#### Introduction

The γ-secretase is a four-subunit [protease](https://en.wikipedia.org/wiki/Protease) complex*,* consisting of PSEN1,PEN-2,APH-1 and nicastrin[[1](#_ENREF_1)] and mediates the cleavage of single-pass [transmembrane proteins](https://en.wikipedia.org/wiki/Transmembrane_protein) at residues within the transmembrane domainincluding beta-amyliod precursor protein (APP)*,* Notch*,* vascular endothelial growth factor receptor-1 (VEGFR-1)*,* insulin-like growth factor (IGF)-1R*,* EbrB4*,* cadherin*,* and CD44. and translocateintracellular domains (ICDs) of those proteins into nucleus[[1](#_ENREF_1); [2](#_ENREF_2); [3](#_ENREF_3)]. *PSEN1* encodes the catalytic subunit ofγ-secretase complex*,* whose mutation has been linked to the type III Alzheimer disease[[4](#_ENREF_4)]. Until recently*,* the pathological contribution of the aberrant status of the γ-secretase has been described in various types of cancer. The *PSEN1* gene is frequently genetically altered and expressionally dysregulated in almost all types of cancer analyzed (http://www.cbioportal.org/index.do). Taking bladder cancer as an example*,* the abnormalityof *PSEN1* gene occurs in over 11% cases*,* including gene amplification*,* deletion*,* truncating and missense mutations as well as aberrant expression. *PSEN1* is a CpG rich promoter containing gene with one CpG island located nearby its transcription initiation site. Although a significant negative correlation was identified between DNA methylation of this region and steady status of mRNA level in a cohort of 412 bladder cancer samples (http://www.cbioportal.org/) (P <4.2x10-6 calculated by a linear model and P <2.2x10-16 by a linear mixture model*,* Fig. S1)*,* this CpG island is hypomethylated in majority bladder cancer samples (beta<0.1 in 92% TCGA bladder cancer samples)*.* Thus*,* the DNA methylation mediated mechanism is less likely attributive for the aberrant expression of *PSEN1* gene in bladder cancer.

##### Statistical analysis

The DNA methylation and gene expression data derived from TCGA are downloaded from cBioportal website(http://www.cbioportal.org/index.do?cancer\_study

\_list=blca\_tcga&cancer\_study\_id=blca\_tcga&genetic\_profile\_ids\_PROFILE\_MUTATION\_EXTENDED=blca\_tcga\_mutations&genetic\_profile\_ids\_PROFILE\_COPY\_NUMBER\_ALTERATION=blca\_tcga\_gistic&Z\_SCORE\_THRESHOLD=2.0&RPPA\_SCORE\_THRESHOLD=2.0&data\_priority=0&case\_set\_id=blca\_tcga\_methylation\_hm450&case\_ids=&patient\_case\_select=sample&gene\_set\_choice=user-defined-list&gene\_list=PSEN1&clinical\_param\_selection=null&tab\_index=tab\_visualize&Action=Submit&show\_samples=false&).). Z-score of the logit transformed beta value and log2 transformed read counts with RSEM method [[5](#_ENREF_5" \o "Li, 2011 #203)]were integrated and analyzed[[6](#_ENREF_6)]. Simple linear model and linear mixture model were conducted to explore the correlation between gene expression and DNA methylation and the most significant regression model**[7]**were reported in current study. Other mean-based statistical inferences were conducted with *t*-test or *Wilcox* test based on the appreciated assumption. All the analysis was conducted in R (3.2.3).

##### Fig. S1. A correlative analysis between DNA methylation and gene expression of PSEN1 gene in a cancer genome study of 412 bladder cancer patients

Both the DNA methylation and gene expression data derived from TCGA project were downloaded from cBioportal website(http://www.cbioportal.org/index.do?cancer\_study

\_list=blca\_tcga&cancer\_study\_id=blca\_tcga&genetic\_profile\_ids\_PROFILE\_MUTATION\_EXTENDED=blca\_tcga\_mutations&genetic\_profile\_ids\_PROFILE\_COPY\_NUMBER\_ALTERATION=blca\_tcga\_gistic&Z\_SCORE\_THRESHOLD=2.0&RPPA\_SCORE\_THRESHOLD=2.0&data\_priority=0&case\_set\_id=blca\_tcga\_methylation\_hm450&case\_ids=&patient\_case\_select=sample&gene\_set\_choice=user-defined-list&gene\_list=PSEN1&clinical\_param\_selection=null&tab\_index=tab\_visualize&Action=Submit&show\_samples=false&) and they were merged for the further statistical analysis. The correlation analysis between gene expression and DNA methylation was conducted with both linear model and linear mixture models based calculation was conducted in the correlation analysis as well as the most significant regression model. The Y axis represents the log-transformed read counts and X axis represents logit transformed beta-value of DNA methylation.

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[2]T. Wakabayashi, B. De Strooper, Presenilins: members of the gamma-secretase quartets, but part-time soloists too. Physiology (Bethesda) 23 (2008) 194-204.

[3]M.E. Boulton, J. Cai, M.B. Grant, gamma-Secretase: a multifaceted regulator of angiogenesis. Journal of cellular and molecular medicine 12 (2008) 781-795.

[4]L. Chavez-Gutierrez, L. Bammens, I. Benilova, A. Vandersteen, M. Benurwar, M. Borgers, S. Lismont, L. Zhou, S. Van Cleynenbreugel, H. Esselmann, J. Wiltfang, L. Serneels, E. Karran, H. Gijsen, J. Schymkowitz, F. Rousseau, K. Broersen, B. De Strooper, The mechanism of gamma-Secretase dysfunction in familial Alzheimer disease. The EMBO journal 31 (2012) 2261-2274.

[5]B. Li, C.N. Dewey, RSEM: accurate transcript quantification from RNA-Seq data with or without a reference genome. BMC bioinformatics 12 (2011) 323.

[6]Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 507 (2014) 315-322.