Critical Role Of Proline And Glycine Conservation With Repeats In Neurodegenerative Disorders

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Citation

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Abstract

Progressive neurodegenerative diseases like Huntington's, Alzheimer's disease, Down's syndrome, Tay Sachs disease, spino cerebellar ataxia 2,kennedy disease, Dentatorubral – pallidoluysian atrophy and ALS have been gradually realized to be evolved from the common cellular and physiological pathways. The aim was to identify possible biases in the amino acid repeat patterns with respect to the repeats in other sequences responsible for neurodegenerative disorders, as this could be informative for specific constraints operating in the repetitive structures. Previous studies suggest the misfolding of the amyloid proteins as one of the most prominent causes. Our study reveals the critical role of proline and glycine conservation with Alanine, glycine, proline residue repeat polymorphism levels. Proline toxicities have been found involved in cardiac muscle disorder, neuro transmitter disorder, congestive heart failure and major depression found in most of the degenerative diseases worked on. We inspected the relative position 58 where proline conservation was seen in spino cerebellar ataxia 2 and Huntington giving rise to the common symptoms of the disease. Our study also suggests that Q repeats mostly fall in helical regions indicating responsible Proteins to be the surface proteins which cause different severe symptoms and effects.

INTRODUCTION

Neurological and psychiatric disorders taken together account for more chronic suffering than all other disorders combined[1].The sunset has been a prolonged one, as is usual in most neurodegenerative disorders, of which Huntington's and Alzheimer's are the prototype. All have an insidious onset, progress slowly over years, and death is usually due to an intercurrent illness and not directly due to the disease itself. The diseases will rise with increasing longevity. Much of the burden is also borne by carriers and relatives. Brain parenchyma is supposed to be the layer in brain where the illicit protein deposits take place and give rise to different neurodegenerative disorders[2]. Previous studies reveal the role of proteins like amyloid which are rich in beta sheets to be involved in the toxicity and lethality of the progression of the disease. Our study suggests role of the alpha helical residues in toxicity and lethality of the diseases which are also supported with the conservation of proline and glycine residues. Previous animal trials by beta sheet breaker residues may have failed because of the of proline conservation in the neurodegenerative studies[3]. As per our study on proline repeats a suitable therapy for the treatment of the neurodegenerative disorders may be obtained. Proline-rich domain, along with a charged domain, is critical for PQE-1 protein function. Analysis of pqe-1 suggests that proteins exist that specifically protect neurons from the toxic effects of expanded polyQ disease proteins[4]. Proline derivatives have affinity for the calcium channel alpha -2 delta subunit which is useful in the treatment of epilepsy, feats, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, fibromyalgia, arthritis, neuropathalogical disorders, sleep disorders, visceral pain disorders and gastrointestinal disorders[5]. Glycine and proline residues are frequently found in turn and loop structures of proteins and are believed to play an important role during chain compaction early in folding[6]. The proteins worked out in our study have a good composition of proline repeats as well as conservation which may be worked out for the therapeutical aspects.

PROCEDURE

Insilico analysis of the worked out proteins in the present study is concluded to be correlated with some proteins like titin, synapsin, natriuretic peptides, beta casein which causes different lethal conditions like Cardiac muscle disorder, neurotransmitter disorder, congestive heart failure, Parkinson's, major depression etc.

1. CONSERVATION OF PROLINE (P) AND GLYCINE (G) RESIDUES –

We found proline and glycine residues to be conserved in all the model neurodegenerative diseases. For this analysis, we used CLUSTAL W Boxshade (fig 1) and texshade (fig 2) which gave us the conservation pattern of proline and glycine.

FIG 1 (Green Color shows complete conservation)

Figure 1

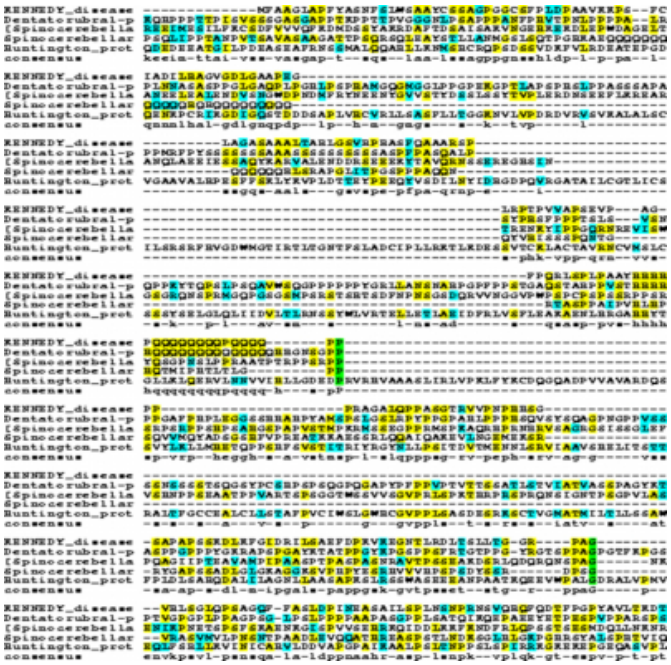
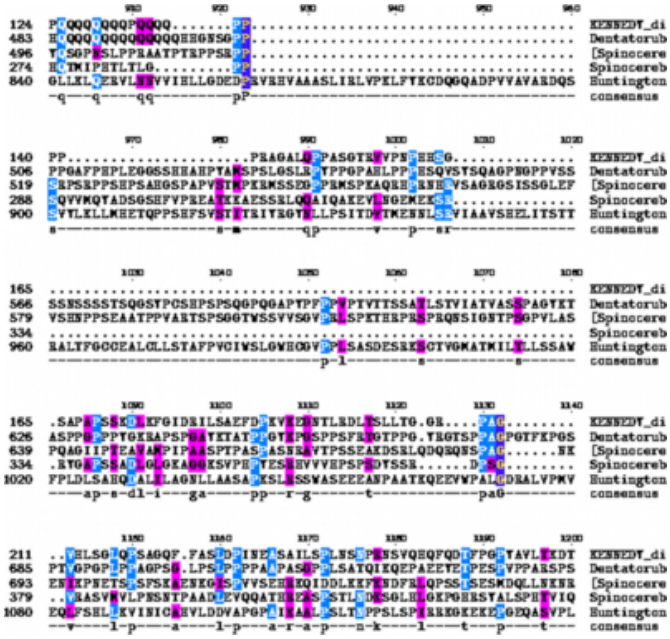


FIG 2 (Dark Blue color shows complete conservation)

Figure 2



2.FORMATION OF HELICES BY GLUTAMINE (Q) REPEATS-

Using PREDATOR it was found that repeats of glutamine form the helices, whereas a glutamine repeat can also be responsible for formation of strand.

3. GENE EXPRESSION LEVEL-

Gene card detected the expression of all the selected genes to be expressed in brain with a higher percentage.

1. HUNTINGTON DISEASE PROTEIN

>gi|1170192|sp|P42858|HD_HUMAN Huntingtin (Huntington disease protein) (HD protein)

1
MATLEKLMKAFESLKSFQQQQQQQQQQQQQQQQQQ
QQQQPPPPPPPPPP 50
HHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHHH
HH_____

2.DENTATORUBRAL-PALLIDOLUYSIAN ATROPHY PROTEIN

>gi|29429203|sp|P54259|ATN1_HUMAN Atrophin-1 (Dentatorubral-pallidoluysian atrophy protein)

101
PSEVPAGFPQRLSPLPAAYHHHHPQQQQQQQQPQQQ
QPPPPPRAGALQPP 150

HHHHHH_____

4.SPINOCEREBELLAR ATAXIA TYPE 1 PROTEIN

>gi|1710863|sp|P54253|ATX1_HUMAN Ataxin-1 (Spinocerebellar ataxia type 1 protein)

201 QQQQQQQQHQHQQQQQQQQQQ 250
HHHHHHHHHHHHHHHHHHHHHHHHHHHHHH_____
_____EEE

5.Spinocerebellar ataxia type 2 protein

>gi|52000732|sp|Q99700|ATX2_HUMAN Ataxin-2 (Spinocerebellar ataxia type 2 protein) (Trinucleotide repeat-containing gene 13 protein)

151

ACEPVYGPLTMSLKPQQQQQQQQQQQQQQQQQQQ
QQPPPAAANVRKP 200
HHHHHHHHHHHHHHHHHHHH_____EEEE___

Figure 3

GeneCard for huntington disease

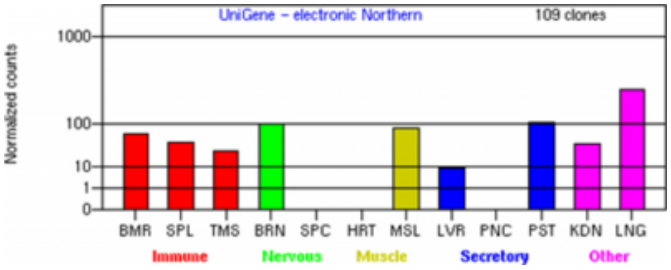
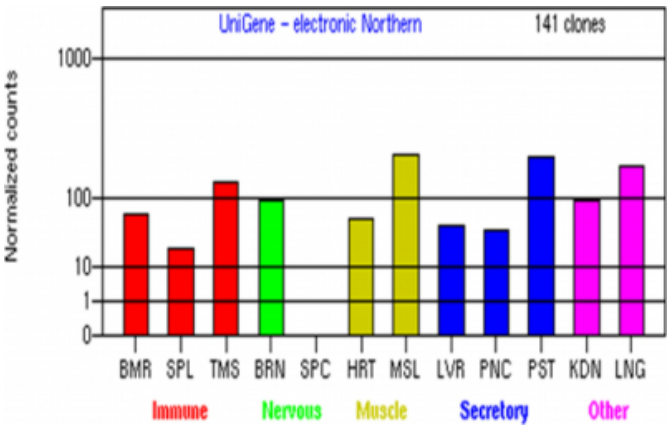


Figure 4

Geneards for spinocereballar ataxia type 1



CONCLUSION

The identification of main cause of neurological disorders is still a big question to the scientific world. Many genetic variations occurring at chromosome / nucleotide / protein level are known to accumulate or get conserved in course of time. The existence of disorders associated with repeats of different amino acid at protein level attracted us to perform the above analysis. Our study reveals that in many neurodegenerative conditions proline and glycine residues were found conserved. Previously, it was shown that poly Q repeats are responsible but our study reveals that conservation and repetition of proline also has significance in development of neurological disorders. Also further studies on proline may open a way for a conventional drug for the neurodegenerative disorders. We have also revealed that poly Q repeats are responsible for formation of helices and their expression is responsible for the toxic and lethal symptoms present with the neurodegenerative diseases.

ACKNOWLEDGMENT

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References

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3. http://www.pnas.org/cgi/content/full/99/26/17131 Published online before print December 16, 2002,
4. 10.1073/pnas.262544899Glutamine/proline-rich PQE-1 proteins protect Caenorhabditis elegans neurons from huntingtin polyglutamine neurotoxicity
5. Effect of Proline and Glycine Residues on Dynamics and \ Barriers of Loop Formation in Polypeptide

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