SCA8 repeat expansion: large CTA/CTG repeat alleles in neurological disorders and functional implications

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Abstract  Spinocerebellar ataxia type 8 (SCA8) involves bidirectional expression of CUG (ATXN8OS) and CAG (ATXN8) expansion transcripts. The pathogenesis of SCA8 is complex and the spectrum of clinical presentations is broad. In the present study, we assessed the SCA8 repeat size ranges in Taiwanese Parkinson’s disease, Alzheimer’s disease and atypical parkinsonism and investigated the genetic variation modulating ATXN8 expression. Thirteen large SCA8 alleles and a novel ATXN8 ¡ 62 G/A promoter SNP were found. There is a significant difference in the proportion of the individuals carrying SCA8 larger alleles in atypical parkinsonism (P = 0.044) as compared to that in the control subjects. In lymphoblastoid cells carrying SCA8 large alleles, treatment of MG-132 or staurosporine significantly increases the cell death or caspase 3 activity. Although expressed at low steady-state, ATXN8 expression level is significantly higher (P = 0.012) in cells with SCA8 large alleles than that of the control cells. The ATXN8 transcriptional activity was significantly higher in the luciferase reporter construct containing the ¡62G allele than that containing the ¡62A allele in both neuroblastoma and embryonic kidney cells. Therefore, our preliminary results suggest that ATXN8 gene ¡62 G/A polymorphism may be functional in modulating ATXN8 expression.

Introduction  Spinocerebellar ataxia type 8 (SCA8) is an autosomal dominant ataxia involving the expression of a CTG/CAG expansion mutation from opposite strands producing CUG expansion transcripts (ATXN8OS) and a polyglutamine expansion protein (ATXN8) (Ikeda et al. 2008). The 5’ end of the ATXN8OS gene overlaps with the 5’ region of the Kelch-like 1 (KLHL1) gene (Nemes et al. 2000). SCA8 cases can be familial or sporadic. The clinical findings include cerebellar ataxia with upper motor neuron dysfunction, dysphagia, peripheral sensory disturbances, or cognitive impairments (Day et al. 2000; Ikeda et al. 2000; Juvonen et al. 2000). The reported repeat lengths associated with ataxia range from 68 (Stevanin et al. 2000) to >1,000 repeats (Ikeda et al. 2004), mostly 85–130. In the general population more than 99% of the alleles have 16–37 combined repeats (Koob et al. 1999). In addition to ataxia, SCA8 expansions can also be found in rare instances in normal and non-ataxic diseased populations (Worth et al. 2000; Sobrido et al. 2001; Schols et al. 2003). The reported sporadic SCA8 mutation resembling corticobasal degeneration (Baba et al. 2005) and white matter hyperintense lesions in genetically proven SCA8 (Kumar and Miller 2008) also suggest the phenotypic variability in SCA8.

Although the pathology of SCA is mainly in cerebellum, most SCA genes are ubiquitously distributed including...
peripheral lymphocytes. Lymphoblastoid cells are frequently used as a model to study SCA (Wen et al. 2003; Tsai et al. 2005). In this study, we examined the length of the SCA8 repeats in ethnic Chinese Parkinson’s disease (PD), Alzheimer’s disease (AD) and atypical parkinsonism in Taiwan. Furthermore, we investigated the ATXN8, ATXN8OS and KLHL1 expression level, cell toxicity and genetic variation modulating ATXN8 expression using lymphoblastoid cell model and dual luciferase reporter assay.

Materials and methods

Subjects

The study group comprised 593 sporadic PD patients (46.5% females, aged 69.4 ± 10.5 years), 228 sporadic AD patients (61.4% females, aged 75.8 ± 8.7 years) and 51 atypical parkinsonism patients (47.1% females, aged 68.3 ± 11.2 years) recruited from the outpatient clinic of Chang Gung Memorial Hospital. All PD patients were diagnosed according to the published criteria (Gelb et al. 1999). Probable AD was diagnosed by consensus based on the criteria for probable AD of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al. 1984). Subjects with atypical parkinsonism include subgroups of corticobasal degeneration, progressive supranuclear palsy, dementia with Lewy bodies and multiple system atrophy (Boeve 2007). A group of 659 subjects (47.7% females, aged 59.2 ± 14.6 years) was enrolled as the normal control group. The age difference was statistically significant between cases and controls. All the cases and controls in the study were Han Chinese in Taiwan and not related to each other. Each control was interviewed by one of the neurologists (Y.-R. Wu and C.-M. Chen) to rule out the possibility of parkinsonism, dementia, ataxia, and other neurological diseases. Each subject was informed of the study goals, and all examinations were performed after obtaining informed consent.

Genetic analysis of SCA8 CTA/CTG repeats

DNA was extracted from leukocytes, and the SCA8 repeats were determined by polymerase chain reaction (PCR) amplification (Koob et al. 1999) and the PCR products resolved on a linear polyacrylamide gel using an automated MegaBACE Analyzer. Allele sizes were determined by comparing the migration relative to the standard molecular weights. DNA sequencing directly or after cloning was performed to assess the repeat size. Allele frequencies at each locus were estimated using the gene count method. A chi-square goodness of fit test was used to examine whether the controls used in this study were in the Hardy-Weinberg equilibrium. For this test, we combined all the rare genotypes (expected probability, <1%) into one group so that the expected frequencies of all genotype groups would be larger than 5 (Zar 1999); ultimately, there were 31 groups. Fisher’s exact test was used to compare the probability of rare expanded alleles in the genotypes of the PD, AD and atypical parkinsonism patients with that of the controls.

Lymphoblastoid cell lines

Lymphoblastoid cell lines from two SCA patients (P1, 88 repeats; P3, 95–185 repeats) and four PD patients (P2, 92 repeats; P4, 87 repeats; P5, 82 repeats; P6, 84 repeats) as well as five normal controls (C1–C5, 18–30 repeats) were established (Food Industry Research and Development Institute, Taiwan) after obtaining informed consent. Patients P1 and P3 were recruited from Taipei Veterans General Hospital; the rest patients and controls were recruited from Chang Gung Memorial Hospital. Cells were maintained in RPMI 1640 medium (GIBCO) containing 10% FCS.

Cell viability and caspase assays

To evaluate the cell viability, the cultured cell suspensions (10³ in 100 μl) were treated with MG-132 (0–200 nM) or staurosporine (0–50 nM). After 24 h, 20 μl 0.4% Trypan blue (Gibco) was mixed with 20 μl cell suspension sampled from each well for 1 h. Cell viability was determined by light microscope. Cells that excluded trypan blue were considered viable. The counts were performed in quadruplicate. Caspase 3 activity was measured using an EnzChek Caspase-3 Assay Kit #2 according to the manufacturer’s instructions (Molecular Probes).

Analysis of ATXN8, ATXN8OS and KLHL1 expression

Total RNA was extracted from lymphoblastoid cells using the Trizol (Invitrogen). The RNA was DNase (Stratagene) treated, quantified, and reverse-transcribed to cDNA using High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Carlsbad, CA, USA) with random primers. Using ABI PRISM® 7000 Sequence Detection System (Applied Biosystems, Carlsbad, CA, USA), real-time quantitative PCR was performed on a cDNA amount equivalent to 250 ng total RNA with TaqMan fluorogenic probes Hs01382089-m1 for ATXN8OS, Hs00252991_m1 for KLHL1 and 4326321E for HPRT1 (endogenous control) (Applied Biosystems, Carlsbad, CA, USA). The amount of ATXN8 mRNA was determined by customized Assays-by-Design probe (Forward primer: ACTTAGATGACAGG TCAAGATGGTTAGT, Reverse primer: TCGAAGTATG
AGAAGTACCTATCATTTTGGTA, TaqMan® probe: CTGGAGCCAAGAACTAG) (4331348, Applied Biosystems, Carlsbad, CA, USA). Fold change was calculated using the formula \(2^{\Delta\Delta C_T} = C_T^{\text{control}} - C_T^{\text{target}}\), in which \(C_T\) indicates cycle threshold. Statistical analysis of differences between the groups was carried out using one-way analysis of variance (ANOVA).

**ATXN8 promoter cloning and functional assay**

ATXN8 promoter fragments (-99 to -62) containing -62 G and -62 A (a novel SNP identified during DNA sequencing to assess the SCA8 repeat size) were cloned into the pGEM-T Easy vector (Promega) and sequenced. The cloned promoter fragments were placed upstream of the firefly luciferase reporter gene at the EcoRI site added between the HindIII/XhoI sites of the pGL3-basic vector (Promega). The orientation of the insert in the ATXN8-pGL3 construct was confirmed by restriction analysis. Human neuroblastoma SK-N-SH, IMR-32 and embryonic kidney HEK-293 cells cultivated in Dulbecco's modified Eagle’s medium containing 10% fetal calf serum were plated into 24-well dishes (10^4/well), grown for 20 h, and transfected by the lipofection method (GibcoBRL). The test plasmid (0.95 μg) and internal Renilla luciferase control plasmid (phRL-TK, 0.05 μg) were co-transfected into cells. After 48-h incubation, cell lysates were prepared and the activity of each promoter was directly measured by the ratio of the firefly luciferase level to the Renilla luciferase level using a dual luciferase assay system (Promega). For each reporter construct, three independent transfection experiments each performed in triplicate were carried out. An allele-specific difference in luciferase activity was tested using the two-tailed Student’s t test.

**Results**

Frequency distributions of SCA8 repeat lengths

PCR amplification of the SCA8 locus yielded a pattern of 2 distinct alleles in 86% of the cases analyzed. Figure 1 shows the distributions of the SCA8 repeat lengths in both alleles in the 593 PD patients, 228 AD patients, 51 atypical parkinsonism patients, and 659 normal control subjects. The controls were found to be in the Hardy–Weinberg equilibrium \(\chi^2 = 28.60, df = 30, P = 0.538\). In both control and patient groups, the most common length was 18 repeats (24–27%); the second class of normal alleles comprised repeat sizes of 22–39 units. Large SCA8 repeats of 66–120 were found in three normal controls (85–90 repeats), eight PD (66–92 repeats) and two atypical parkinsonism (97 and 120 repeats). As compared to that in the control subjects (3/659 (0.2%)), Fisher’s exact test revealed no difference in the proportion of individuals carrying SCA8 larger alleles (≥66 repeats) in PD (8/593 (1.3%); \(P = 0.129\)) or AD (0/228 (0.0%); \(P = 0.574\)), whereas significant difference in the proportion of individuals carrying SCA8 larger alleles in atypical parkinsonism (2/51 (3.9%); \(P = 0.044\)) was observed. Since the size of atypical parkinsonism patients is relatively small, using the current sample size (51 atypical parkinsonism and 659 controls) in our study, we evaluated the ability to detect an association between the larger allele and atypical parkinsonism by power calculation implemented in PAWE version 1.2 (Gordon et al. 2002).

Using the genetic model-free method, we had power of 0.85 to identify the association with larger allele frequency equal to 0.04 in atypical parkinsonism. Among the patients with larger SCA8 alleles, two (cases 4 and 9, Table 1) also carry SCA17 CAG expansion (44 and 46 CAG repeats).

Clinical analysis of PD and atypical parkinsonism patients with SCA8 CTG expansions

The clinical features and repeat sequences of the eight PD patients and two atypical parkinsonism patients who carried the large SCA8 alleles (66–120 repeats) are displayed in Table 1. None of the patients has family history. For the eight PD patients, all presented with resting tremor, bradykinesia, and cogwheel rigidity and had a continuous excellent response to the levodopa after a long term treatment. No evidence of secondary parkinsonism caused by another neurologic disease, known drugs, or toxins exposure was found.

Effects of MG-132 and staurosporine on lymphoblastoid cells with SCA8 expansion

The sensitivity of cells containing SCA8 expansions to MG-132, an inhibitor of the proteasome, was first examined. Lymphoblastoid cell lines from three age- and gender-matched patient-control pairs, including two SCA8 patients (P1, 86 years, male; P3, 72 years, male), one PD patient (P2, 64 years, female) and three normal controls (C1, 80 years, male; C2, 63 years, female; C3, 68 years, male), were used. As shown in Fig. 2a, with 50 nM MG-132 treatment and trypan blue exclusion assay, the cell death increased from 8.2–9.1% to 9.0–12.2% \(P = 0.082–0.276\) for cells with SCA8 expansions and from 7.7–8.8% to 8.5–10.1% \(P = 0.134–0.488\) for cells without SCA8 expansions, as compared to the untreated cells. When the MG-132 treatment increased to 200 nM, the cell death increased significantly to 18.8–25.1% for cells with SCA8 expansions \(P = 0.029–0.039\), whereas the increase remains non-significant for cells without SCA8 expansions (13.0–13.9%, \(P = 0.050–0.092\)). Moreover, a significant increased
sensitivity of cells with SCA8 expansions to 50 nM staurosporine treatment, an external apoptotic stimulus, was seen: from 8.4–9.1% to 20.2–23.6%, $P = 0.034–0.004$. This effect was not seen in cells without SCA8 expansions: from 7.7–9.0% to 11.7–15.4%, $P = 0.074–0.191$ (Fig. 2b). Measurement of caspase 3 activity also revealed a significant

**Fig. 1** Distributions of the SCA8 repeat lengths in controls and patients with PD, AD, or atypical parkinsonism. The percentages of the large alleles (66–120 repeats) (a) or genotypes (b) in each group are shown in parentheses. Noted that the spots representing the genotypes of two PD patients (18/87 and 18/88) are overlapped.

**Table 1** Clinical features and repeat sequences in PD (cases 1–8) and atypical parkinsonism (cases 9 and 10) patients carrying large SCA8 allele

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex, onset age, present age (year)</th>
<th>Clinical features at examination</th>
<th>Repeat sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1 (H31)</td>
<td>F, 60, 78</td>
<td>RT, B, R, P, D, DYS, LR</td>
<td>(CTA)$<em>8$CCACTACTGCTACTGCTA(CTG)$</em>{74}$</td>
</tr>
<tr>
<td>Case 2 (H168)</td>
<td>F, 72, 85</td>
<td>RT, B, R, P, D, DYS, LR</td>
<td>(CTA)$_{20}$(CTG)$<em>2$CTC(CTG)$</em>{52}$</td>
</tr>
<tr>
<td>Case 3 (H327)</td>
<td>F, 66, 75</td>
<td>RT, B, R, P, DYS, LR</td>
<td>(CTA)$<em>1$(CTG)$</em>{70}$</td>
</tr>
<tr>
<td>Case 4 (H600)</td>
<td>F, 57, 64</td>
<td>RT, B, R, LR</td>
<td>(CTA)$_2$(CTG)$<em>2$CTACTGCTA(CTG)$</em>{60}$</td>
</tr>
<tr>
<td>Case 5 (H1173)</td>
<td>F, 40 (expired at 65)</td>
<td>RT, B, R, DYS, D, LR</td>
<td>(CTA)$<em>3$(CTG)$</em>{25}$</td>
</tr>
<tr>
<td>Case 6 (H1320)</td>
<td>M, 72, 78</td>
<td>RT, B, R, LR</td>
<td>(CTA)$<em>3$(CTG)$</em>{57}$</td>
</tr>
<tr>
<td>Case 7 (H1410)</td>
<td>M, 62, 71</td>
<td>RT, B, R, DYS, D, LR</td>
<td>(CTA)$<em>3$(CCACTACTGCTACTGCTA(CTG)$</em>{74}$</td>
</tr>
<tr>
<td>Case 8 (H1415)</td>
<td>F, 45, 53</td>
<td>RT, B, R, DYS, LR</td>
<td>(CTA)$<em>3$(CCACTACTGCTACTGCTA(CTG)$</em>{73}$</td>
</tr>
<tr>
<td>Case 9 (H1387)</td>
<td>F, 75, 80</td>
<td>RT, B, R, D</td>
<td>(CTA)$<em>3$(CTG)$</em>{68}$</td>
</tr>
<tr>
<td>Case 10 (H1691)</td>
<td>F, 52, 53</td>
<td>B, P, AT, ANS</td>
<td>(CTA)$<em>3$(CTG)$</em>{110}$</td>
</tr>
</tbody>
</table>

RT resting tremor, B bradykinesia, R cogwheel rigidity, P postural instability, D dementia, DYS levodopa-induced dyskinesia, LR levodopa responsive, AT ataxia, ANS autonomic dysfunction.
increase of rhodamine 110 fluorescence (from 0.594–1.021 to 1.222–1.872 μM) in cells with SCA8 expansions treated with 50 nM staurosporine (P = 0.034–0.004) (Fig. 2c).

Analysis of ATXN8, ATXN8OS and KLHL1 expression

ATXN8, ATXN8OS and KLHL1 mRNA levels in lymphoblastoid cells from six patients with SCA8 large alleles as well as five normal controls were measured by quantitative real-time PCR using ATXN8, ATXN8OS and KLHL1-specific probes (Fig. 3a) and primers. Compared with endogenous HPRT1, the expression level of ATXN8, ATXN8OS and KLHL1 were relatively low (2⁻¹⁰–2⁻¹³). As shown in Fig. 3b, when the expressed level in control C1 was set as 1.0, ATXN8 median (range) for patients and controls were 3.380 (1.670–5.754) and 1.284 (0.542–1.992), respectively. The difference in the ATXN8 expression level between patients and controls was significant (P = 0.012). The median (range) expression value of ATXN8 mRNA for the two SCA8 patients was higher (but not significantly) than the four PD patients: 4.387 (3.020–5.754) and 2.876 (1.670–4.060), respectively (P = 0.457). Contrarily, no significant difference was observed for ATXN8OS median (range) between patients (2.110 (0.993–3.667)) and controls (1.551 (0.929–2.512)) (P = 0.364) as well as KLHL1 median (range) between patients (0.679 (0.321–1.205)) and controls (0.913 (0.767–1.231)) (P = 0.137).

–62 G/A SNP and ATXN8 expression

During DNA sequencing to assess the SCA8 repeat size, a novel C/T SNP 62 nucleotides downstream from the CTG repeats was detected (Fig. 4a). The SNP was named –62 G/A, where translation initiation of polyglutamine protein +1 is used as temporary transcription start site of ATXN8. The SNP can be differentiated using mismatched PCR and Mph1103I restriction analysis (Fig. 4b). As the promoter activity upstream of the repeat tract in the CAG direction was suggested (Moseley et al. 2006), ATXN8 promoter fragments (-99 ~ -6) containing –62 G and –62 A were fused to firefly luciferase reporter construct and transient transfection experiments were carried out to assess the promoter activity by measuring the ratio of firefly luciferase activity to Renilla luciferase activity in HEK-293, SK-N-SH and IMR-32 cells. As shown in Fig. 4c, ATXN8 proximal promoter construct containing –62G displayed significantly higher luciferase activity compared with –62A in all three cell lines tested (P = 0.000). The median (range) relative expression value of ATXN8 mRNA for GG homozygote (three patients and one control) was higher (but not significantly) than GA heterozygote (three patients and four controls): 3.422 (1.847–5.754) and 1.859 (0.542–4.060), respectively (P = 0.160) (Fig. 4d).

Discussion

This study examined the length of the SCA8 repeats in Taiwanese patients with PD, AD and atypical parkinsonism and in normal control subjects. SCA8 large alleles were found in three normal controls (85–90 repeats), eight PD (66–92 repeats) and two atypical parkinsonism (97 and 120 repeats) (Fig. 1). The range of SCA8 large alleles observed is not much different from that reported in the literature (mostly 85–130). Marginal or significant difference in the proportion of SCA8 larger allele (66–120) carriers in PD (8/593 (1.3%), P = 0.129) or atypical parkinsonism (2/51 (3.9%), P = 0.044) was observed as compared to that in the control subjects (3/659 (0.2%)). Although the size of atypical parkinsonism patients is relatively small, the power of the present study to detect a genetic association for such a number of cases is approximately 0.85 which is acceptable. It is also notable that the age difference was statistically significant between cases and controls, which may result in a sampling bias toward the underestimated frequency of larger allele in the controls. Nevertheless, that SCA8
expanded alleles detected in PD or atypical parkinsonism patients from the present, our previous (Wu et al. 2004) and other studies (Worth et al. 2000; Izumi et al. 2003; Baba et al. 2005) suggests that SCA8 CTG repeat expansion may play a role in the development of sporadic PD or atypical parkinsonism. The expression of transcripts containing SCA8 CTG repeats in various brain tissues (Koob et al. 1999; Nemes et al. 2000) as well as the reported white
We thank Taiwan Foundation for Rare Disorders (Kumar and Miller 2008) to reinforce the notion that the molecular pathology in SCA8 extends beyond the cerebellum. The definition of atypical parkinsonism included many neurodegenerative diseases with many different neuropathology and the small sample size may explain why larger SCA8 alleles are significantly associated with atypical parkinsonism and not PD in the present study.

Previously intranuclear polyglutamine inclusions in cerebellar Purkinje and brainstem neurons were reported in SCA8 expansion mice (Moseley et al. 2006). Clinicopathologic investigation of a SCA8 patient also revealed intracytoplasmic 1C2-positive granular structures (Ito et al. 2006). However, may be due to low ATXN8 expression level, we did not observe polyglutamine inclusions in the lymphoblastoid cells from patients with expanded SCA8 alleles (data not shown). Nevertheless, a problem with protein folding may still be involved in SCA8 pathogenesis. Using lymphoblastoid cells from three patient-control pairs, we found patients’ cells were more sensitive to MG-132 (proteasome inhibitor) treatment (Fig. 2a). Increased cell death (Fig. 2b) and caspase 3 activities (Fig. 2c) were also observed upon staurosporine (apoptosis inducer) treatment. These observations coincide with the length-dependent toxicity of DMPK CUG repeats on Caenorhabditis elegans (Chen et al. 2007). Although lymphoblastoid cells we used are not of neuronal origin, immortalized lymphoblast cells from patients with Alzheimer’s disease are frequently used to mirror changes thought to occur in the brain (Muñoz et al. 2008; Sala et al. 2008). Thus, our results suggest that the SCA8 88–95 repeats are toxic to human cells.

SCA8 involves bidirectional expression of the CTG/CAG expansion mutation, with ATXN8 transcribed in the CAG direction encoding a nearly pure polyglutamine expansion protein, and ATXN8OS transcribed in the CTG direction with apparently non-protein coding function (Ikeda et al. 2008). In the CTG direction, ATXN8OS transcripts overlap with the 5′ region of the KLHL1 transcripts (Nemes et al. 2000). In lymphoblastoid cells transcripts encoded by ATXN8, ATXN8OS and KLHL1 genes are expressed at low steady-state. Real-time PCR analysis revealed that ATXN8 expression level is significant higher in patients with SCA8 large alleles than controls (Fig. 3b). Within patient group, the ATXN8 expression level was not related to disease onset. However, the two SCA8 patients displayed higher (although not significantly) median ATXN8 expression level than that of the four PD patients, indicating that higher ATXN8 expression levels may be more likely to be associated with a SCA phenotype. Nevertheless, no significant difference was observed for ATXN8OS and KLHL1 expression levels between patients and controls. As major haplotypes are found among patients with ataxia (Ikeda et al. 2004), genetic variation(s) in linkage disequilibrium with expanded repeats may affect ATXN8 expression leading to the observed increased expression level in patients with SCA8 large repeats. During assessing the SCA8 repeat size, a novel –62 G/A SNP was identified with 90% (9/10) expanded alleles associated with G allele. Using luciferase reporter assay, fragment containing –62G displayed significant higher promoter activity compared to fragment containing –62A in all three human cell lines tested (Fig. 4c). Thus the increased ATXN8 expression level in patients with SCA8 large alleles was likely resulted from the –62 G/A variation. As the correlation of ATXN8 mRNA expression with –62 G > A genotype is not absolute (Fig. 4d), possible hairpin formation and protein binding to increase the stability of expanded CUG repeat transcripts (Tian et al. 2000; Houseley et al. 2005) may also contribute to the observed increased ATXN8 expression level in patients with SCA8 large alleles. The G > A change lies within the regulatory element (RNRTKNNMAAKNN, K = G or T) involved in the binding of CCAAT/enhancer binding protein β (C/EBPβ) (Akira et al. 1990). Work is now in progress to examine the role of CEBPβ on the observed –62G-associated increase of ATXN8 expression.

In summary, our data provide evidence of SCA8 CTG repeat expansion as a rare cause of sporadic PD or atypical parkinsonism and the novel ATXN8 –62 G/A promoter polymorphism functioning in modulating ATXN8 expression. Our study may shed insights into the better understanding of the disease nature.

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References


