

# PROGRANULIN [PGRN]

## Introduction

Progranulin [1, 2] (PGRN; granulin (precursor); GRN [3-6], epithelin precursor [7, 8]; proepithelin (PEPI) [9]; PC cell-derived growth factor (PCDGF) [10]; acrogranin [11, 12]; paraganulin) is a 593aa cysteine-rich protein of 68.5kDa, that is typically secreted in a highly glycosylated 88kDa form. As a result of proteolytic cleavage of PGRN by extracellular proteases, a family of active 6kDa peptides (granulins (GRNs) A to G and paraganulin) are formed that each contain 10-12 highly conserved cysteine residues. The *PGRN* gene is widely expressed, particularly in epithelial and hematopoietic cells.

In the periphery, PGRN is implicated in many processes such as tumorigenesis, wound repair and inflammation [13]. Accordingly, *PGRN* has been reported to be highly expressed in a variety of cancer cell lines and to modulate different aspects of tumorigenesis such as proliferation, invasion and survival [14]. After injury, PGRN is induced in fibroblasts and endothelial cells promoting neovascularization [2]. By interacting with the leukocyte protease inhibitor (SLPI) PGRN modulates wound healing [9]. PGRN and GRNs have opposing inflammatory effects. SLPI inhibits the cleavage of PGRN into pro-inflammatory GRNs [9, 15]. PGRN is important for the sexual differentiation of the rat brain [16, 17]. PGRN also promotes neuronal survival and enhance neurite outgrowth in cultured neurons [18]. It has been proposed that PGRN is a stress-response factor in fibroblasts subjected to hypoxia and acidosis [19].

## PGRN & FTLD

Recent interest regarding PGRN's role in the central nervous system (CNS) was raised after mutations in the *PGRN* gene, located on chromosome 17, have been identified to cause fronto-temporal lobar degeneration (FTLD) [20, 21]. FTLD is a common cause of dementia. The most frequent subtype of FTLD shows ubiquitinated-immunoreactive, tau-negative inclusions (FTLD-U) [22, 23]. More recently it was shown that the transactivation of hyperphosphorylated nuclear protein TDP-43 (transactivation response DNA-binding protein 43; TAR DNA-binding protein 43; TARDBP) is the main component of most of these FTLD-U inclusions [24, 25]. The term FTLD-TDP was introduced to specify these FTLD-U inclusions which are TDP-43 positive, what is indeed not always the case [26]. It was further shown that all *PGRN* mutation carriers have a common FTLD-TDP subtype, referred to as Type 1 [27] or Type 3 [28]. One study provided a possible link between the loss of functional PGRN and TDP-43 pathology, by showing that decreased PGRN levels can induce caspase-dependent accumulation of TDP-43 fragments *in vitro* [29]. However, this finding was not confirmed by a second study [30].

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## Progranulin (human) ELISA Kit

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A total of 66 different loss of function mutations, scattered over all *PGRN* exons, except exon 13, have been reported. One complete and two partial *PGRN* deletions have also been identified. An additional 39 patient specific mutations with unknown pathogenic importance were identified in neurodegenerative disease patients. These include 28 missense mutations, 10 silent mutations and one nonsense mutation in *PGRN* exon 13. Another publication indicated the association of SNPs (single nucleotide polymorphisms) with FTL-D-TDP. The fact that rs5848 showed altered *PGRN* expression is under discussion [31, 32].

## **PGRN – A Marker?**

Interestingly, several studies detected decreased *PGRN* levels in serum [33], plasma [34, 35] and CSF [35] of *PGRN* mutation carriers. Therefore *PGRN* can be considered to be a marker for detecting a *PGRN* mutation. The measurement of decreased *PGRN* protein levels in plasma could be a quick and inexpensive test for the presence of a *PGRN* mutation in a patient [34, 35].

Another study detected serum progranulin concentrations associated to visceral obesity, elevated plasma glucose, and dyslipidemia [36]. *PGRN* might evolve as novel marker for chronic inflammation in obesity and type-II diabetes (T2D).

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## **Latest Insight**

### ***Serum Progranulin Concentrations May Be Associated To Obesity***

B.-S. Youn, et al. demonstrated that elevated progranulin serum concentrations are associated with visceral obesity, elevated plasma glucose, and dyslipidemia. They identified progranulin as a novel marker of chronic inflammation in obesity and type-II diabetes (T2D) that closely reflects omental adipose tissue macrophage infiltration. Physical training significantly reduces elevated circulating progranulin in patients with T2D.

**LIT:** Serum Progranulin Concentrations May Be Associated With Macrophage Infiltration Into Omental Adipose Tissue: B. -S. Youn, et al.; *Diabetes* **58**, 627 (2009)

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# Progranulin Products

## Proteins

### Progranulin (human) (rec.)

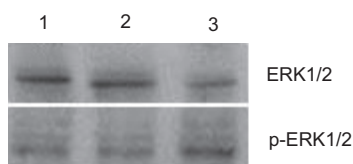
ALX-201-377-C010 10 µg  
ALX-201-377-C050 50 µg

Produced in HEK293 cells. Signal peptide and mature human progranulin (aa 1-593) is fused at the C-terminus to a FLAG®-tag. **PURITY:** ≥90% (SDS-PAGE).

### Progranulin (mouse) (rec.)

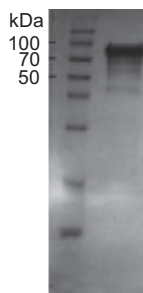
ALX-201-389-C010 10 µg  
ALX-201-389-C050 50 µg

Produced in HEK293 cells. Signal peptide and mature mouse progranulin (aa 1-589) is fused at the C-terminus to a FLAG®-tag. **PURITY:** ≥90% (SDS-PAGE).

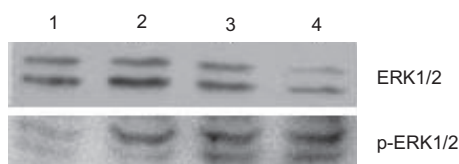


**FIGURE 1:** The effects of phospho-ERK1/2 and non-phospho-ERK1/2 by progranulin (human) (rec.) (Prod. No. ALX-201-377) in THP-1 cells.

**METHOD:** To examine the signal of phospho-p44/42 MAP kinase, reactions were carried out at 37°C over 0, 30, 60 min., respectively by adding the recombinant protein (100ng/ml) to the THP-1 monocyte cells, which were maintained with serum starvation for 24 hours. Recombinant proteins in lanes 1, 2 and 3 were subjected to THP-1 monocyte cell treatments over 0, 30, 60 min., respectively.



**FIGURE 2:** SDS-PAGE of progranulin (human) (rec.) (Prod. No. ALX-201-377).



**FIGURE 3:** The effects of phospho-ERK1/2 and non-phospho-ERK1/2 by progranulin (human) (rec.) (Prod. No. ALX-201-377) in MCF10A cells.

**METHOD:** To examine the signal of phospho-p44/42 MAP kinase, reactions were carried out at 37°C over 0, 30, 60 min., respectively by adding the recombinant protein (500ng/ml) to the MCF10A human breast epithelial cells, which were maintained with serum starvation for 24 hours. Recombinant proteins in lanes 1, 2, 3 and 4 were subjected to MCF10A human breast epithelial cell treatments over 0, 30, 60 min., respectively.

## Antibodies

### Progranulin (human), mAb (PG359-7)

ALX-804-737-C100 100 µg

**CLONE:** PG359-7. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Recombinant human progranulin. **SPECIFICITY:** Recognizes human progranulin. Detects a band of ~90kDa by Western blot. **APPLICATION:** IHC, IP, WB.

### Progranulin (mouse), mAb (PG319-1)

ALX-804-760-C050 50 µg  
ALX-804-760-C100 100 µg

**CLONE:** PG319-1. **ISOTYPE:** Rat IgG2. **IMMUNOGEN:** Recombinant mouse progranulin. **SPECIFICITY:** Recognizes mouse progranulin. Detects a band of ~90kDa by Western blot. **APPLICATION:** WB.

### Progranulin (mouse), pAb

ALX-210-497-C100 100 µg

From rat. **IMMUNOGEN:** Recombinant mouse progranulin. **SPECIFICITY:** Recognizes mouse progranulin. Weakly cross reacts with human progranulin. Detects a band of ~90kDa by Western blot. **APPLICATION:** WB.

## Granulin C

Granulin C is a secreted, glycosylated peptide cleaved from the precursor protein progranulin. Granulins regulate cell growth and are important in normal development, wound healing, and tumorigenesis.

### Granulin C (human) (rec.) (His)

ALX-201-438-C010 10 µg  
ALX-201-438-C050 50 µg

Produced in *E. coli*. The mature peptide of human granulin C (aa 364-430) is fused at the C-terminus to a His-tag.

### Granulin C (human), pAb

ALX-210-494-C100 100 µg

From rabbit. **IMMUNOGEN:** Recombinant human granulin C. **SPECIFICITY:** Reacts with human granulin C and human progranulin. **APPLICATION:** WB.

## Selected Review Articles

Progranulin in frontotemporal lobar degeneration and neuroinflammation: Z. Ahmed, et al.; *J. Neuroinflammation* **4**, 7 (2007) • Progranulin and frontotemporal lobar degeneration: S.M. Pickering-Brown; *Acta Neuropathol.* **114**, 39 (2007) • The molecular genetics and neuropathology of frontotemporal lobar degeneration: recent developments: I.R. Mackenzie & R. Rademakers; *Neurogenetics* **8**, 237 (2007) • Progranulin: normal function and role in neurodegeneration: J.L. Eriksen & I.R. Mackenzie; *J. Neurochem.* **104**, 287 (2008) • Loss of progranulin function in frontotemporal lobar degeneration: M. Cruts & C. Van Broeckhoven; *Trends Genet.* **24**, 186 (2008) • Mutations in progranulin (GRN) within the spectrum of clinical and pathological phenotypes of frontotemporal dementia: J.C. van Swieten & P. Heutink; *Lancet Neurol.* **7**, 965 (2008) • Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration: consensus recommendations: I.R. Mackenzie, et al.; *Acta Neuropathol.* **117**, 15 (2009) • Clinical Features and Diagnosis of Frontotemporal Dementia: A. Kertesz; *Front. Neurol. Neurosci.* **24**, 140 (2009) • The molecular basis of frontotemporal dementia: M. Neumann, et al.; *Exp. Rev. Mol. Med.* **11**, (2009) • Recent insights into the molecular genetics of dementia: R. Rademakers & A. Rovelet-Lecrux; *TINS* **32**, 451 (2009)

## Progranulin ELISA Kits

### Progranulin (human) ELISA Kit

AG-45A-0018EK-KI01	1 x 96 wells
AG-45A-0018TP-KI01	2 x 96 wells
AG-45A-0018PP-KI01	5 x 96 wells

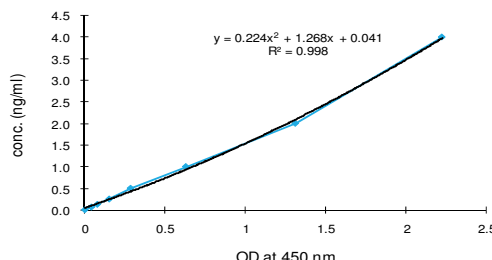
Direct measurement of human progranulin in human serum, plasma or cell culture supernatants. **SENSITIVITY:** 32pg/ml.

**LIT:** Low plasma progranulin levels predict progranulin mutations in frontotemporal lobar degeneration: R. Ghidoni, et al.; *Neurology* **71**, 1235 (2008) • Common variation in the miR-659 binding-site of GRN is a major risk factor for TDP43-positive frontotemporal dementia: R. Rademakers, et al.; *Hum. Mol. Genet.* **17**, 3631 (2008) • Plasma progranulin levels predict progranulin mutation status in frontotemporal dementia patients and asymptomatic family members: N. Finch, et al.; *Brain* **132**, 583 (2009) • Serum Progranulin Concentrations May Be Associated With Macrophage Infiltration Into Omental Adipose Tissue: B. -S. Youn, et al.; *Diabetes* **58**, 627 (2009)

### Progranulin (mouse) ELISA Kit **NEW**

AG-45A-0019EK-KI01	1 x 96 wells
AG-45A-0019TP-KI01	2 x 96 wells
AG-45A-0019PP-KI01	5 x 96 wells

Direct measurement of mouse progranulin in mouse serum or cell culture supernatants. **SENSITIVITY:** 60pg/ml.



**FIGURE:** Typical standard curve for Progranulin (human) ELISA Kit.



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