu1. MM-PBSA calculations were employed to evaluate the binding free energy of ATP/ADP with VCP protein (Baker et al., 2006). The binding energies of the simulated complexes show that the ADP/ATP transition in R155C variant was affected the most. ATP showed the least binding of −163.901 (+/− 32.714) kJ/mol with R155C and the difference between ATP and ADP binding also least in this variant. These changes can alter the functioning of VCP (Tang and Xia, 2016).

5. Conclusions

Incongruities in ATP binding domain of any kinase enzyme and disease aetiology are synonyms. The occurrence of the mutation in protein like VCP is a contributing factor to a clinical multiple-disorder condition known as IBM-FPD. Mutation at codon 155, a known mutational hotspot in VCP protein is an important factor that could impair ATPase activity of the D1-domain by affecting D1-D2 linker, the linker is capable of inducing asymmetry in subunit association into a VCP hexamer. The effect of D1-D2 linker on the ATPase activity of the D1-domain is already known and a significant genetic polymorphism in VCP will have an effect on its ATPase activity. As none of the studies till date has reported molecular dynamics simulation analysis of mutation in codon 155 of VCP, it has primarily prompted us to look into the possibility of computationally analysing of ATP/ADP transition. The structural transitions observed in secondary structure elements show that R155C mutant is showing the maximum variations, a factor that could influence ATP/ADP transition. The Rg of R155C mutant also shows that the structure is showing maximum deviation from Wt, the change can hamper VCP hexameric assembly. The conformational variability of D1-domain prompted us to look into ATP/
ADP transition kinetics. The molecular docking and MM-PBSA calculations reveal that ATP/ADP, despite binding to the same binding pocket shows a varying pattern in ATP/ADP-binding affinity coefficient. The analysis of the effect of mutations (R155C/ R155H/R155P) using molecular dynamics simulation reveal the change in the secondary structure architecture, the change in intra-hydrogen bond pattern and ATP-ADP transition as major factors that presumptuously act as trigger for the onset of IBMPFD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Further Reading

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