

# Mechanism of REST/NRSF Regulation of Clustered Protocadherin $\alpha$ Genes

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**Manuscript Source:** <https://www.biorxiv.org/content/10.1101/2021.03.06.434230v1>

**Manuscript Authors:** Yuanxiao Tang, Zhilian Jia, Honglin Xu, Lin-Tai Da & Qiang Wu

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### Research Paper Sections:

The sections of the research paper input text parsed in this audit.

[illegible]

Title      **Mechanism of REST/NRSF Regulation of Clustered Protocadherin  $\alpha$  Genes**

**S1 [001]      ABSTRACT**

**S1 [002]**      Repressor element-1 silencing transcription factor (REST) or neuron-restrictive silencer factor (NRSF) is a zinc-finger (ZF) containing transcriptional repressor that recognizes thousands of neuron-restrictive silencer elements (NRSEs) in mammalian genomes.

Repressor element-1 silencing transcription factor ...  
... (REST) ...  
... or neuron-restrictive silencer factor ...  
... (NRSF) ...  
... is a zinc-finger ...  
... (ZF) ...  
... containing transcriptional repressor ...  
... that recognizes thousands ...  
... of neuron-restrictive silencer elements ...  
... (NRSEs) ...  
... in mammalian genomes.

**S1 [003]**      How REST/NRSF regulates gene expression remains incompletely understood.

How REST/NRSF regulates gene expression remains incompletely understood.

**S1 [004]**      Here, we investigate the binding pattern and regulation mechanism of REST/NRSF in the clustered protocadherin (PCDH) genes.

Here, ...  
... we investigate the binding pattern ...  
... and regulation mechanism ...  
... of REST/NRSF ...  
... in the clustered protocadherin ...  
... (PCDH) ...  
... genes.

**S1 [005]**      We find that REST/NRSF directionally forms base-specific interactions with NRSEs via tandem ZFs in an anti-parallel manner but with striking conformational changes.

We find ...  
... that REST/NRSF directionally forms base-specific interactions ...  
... with NRSEs ...  
... via tandem ZFs ...  
... in an anti-parallel manner ...  
... but with striking conformational changes.

**S1 [006]** In addition, REST/NRSF recruitment to the HS5-1 enhancer leads to the decrease of long-range enhancer-promoter interactions and downregulation of the clustered PCDH $\alpha$  genes.

In addition, ...  
... REST/NRSF recruitment ...  
... to the HS5-1 enhancer leads ...  
... to the decrease ...  
... of long-range enhancer-promoter interactions ...  
... and downregulation ...  
... of the clustered PCDH $\alpha$  genes.

**S1 [007]** Thus, REST/NRSF represses PCDH $\alpha$  gene expression through directional binding to a repertoire of NRSEs within the distal enhancer and variable target genes.

Thus, ...  
... REST/NRSF represses PCDH $\alpha$  gene expression ...  
... through directional binding ...  
... to a repertoire ...  
... of NRSEs ...  
... within the distal enhancer ...  
... and variable target genes.

## **S2 [008] INTRODUCTION**

**S2 [009]** During early neurogenesis, the orderly acquisition and maintenance of neural identities are controlled epigenetically by de-repression of neural genes through downregulating transcriptional repressors and corepressors (1).

During early neurogenesis, ...  
... the orderly acquisition ...  
... and maintenance ...  
... of neural identities are controlled epigenetically ...  
... by de-repression ...  
... of neural genes ...  
... through downregulating transcriptional repressors ...  
... and corepressors ...  
... (1).

**S2 [010]** REST (repressor element-1 silencing transcription factor), also known as NRSF (neuron-restrictive silencer factor), is a crucial repressor for neural genes (2, 3), reviewed in (4).

REST ...  
... (repressor element-1 silencing transcription factor), ...  
... also known ...  
... as NRSF ...  
... (neuron-restrictive silencer factor), ...  
... is a crucial repressor ...  
... for neural genes ...  
... (2, 3)...

... , ...  
... reviewed ...  
... in ...  
... (4).

**S2 [011]** Specifically, REST/NRSF represses the expression of numerous neural-specific genes in neural progenitors as well as non-neural tissues (5–8).

Specifically, ...  
... REST/NRSF represses the expression ...  
... of numerous neural-specific genes ...  
... in neural progenitors ...  
... as well ...  
... as non-neural tissues ...  
... (5–8).

**S2 [012]** In differentiated non-neural cells, REST/NRSF represses neural genes in collaboration with its corepressors (6,8–11).

In differentiated non-neural cells, ...  
... REST/NRSF represses neural genes ...  
... in collaboration ...  
... with its corepressors ...  
... (6,8–11).

**S2 [013]** In embryonic stem cells, REST/NRSF is highly expressed (8, 12).

In embryonic stem cells, ...  
... REST/NRSF is highly expressed ...  
... (8, 12)...  
... .

**S2 [014]** During transition to neural progenitor cells (NPCs) and finally to mature neurons, REST/NRSF is degraded to minimal levels in NPCs and to an undetectable level in mature neurons (8, 13).

During transition ...  
... to neural progenitor cells ...  
... (NPCs) ...  
... and finally ...  
... to mature neurons, ...  
... REST/NRSF is degraded ...  
... to minimal levels ...  
... in NPCs ...  
... and to an undetectable level ...  
... in mature neurons ...  
... (8, 13)...  
... .

**S2 [015]** Recent studies revealed that REST/NRSF also has a protective role in genome stability (14).

Recent studies revealed ...  
... that REST/NRSF also has a protective role ...

... in genome stability ...  
... (14).

**S2 [016]** REST/NRSF contains a central DNA-binding domain with eight tandem C2H2 ZFs and two repressor domains residing in the amino and carboxyl termini, respectively (Figure 1A) (2,3,15).

REST/NRSF contains a central DNA-binding domain ...  
... with eight tandem C2H2 ZFs ...  
... and two repressor domains residing ...  
... in the amino ...  
... and carboxyl termini, ...  
... respectively ...  
... (Figure 1A) ...  
... (2,3,15).

**S2 [017]** REST/NRSF has been shown to bind to thousands of NRSEs which can be divided into three groups: canonical, noncanonical, and half-site only motifs (16, 17).

REST/NRSF has been shown ...  
... to bind ...  
... to thousands ...  
... of NRSEs ...  
... which can be divided ...  
... into three groups: ...  
... canonical, ...  
... noncanonical, ...  
... and half-site ...  
... only motifs ...  
... (16, 17)...  
... .

**S2 [018]** Intriguingly, canonical and noncanonical NRSEs contain very different gap sizes between the left- and right-half sites.

Intriguingly, ...  
... canonical ...  
... and noncanonical NRSEs contain very different gap sizes ...  
... between the left- ...  
... and right-half sites.

**S2 [019]** ZF domains are small DNA-recognition units that are usually organized in tandem and there are more than 800 ZF transcription factors in the human genome (18–21).

ZF domains are small DNA-recognition units ...  
... that are usually organized ...  
... in tandem ...  
... and there are more than 800 ZF transcription factors ...  
... in the human genome ...  
... (18–21).

**S2 [020]** The DNA-recognition mechanisms of ZF proteins are largely unknown.

The DNA-recognition mechanisms ...

## **End of Sample Audit**

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