



# Excessive Startle with Novel *GLRA1* Mutations in 4 Chinese Patients and a Literature Review of *GLRA1*-Related Hyperekplexia

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**Background and Purpose** Hyperekplexia (HPX), a rare neurogenetic disorder, is classically characterized by neonatal hypertonia, exaggerated startle response provoked by the sudden external stimuli and followed by a shortly general stiffness. Glycine receptor alpha 1 (*GLRA1*) is the major pathogenic gene of the disease. We described the clinical manifestations of genetically confirmed HPX patients and made a literature review of *GLRA1*-related HPX to improve the early recognition and prompt the management of the disorder.

**Methods** Extensive clinical evaluations were analyzed in 4 Chinese HPX patients from two unrelated families. Next generation sequencing was conducted in the probands. Sanger sequence and segregation analysis were applied to confirm the findings.

**Results** All four patients including 3 males and 1 female presented with excessive startle reflex, a cautious gait and recurrent falls. Moreover, startle episodes were dramatically improved with the treatment of clonazepam in all cases. Exome sequencing revealed 2 homozygous *GLRA1* mutations in the patients. The mutation c.1286T>A p.I429N has been previously reported, while c.754delC p.L252\* is novel.

**Conclusions** HPX is a treatable disease, and clonazepam is the drug of choice. By studying and reviewing the disorder, we summarized the phenotype, expanded the genotype spectrum, and discussed the possible pathogenic mechanisms to enhance the understanding and recognition of the disease. Early awareness of the disease is crucial to the prompt and proper administration, as well as the genetic counseling.

**Key Words** hyperekplexia, startle reaction, glycine receptor alpha 1, mutation, clonazepam.

## INTRODUCTION

Hyperekplexia (HPX), also referred to as Startle disease, is a rare inherited neurological disorder which is clinically characterized by neonatal hypertonia, generalized muscle stiffness and exaggerated startle reflexes provoked by sudden, unexpected auditory, tactile, and visual stimuli.<sup>1,2</sup> In 1958 Kirstein and Silfverskiold firstly described a family of which affected members suffered sudden falls precipitated by 'emotional' stimuli.<sup>3</sup> In 1966 Suhren investigated a large Dutch pedigree with the similar symptoms and firstly named the disorder "HPX."<sup>4</sup> Clinically, a generalized stiffness is always noted early after birth, which may be associated with apnea attacks and sudden infant death syndrome,<sup>5</sup> or some may be gradually improved in the first few years of life. While excessive startling may last throughout life which can occasionally cause serious traumatic injuries and impaired social interactions in older children.<sup>1</sup> Periodic limb movements in sleep and a characteristic head retraction reflex (nose-tapping test) can be observed in most patients with HPX.<sup>6</sup> Genetically, the disorder

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der shows genetic heterogeneity.<sup>7</sup> Among the causative genes, *GLRA1* is the major one, which accounts for about 80% of all cases.<sup>8</sup> To date, the pathogenic mechanism of the disease is still not fully understood. However, HPX has relatively a good prognosis with clonazepam to effectively respond to the startle episodes.<sup>9</sup>

Although potentially treatable, HPX is not necessarily a benign condition. In practice, it can be easily misdiagnosed and missed the prompt and appropriate treatment due to limited attention understanding of the disease.<sup>8</sup> Herein, clinical and genetic investigation of 4 Chinese patients from two unrelated families with novel *GLRA1* mutations were described, and a further detailed literature review of the *GLRA1*-related HPX was made to summarize the clinical manifestations, expand the genetic spectrum, and discuss the possible pathogenic mechanisms to enhance the early recognition, shed light on the pathogenetic studies and improve the systematic management for the disorder.

## METHODS

### Patients

A total of 4 patients from 2 unrelated families were enrolled in this study. Clinical diagnosis of HPX was based on the following performances: exaggerated startle reflex, muscle stiffness, a positive nose-tapping test, and a good response to clonazepam. All patients came from the neurology department of Ruijin Hospital and were evaluated by two senior neurologists at least. The ethics committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China approved the study (2017-38). All participants or their guardians provided written informed consents.

### Exome sequencing and data analysis

Genomic DNA was extracted using the standardized phenol/chloroform extraction protocol. Exome sequencing was performed on the proband of each family. The variants were analyzed as follows: firstly, the 1,000 Genomes Project (<http://www.internationalgenome.org>), dbSNP database (<http://www.ncbi.nlm.nih.gov/projects/SNP>), and the Exome Aggregation Consortium (ExAC, <http://exac.broadinstitute.org/>) were as references to exclude all variants present in the population at greater than 5% frequency. Then, the pathogenicity of the nucleotide and amino acid conservation was predicted by Mutationtaster (<http://www.mutationtaster.org>), PolyPhen-2 (<http://genetics.bwh.harvard.edu/pph2>), and SIFT (<http://sift.jcvi.org>). Finally, the pathogenic of the variant was interpreted and classified following the American College of Medical Genetics and Genomics Standards and Guidelines.<sup>10</sup> Putative pathogenic variants were further con-

firmed by Sanger sequencing, as well as co-segregation analysis among family members.

## RESULTS

### Clinical findings

Clinical profiles of the 4 patients are summarized in Table 1. Total 4 patients from 2 unrelated families, including 3 males and 1 female were enrolled. All patients had no remarkable neonatal problems. Muscle stiffness and/or excessive startle response were noticed during the neonatal period. The abnormal startle response was usually triggered by unexpected noises and constituted sudden stiffness, recurrent rigid falls to the ground with arms by two sides, but without loss of consciousness. All cases showed a cautious gait with a wide stride in adult life. Interestingly, all patients dared not to walk on hard ground, but could walk freely without fear on the green-sward, or with something relied on, such as wall, wheelchair, umbrella or stick (the video of the cautious gait and the improved therapeutic effects in siblings of the family 1<sup>11</sup>). The non-specific abnormalities in electroencephalogram (focal spike or slow waves) were found in two patients (family 1). All patients were previously judged as epilepsy or dystonia, and endured long time fear and frequent traumatic falls before correctly diagnosed. There was no developmental delay or intellectual disturbance in all patients. The other examinations such as, routine laboratory test, brain imaging showed no notable abnormalities in all cases. Moreover, clonazepam was administrated to all patients soon after the consideration of HPX, stiffness and startle reflex were dramatically or partially improved.

### Genetic findings

Exome sequencing revealed 2 homozygous mutations in *GLRA1* (NM\_000171) (Fig. 1). In consanguineous family 1, the two siblings had a novel homozygous deletion mutation c.754delC (p.L252\*), while their asymptomatic mother is a heterozygous carrier. In family 2, the proband and his younger brother carried a documented homozygous missense mutation c.1286T>A (p.I429N), his asymptomatic sister and son are heterozygous carriers. All the patients showed an autosomal recessive inheritance mode. The mutations above were not found in 1,000 Genomes Project, dbSNP, and ExAC database, and Mutationtaster predicted the mutations to be disease-causing.

## DISCUSSION

In this study, we investigated the clinical features of 4 patients from 2 unrelated families with genetically confirmed diagno-

**Table 1.** Clinical, medications, and genetic aspects of the patients

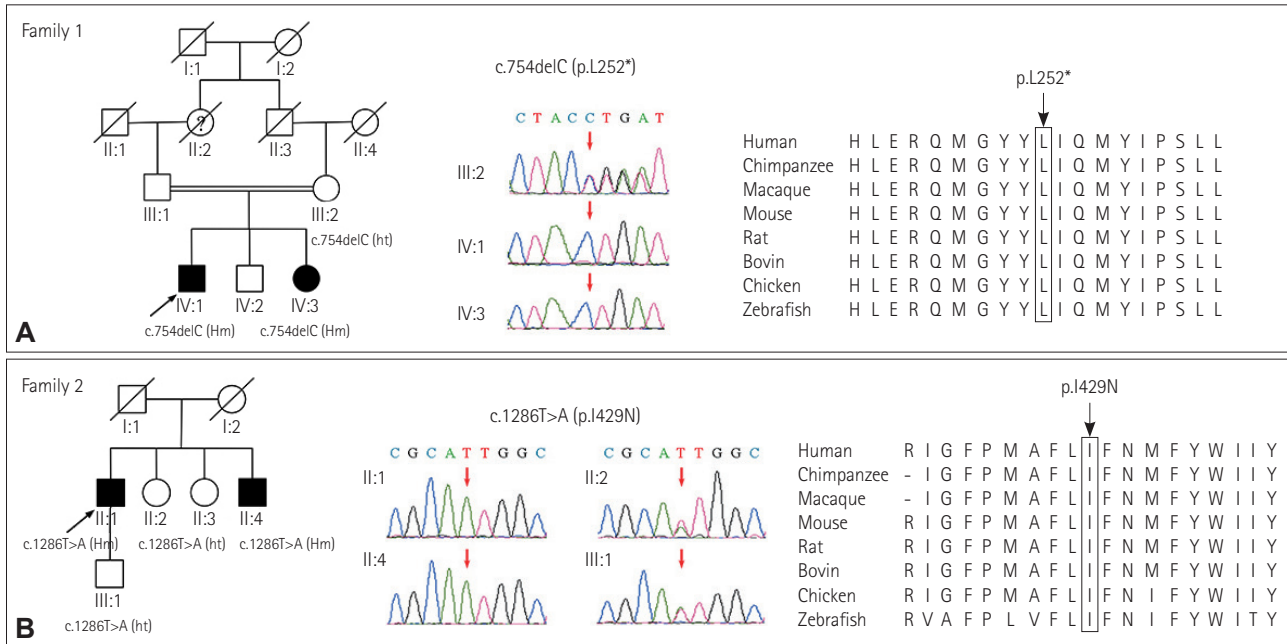
Patient no.	Sex	Age when noticed (year)	Age at diagnosis (year)	Inheritance	Phenomenology	Complications	EEG	Previous diagnosis	Responsive to CZP	<i>GLRA1</i> mutations/ACMG classification
Family 1										
IV:1	M	Neonate	48	Autosomal recessive	Neonatal hypertonia, exaggerated startle reflexes, stiff in 4 limbs, expressionless face, timid	Cerebral hemorrhage and skull fractures caused by recurrent falls	Focal spike and slow waves	Epilepsy, dystonia	Significantly improved (1 mg/day)	c.754delC p.L252* (Hm) "pathogenic"
IV:2	F	Neonate	41	Autosomal recessive	Neonatal hypertonia, exaggerated startle reflexes, stiff in 4 limbs, expressionless face, timid	Head trauma caused by recurrent falls	Focal slow waves	Epilepsy, dystonia	Significantly relieved (1 mg/day)	c.754delC p.L252* (Hm) "pathogenic"
Family 2										
II:1	M	Neonate	51	Autosomal recessive	Exaggerated startle reflexes, timid	Recurrent falls and dizziness	Not done	PNKD	Partially relieved (0.5 mg/day)	c.1286T>A p.I429N (Hm) "pathogenic"
II:4	M	Neonate	46	Autosomal recessive	Exaggerated startle reflexes, timid	Recurrent falls	Not done	-	Partially relieved (0.5 mg/day)	c.1286T>A p.I429N (Hm) "pathogenic"

Responsive to CZP: significantly improved (can walk freely with nothing rely on, startle reflexes almost vanished); partially relieved (maintain a slight sense of alertness, mild cautious gait); nonresponsive/insensitive (still with strong startle response when the dosage was increased to 2–5 mg daily).

ACMG: American College of Medical Genetics and Genomics Standards and Guidelines, CZP: clonazepam, EEG: electroencephalogram, F: female, Hm: homozygous, M: male, PNKD: paroxysmal non-kinesigenic dyskinesia.

sis of HPX. All cases were onset shortly after birth and showed an excessive startle response to unexpected stimuli, along with a wide-based and stiff gait in adulthood. While delayed diagnosis of all patients due to lack of awareness. Two *GLRA1* homozygous mutations in the patients have been detected, including 1 novel nonsense mutation (c.754delC p.L252\*), 1 documented missense mutation (c.1286T>A p.I429N).<sup>12</sup> All mutations were highly conservative in the related species. HPX is a rare neuromotor disorder classically characterized by neonatal hypertonia and an exaggerated startle reflex, which is caused by defects in mammalian glycinergic neurotransmission. Only a few cases have been reported in China, including 6 patients from 5 unrelated families carry *GLRA1* mutations,<sup>12–16</sup> one patient carry *GLRB* mutation.<sup>17</sup> There are two clinical forms of the disorder: a major and a minor form. The major form is typically characterized by generalized stiffness after birth, excessive startling to a sudden stimulus and generalized stiffness after a startle reflex, while the minor form only has excessive startle response.<sup>1,9</sup> HPX can also be complicated by umbilical/inguinal hernia, hip dislocation, epilepsy, myoclonus, periodic limb movement during sleep, delayed motor development or social dysfunction.<sup>6,9,18</sup> Hypertonicity is noted during neonatal or early infancy time, which may cause prolonged apnea and even sudden death, or gradually diminished spontaneously during the first few years of life. Excessive startle reflexes may persist throughout life, although the severity differs among the patients. The disorder always has a neonatal onset, which requires more attention in paediatrician's clinical practice. In our study, the electroencephalogram (EEG) abnormalities may be a non-specific pathological change, which might due to the severe craniocerebral trauma caused by the recurrent falls. As reported in previous study, fast spikes followed by slow background activity and flattening can be observed on EEG without epileptic discharges of the patient.<sup>19</sup> In addition, phenotype disparities existed between the affected members in the same pedigree, which is consisted with the previous reports,<sup>1,8,20</sup> suggesting an underlying mechanism of variable expressivity. Currently, clonazepam is the drug of choice that dramatically improves the exaggerated startling, which through enhancing GABA-gated chloride channel function and presumably compensating for the defective glycine-gated chloride channel function.<sup>9</sup>

Pathogenic variants in 5 genes relating to the glycinergic neurotransmission system have been identified in HPX. *GLRA1* and *GLRB* encode the  $\alpha 1$  and  $\beta$  subunit of the postsynaptic inhibitory glycine receptor respectively. *SLC6A5* encodes the cognate presynaptic glycine transporter 2. It was reported that patients with *GLRB* and *SLC6A5* mutations are more likely to have apnea attacks, or mild to severe delay in

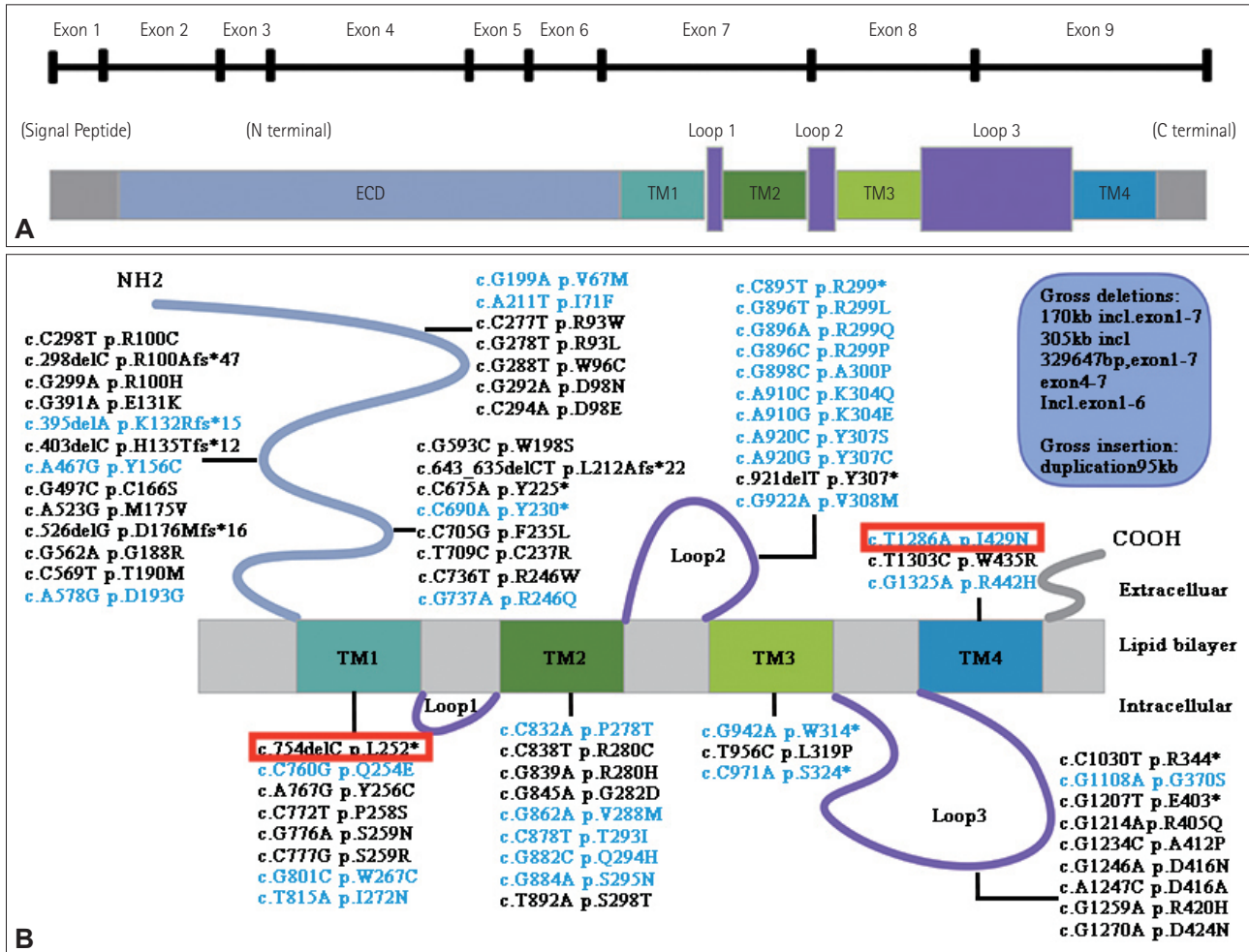


**Fig. 1.** The family pedigrees with a diagnosis of hyperekplexia. The family trees, the chromatograms and the mutations located in the highly-conserved region of proteins are shown from left to right respectively. A: Homogenous *GLRA1* c.754delC (p.L252\*) identified in the two siblings (IV:1 and IV:3), their asymptomatic mother (III:2) is a heterozygous carrier. B: Homogenous *GLRA1* c.1286T>A (p.I429N) identified in the proband and his younger brother (II:1 and II:4), his asymptomatic sister and son are heterozygous mutation carriers (II:2 and III:1).

development or speech acquisition.<sup>7,21</sup> While the mutations in *GPHN* and *ARHGEF9*, of which the encoding proteins gephyrin and collybistin are involved in GlyR synaptic clustering, have also been reported to result in more complex or atypical phenotype.<sup>22,23</sup> All these proteins are implicated in the normal functioning of inhibitory glycinergic synapses, which are located predominantly in the spinal cord and brainstem.<sup>24</sup> In human, four  $\alpha$  subunits ( $\alpha 1$ – $\alpha 4$ ) and a single  $\beta$  subunit formed the GlyRs, which belong to the Cys-loop family of pentameric ligand-gated ion channel receptors. Binding with its ligand glycine, which is an essential inhibitory neurotransmitter in the adult nervous system, the glycinergic signaling plays a vital role in neural development, including spinal cord, brain, retina.<sup>24</sup> The abnormalities in electrophysiological studies also indicated that abnormal reciprocal inhibition or increased excitability in pontomedullary reticular neurons may contribute to generalized stiffness in hyperekplexia.<sup>25,26</sup>

The causative gene *GLRA1* is the most common one, which has 9 exons (Fig. 2A). The encoding protein  $\alpha 1$  subunit of GlyR contains an extracellular domain (ECD) that harboring the neurotransmitter binding site and a transmembrane domain (TMD) that comprising 4  $\alpha$ -helices, termed TM1–TM4<sup>27</sup> (Fig. 2A). It demonstrated both dominant and recessive inheritance in *GLRA1*. So far, about 77 various mutations have been reported, including 64 missense/nonsense mutations, 7 small deletions (including this study), 5 gross deletions and 1 gross insertion. The mutations are distributed in all domains,

clustering in ECD, TM1, TM2 domains and Loop2 (Fig. 2B). Among all the mutations, we found that 40.0% (30/77) are dominant, 50.6% (39/77) are recessive (missense and nonsense), 7.8% (6/77) are recessive frameshift variants. Dominant mutations are mainly located in and around TM2 domain and Loop2, while the recessive or compound variants are scattering in all the domains. Localized at the extracellular end of TM2 domain, R299 is the most frequent mutant locus. Numerous studies suggested that dominant mutations could compromise glycine ligand binding, decrease the glycine sensitivity by disrupting the hydrogen bond, or cause chloride conductance defects.<sup>28</sup> Besides, a few dominant mutations which located in ECD, TM1, TM2 domain could cause fast desensitization to limit chloride flux.<sup>29,30</sup> For many recessive mutations, reduced expression or a deficiency of cell surface targeting of GlyRs might be implicated, in which the related glycine-activated currents could be observed when co-expressed with  $\alpha 1$  and/or  $\beta$  wild-type subunits.<sup>28,29</sup> Additionally, as zinc is known to have potentiating effect on glycinergic currents upon neuronal stimulation.<sup>31</sup> Studies showed that the mutant residues which is to be the binding sites for  $Zn^{2+}$  may involve in the loss of zinc potentiation.<sup>27,32</sup> Except for the loss-of-function mechanism above, some gain-of-function mutations can also cause HPX. To date, four dominant mutations (Y156C, Q254E, V308M, R442H) have been demonstrated to induce spontaneous GlyR activation, which result in enhanced sodium and calcium influx rates, and direct-



**Fig. 2.** Schematic drawing of the *GLRA1* gene and protein domains, and distribution of all *GLRA1* mutations. A: Schematic drawing of the *GLRA1* gene and protein with domains. B: Diagram of all *GLRA1* mutations (NM\_000171). Mutations in black: recessive or compound heterozygous mutations; mutations in blue: dominant mutations. The mutations detected in this paper are marked in red. The five gross deletion mutations, including 170 kb inclusive exon 1–7 (–93.3 kb upstream of ATG), 305 kb incl, 329647 bp exon 1–7, exon 4–7 and inclusive exon 1–6. One insertion: duplication 95 kb. ECD: extracellular domain, TM: transmembrane domain.

ly contribute to the reduction in the glycine-induced current amplitude.<sup>28,29</sup> Nevertheless, the exact mechanism of *GLRA1* mutations still beyond fully understand and requires more investigation.

Due to the overlapping clinical signs, HPX can be initially misdiagnosed as epilepsy, cerebral palsy in infancy period, or adult-onset anxiety neurosis. The disorder has a neonatal onset, when newborns showed diffuse muscular rigidity, episodic tonic spasm, apnea, aspiration pneumonia, it should be considered the possibility of HPX. Nose-tapping test can make a preliminary judgement. Once acute hypertonia and apnea episodes occur, a simple intervention called the Vigevano action (flexing of the head and limbs toward the trunk) can relieve the event.<sup>33</sup> Fortunately, HPX is a potentially treatable disease. Clonazepam, which can specifically upgrade the GABARA1 chloride channels, is the main and most effective

administration for HPX patients.<sup>9</sup> The treatment is recommended to start with a dose of 0.5 mg daily, adjust dosage based on effects, up to 6 mg daily if necessary.<sup>34</sup> Some other antiepileptic drugs, like carbamazepine or phenobarbital, can also be used while their therapeutic effect is still in debate. For the psychological problems like social anxiety, timidity and self-basement, psychotherapy and family support are crucial for personality development and alleviating mental problems.

In conclusion, HPX is a treatable neurogenetic disorder, and clonazepam is the drug of choice. Mutations in *GLRA1* account for the most. By studying and reviewing the disorder, we summarized the phenotype, expanded the genotype spectrum, discussed the possible pathogenic mechanisms, to enhance learning, awareness-raising of the HPX and shed light on the pathogenetic studies. Early recognition of the disease is

helpful for prompt and appropriate treatment, to avoid the serious adverse events and improve the quality of life. Moreover, prompt genetic analysis may be useful for early definite diagnosis, genetic counseling and safer care for affected neonates.

### Author Contributions

Conceptualization: Li Cao. Data curation: Feixia Zhan, Chao Zhang, Shige Wang, Zeyu Zhu, Guang Chen, Mingliang Zhao, Li Cao. Formal analysis: Feixia Zhan, Chao Zhang, Li Cao. Funding acquisition: Li Cao. Investigation: Feixia Zhan, Chao Zhang, Shige Wang, Zeyu Zhu, Guang Chen, Mingliang Zhao, Li Cao. Methodology: Feixia Zhan, Chao Zhang, Li Cao. Project administration: Li Cao. Resources: Li Cao. Software: Feixia Zhan, Chao Zhang. Supervision: Li Cao. Validation: Li Cao. Writing—original draft: Feixia Zhan. Writing—review & editing: Li Cao.

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### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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