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Serum progranulin level in a subject carrying 'predicted' pathogenic *PGRN* mutation p.R564C

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Abstract

Although most of the known pathogenic mutations in the progranulin gene (PGRN) are null mutations leading to a reduction in the serum PGRN protein levels, missense mutations also have been identified in patients with frontotemporal lobar degeneration and in patients with Alzheimer disease. Among these, p.R564C mutation was identified in a late-onset AD patient with a reduced serum PGRN level. However, recently, we found the p.R564C mutation in a healthy control subject raising doubts whether this is a pathogenic mutation. In this report, we measured the serum PGRN levels in 20 subjects without the p.R564C mutation and in one subject with the p.R564C mutation, to determine whether the p.R564C mutation is associated with reduced serum PGRN levels. We found that the serum PGRN level in the subject with the p.R564C mutation was not reduced compared to the subjects without the p.R564C mutation. Our result reiterates that p.R564C may not be a pathogenic mutation.

INTRODUCTION

The *PGRN* gene encodes for progranulin, which undergoes proteolytic cleavage giving rise to a family of peptides, the granulins. Progranulin acts as a growth factor in a variety of tissues and is highly expressed in the central nervous system (CNS), but its exact role in the CNS is unknown.[1] Mutations in *PGRN* have been associated with frontotemporal lobar degeneration (FTLD) and related neurodegenerative disorders. Most of the known *PGRN* mutations are null mutations leading to a reduction in PGRN protein levels, which might be causally related to neurodegeneration in FTLD. In this regard, serum PGRN levels have been proposed as a reliable biomarker for the detection of *PGRN* null mutations.[2,3]

Besides null mutations, *PGRN* missense mutations have been identified in patients with FTLD and in patients with Alzheimer disease (AD).[4,5] Some of these missense mutations are presumed to be potentially pathogenic because of the partial loss of mutant PGRN proteins and, in agreement with this, reduced serum PGRN levels have been demonstrated in the carriers of some of the missense mutations.[3,5] Among these, the p.R564C mutation was identified in a late-onset AD patient with a reduced serum PGRN level. However, recently, we found a p.R564C mutation in a healthy control subject raising doubts whether this is a pathogenic mutation.[6]

In this report, we measured the serum PGRN levels in subjects without the p.R564C mutation and in one subject with the p.R564C mutation, to determine whether the p.R564C mutation is associated with reduced serum PGRN levels.

METHODS

This study included 21 subjects in which the sequencing of *PGRN* was done in a previous study.[7] No known pathogenic mutation in *PGRN* was found in these subjects, except for the 'predicted' pathogenic missense mutation p.R564C in one 75-year-old healthy control subject. This man was cognitively normal and had no Parkinsonism. The remaining 20 subjects consisted of 13 healthy control subjects with a mean age of 69.5 ± 5.4 years and seven patients with FTLD and related disorders (5 with progressive supranuclear palsy (PSP), one with frontotemporal dementia, and one with corticobasal syndrome) with a mean age of 71.1 ± 7.8 years. The patient reported in the previous study with PSP harboring the p.R564C mutation was lost from the follow-up and thus, could not be included in this study.

After informed consent was obtained from each subject, blood samples were drawn. Each sample was centrifuged at 2,500 rpm for 5 minutes, and the serum was separated and stored at -80°C until used. Serum PGRN levels were assayed, in duplicate, with an ELISA kit (Human Progranulin

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ELISA Kit, Adipogen Inc., Seoul, Korea). This study protocol was approved by the Institutional Review Board of Seoul National University Hospital.

RESULTS

The mean serum PGRN levels for the 20 subjects without the p.R564C mutation was 171.5 ± 42.0 ng/ml, and ranged from 88.5 to 241.8 ng/ml (Figure 1). The serum PGRN levels in the p.R564C carrier was 118.7 ± 8.3 ng/ml, which was in the range of observed values for the subjects without the p.R564C mutation.

DISCUSSION

In this study, the serum PGRN level was not reduced in the subject with the p.R564C mutation compared to the subjects without the p.R564C mutation or any other known PGRN mutations. This contradicts a previous report, which showed a markedly decreased serum PGRN level in a subject with the p.R564C mutation.[3] Although the serum *PGRN* level of the null mutation carrier was not available in our study, given the clear-cut difference in the distribution of the serum *PGRN* levels between the null mutation carriers and the controls reported in previous studies[2,3,5], our result reiterates that the p.R564C mutation may not be a pathogenic mutation.

Another interesting finding is that, although not significant statistically, probably due to the small number of subjects, the serum PGRN levels tended to be lower in the patients than in the healthy controls (143.6 ± 38.5 vs 181.7 ± 39.6 ng/ml; p=0.07). Similar results have been observed in a previous study where the mean serum PGRN level of AD patients with a benign missense mutation (i.e., without pathogenic mutation) was apparently lower than that of the community control individuals.[3] This suggests that the serum PGRN level can be influenced by factors other than genetic status, such as a change in medical condition during chronic disease. Actually, a recent study showed that serum PGRN levels can be influenced by medical factors such as visceral obesity, elevated serum glucose, and dyslipidemia.[8]

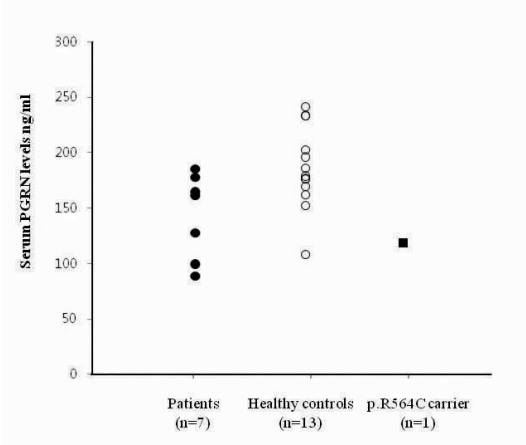

Figure 1. Serum progranulin (PGRN) levels in the study groups. Each data point represents an individual. Patients group comprised five subjects with progressive supranuclear palsy, one with frontotemporal dementia and one with corticobasal syndrome. None of the subjects were carrying pathogenic mutations in *PGRN*.

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DISCLOSURE

Conflicts of interest: None

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