

Pediatric Liddle Syndrome Caused by a Novel *SCNN1G* Variant in a Chinese Family and Characterized by Early-Onset Hypertension

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BACKGROUND

Liddle syndrome (LS), an autosomal dominant disorder, is a common monogenic hypertension in pediatrics. In this study, we reported a novel *SCNN1G* variant in a Chinese family with pediatric LS, and conduct a systematic review of epithelial sodium channel (ENaC)-gene-positive LS cases to conclude the clinical genetic features of LS in childhood.

METHODS

Next-generation sequencing and *in silico* analysis were performed in the proband to discover candidate variants. Sanger sequencing was used to identify the predicted likely pathogenic variant. LS patients in this family were treated with amiloride. The Medline database was searched to summarize clinical features of pediatric LS cases whose age at genetic diagnosis was not more than 18 years.

RESULTS

Genetic analysis identified a novel *SCNN1G* missense variant (c.1874C>T, p.Pro625Leu) in the proband with LS in childhood. *In silico* analysis revealed this heterozygous variant was highly conserved and deleterious.

A total of 38 publications described pediatric LS associated with 25 pathogenic variants in *SCNN1B* and *SCNN1G* in 54 children. Despite the phenotypic heterogeneity, early-onset hypertension is the most common feature. All LS patients in this family or the reviewed cases showed significantly improvements in hypertension and hypokalemia after treatment with ENaC inhibitors.

CONCLUSIONS

This study identified a novel *SCNN1G* missense variant in a patient with pediatric LS, expanding the genetic spectrum of *SCNN1G* and demonstrating the PY motif of γ -ENaC as a potential mutant region. Early identification and specific management of LS in children and adolescents are important to prevent the development of hypertensive end-organ disease.

Keywords: blood pressure; hypertension; Pediatric Liddle syndrome; *SCNN1G* gene

doi:10.1093/ajh/hpaa037

Hypertension has become as an important health issue in the pediatric population in recent years¹; the prevalence of hypertension in children and adolescents in China is 3.1%.² Inherited pathogenic factors make a substantial contribution to pediatric hypertension. In particular, monogenic hypertension is an increasingly recognized type of hypertension in children.^{3,4} Keeping genetic conditions in mind is helpful when diagnosing hypertension in children, because the

younger the child, the more likely it is that their hypertension is due to a secondary cause.⁵

Liddle syndrome (LS, OMIM #177200) is a common monogenic form of hypertension in children, with an autosomal dominant pattern of inheritance.⁴ In 1963, Liddle *et al.* first reported a 16-year-old index case with low renin resistant hypertension, severe hypokalemia, and metabolic alkalosis in a Caucasian family.⁶ Further exploration showed that LS

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Initially submitted February 18, 2020; date of first revision March 2, 2020; accepted for publication March 6, 2020; online publication March 12, 2020.

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is caused by gain-of-function pathogenic variants in the epithelial sodium channel (ENaC) genes.⁷ The prevalence of LS was shown to be 1.52% (5/330)⁸ and 0.91% (7/766)⁹ in patients with early-onset hypertension; that is, those diagnosed at less than 40 years of age. The actual prevalence of LS in the pediatric hypertensive population remains unknown, due to genetic testing is not widespread. Thus, LS might be largely underdiagnosed with a much higher prevalence than currently estimated.^{10,11}

In this study, we reported a male adolescent proband with LS and a novel missense variant in exon 13 of the *SCNN1G* gene. The identified variant was detected in 3 additional relatives. We conducted a systematic review to identify LS cases that were genetically confirmed during childhood. Our review indicated that genetic testing is essential for early identification of LS, especially in children and adolescents with early-onset hypertension.

METHODS

Participants

The index patient (subject III-3), at the age of 14 years, was found to have an average of 3 measurements of blood pressure (BP) during 3 different clinic visits of 150/100 mm Hg, which was above the sex- and age-specific 99th percentile (138/90 mm Hg).¹² To identify the etiology of

early-onset hypertension, the patient was admitted to the hypertension ward of Fuwai Hospital. As well as the proband, 10 family members (Figure 1a) were enrolled in this study for genetic analysis. To exclude common genetic variants, candidate variants were identified in 100 unrelated hypertension patients and 100 normotensive subjects.

This study was approved by the Ethics Committee of Fuwai Hospital and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Biochemical examination

Plasma renin concentration (PRC) and plasma aldosterone concentration were measured by chemiluminescence immunoassay using the LIAISON Direct Renin kit (DiaSorin S.p.A, Vercelli, Italy) and the LIAISON Aldosterone kit (DiaSorin Inc., Stillwater, MN, USA). Plasma was collected from patients after 2 hours of upright position for measuring PRC and plasma aldosterone concentration.

Genetic testing

Genomic DNA was extracted from peripheral blood leukocytes using the QIAamp DNA Blood Mini kit (QIAGEN, Hilden, Germany). We performed targeted

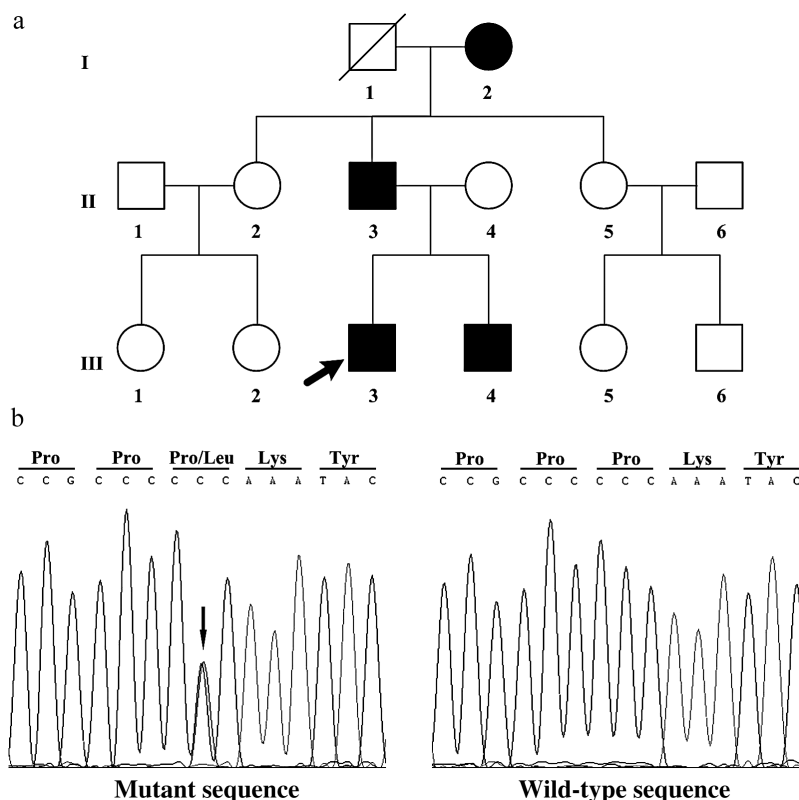


Figure 1. Pedigree and Sanger sequencing results of the 3-generation family with Liddle syndrome. (a) Solid symbols represent the identified variant carriers; open symbols represent normal individuals without the identified variant; the black arrow indicates the proband. (b) Sanger sequencing showing mutant and wild-type sequences in patients with Liddle syndrome and normal individuals, respectively, in this study. The black arrow indicates the identified variant site (c.1874C>T, p.Pro625Leu) in the mutant sequence.

sequencing in the proband, with a panel of 41 genes associated with monogenic hypertension (Supplementary Table S1 online). Sanger sequencing in all subjects was used to identify candidate variants, which were selected by means of *in silico* analysis. Exon 13 of *SCNN1G* was amplified by polymerase chain reaction using a pair of primers according to Yang *et al.*¹³ The polymerase chain reaction products were sequenced using an ABI Prism 377 DNA sequencer (Applied Biosystems, Foster City, CA, USA).

Systematic review

To clarify reported genetic and clinical features of ENaC-gene-positive LS patients in childhood, we retrieved papers on LS published in English on Medline from 1963 to November 2019, using the terms “Liddle syndrome,” “Liddle’s syndrome,” and “pseudoaldosteronism.” In addition, data and references on ENaC gene variants were enriched after searching the Human Gene Mutation Database (www.hgmd.org). Cases were included based on the following criteria: LS patients must have been identified by genetic testing and the patients were aged ≤ 18 years. Two authors completed the study selection independently, with consultation from a third author in case of discrepancies. Statistical analysis was performed using SPSS (SPSS 16.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical features

At the time of hospitalization, the proband had high BP (163/96 mm Hg), low-normal potassium level (3.58 mmol/l, normal range 3.5–5.3 mmol/l), and hypoaldosteronism in the supine position (2.9 ng/dl). He denied a history of vomiting, diarrhea, and use of licorice or other medications. Other hormonal determinations, including PRC, serum cortisol, adrenocorticotropic, catecholamine, metanephrine, normetanephrine, thyroid, and gonadal hormones were within normal limits. Echocardiography and computed tomography showed no abnormality of the heart, aorta, kidney, and adrenal or renal arteries. Polysomnography monitoring excluded sleep apnea syndrome.

Pedigree investigation revealed that the proband’s grandmother, father, and younger brother had early-onset hypertension. His grandmother and father failed to control BP within normal range, even using 3 kinds of antihypertensive medications. The proband’s grandmother (subject I-2) suffered a stroke at the age of 60 years. His grandmother and father had hypokalemia, hyporeninemia, and hypoaldosteronism (Table 1).

Genetic analysis

A novel heterozygous variant in exon 13 of *SCNN1G*, c.1874C>T, was found in the proband (Figure 1b). This missense variant altered proline to leucine at codon 625 (p.Pro625Leu), resulting in a change in the PY motif. To date, the p.Pro625Leu variant in *SCNN1G* had not been reported in the Exome Aggregation Consortium database (<http://exac.broadinstitute.org/>), the 1000 Genomes Project database (<http://browser.1000genomes.org>), or the Human Gene Mutation Database (<http://www.hgmd.org>). *In silico* analysis predicted this variant to be deleterious, using the SIFT (<http://sift.jcvi.org>), Provean (<http://provean.jcvi.org/index.php>), PolyPhen-2 (<http://genetics.bwh.harvard.edu/pph2>), and MutationTaster (<http://www.mutationtaster.org>). In addition, Pro625 in γ -ENaC protein is highly conserved in vertebrates. No pathogenic variant in *SCNN1B* or other genes was identified (Supplementary Table S1 online). The predicted likely pathogenic variant was found in the 3 affected relatives (I-2, II-3, and III-4), but not in other family members. Moreover, none of 100 unrelated patients with hypertension or 100 normotensive individuals had this *SCNN1G* variant (c.1874C>T), indicating that it is not a common genetic variant.

Tailored therapy for LS patients

ENaC inhibitors are effective in the treatment of LS. There are only compound amiloride (amiloride 2.5 mg and hydrochlorothiazide 25 mg each tablet) in the market. The proband and 3 family members were treated with compound amiloride (1–4 tablets/day), and BP and plasma potassium level were reexamined after 1 month of tailored therapy. At reexamination, all patients showed significant improvements in BP and potassium levels (Table 2).

Table 1. Clinical and biochemical characteristics of patients with Liddle syndrome in this family

Subjects	Gender	BMI, kg/m ²	Onset age of hypertension, y	BP ^a , mm Hg	Serum K ⁺ , mmol/l	PAC, ng/dl	PRC, μ IU/ml	ADRR	Treated with amiloride	
									BP, mm Hg	Serum K ⁺ , mmol/l
I-2	F	17.6	28	180/110	3.04	2.9	3.7	0.784	140/90	3.89
II-3	M	24.8	30	180/120	2.94	2.5	4.0	0.625	135/85	3.96
III-3	M	27.8	14	160/100	3.58	3.6	8.8	0.409	120/80	4.13
III-4	M	15.7	3	120/80	3.20	2.8	4.2	0.667	95/65	4.05

Abbreviations: ADRR, plasma aldosterone to direct renin ratio; BMI, body mass index; BP, blood pressure; F, female; K⁺, potassium level (normal range: 3.5–5.3 mmol/l); M, male; PAC, plasma aldosterone concentration (normal range: 3.0–35.3 ng/dl); PRC, plasma renin concentration (normal range: 4.4–46.1 μ IU/ml).

^aThe maximum blood pressure was measured more than 3 times.

Table 2. Systematic review data of clinical characteristics of 54 pediatric patients with Liddle syndrome with identified mutations in epithelial sodium channel genes

Parameters	Summary data	Number of cases available
Male, <i>n</i> (%)	33 (61.11)	54
Median age at genetic diagnosis, y	14 (0.1, 18)	51
Hypertension, <i>n</i> (%)	48 (88.89)	54
Median age at hypertension onset, y	12.75 (0.1, 17)	48
Median Max. systolic/diastolic BP, mm Hg		
Before treatment	153/100 (240/180, 100/51)	50
After treatment ^a	120/78 (150/110, 90/40)	35
Hypokalemia, <i>n</i> (%)	39 (78)	50
Median Min. serum or plasma K ⁺ , mmol/l		
Before treatment	3.2 (1.8, 4.6)	48
After treatment ^a	4.1 (3.01, 4.9)	25
Suppressed PAC, <i>n</i> (%)	37 (72.55)	51
Suppressed PRA or PRC, <i>n</i> (%)	44 (86.27)	51
Family history, <i>n</i> (%)	36 (90)	40

Abbreviations: BP, blood pressure; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PRC, plasma renin concentration.

^aPediatric Liddle syndrome patients were treated with amiloride or triamterene.

Systemic review on genetic and clinical characteristics of pediatric LS

Our review of the literatures found 54 cases (male, 61.11%) of genetically confirmed pediatric LS, including the 2 young patients in the present study. A total of 25 pathogenic variants (including missense, nonsense, and frameshift variants) in *SCNN1B* and *SCNN1G* were identified in pediatric LS (Supplementary Table S2 online). The median age at hypertension onset was 12.75 years, ranging from 0.1 to 17 years, and the median age at genetic diagnosis was 14 years. Phenotypic heterogeneity was reflected in the incidence of hypertension (88.89%), hypokalemia (78%), hypoaldosteronism (72.55%), and hyporeninemia (86.27%). After treatment with ENaC inhibitors, BP (median maximum value: 153/100 vs. 120/78 mm Hg) and potassium level (median minimum value: 3.2 vs. 4.1 mmol/l) were significantly improved (Figure 2). Only 10% cases were sporadic, 90% of patients had a family history of LS (Table 2).

DISCUSSION

In this paper, we reported a novel heterozygous missense variant (c.1874C>T, p.Pro625Leu) in *SCNN1G* in a Chinese family with LS and conducted a systemic review on genetic and clinical features of pediatric LS. A diagnosis of LS should be strongly considered in pediatric cases of monogenic hypertension.

The ENaC, together with renal outer medullar K⁺ channel and Na⁺/K⁺ ATPase, plays essential roles in hydroelectrolytic homeostasis and blood volume.¹⁴ In the kidney, ENaC is expressed in the luminal membrane of the principal cells

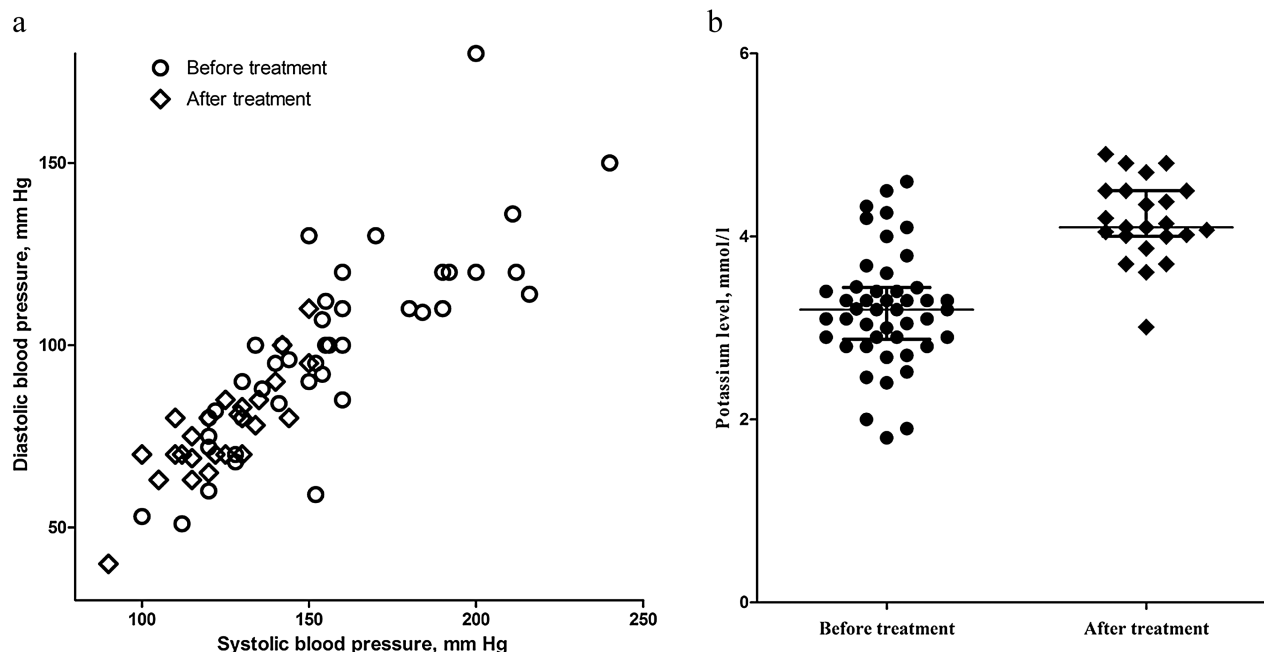


Figure 2. Systematic review data on blood pressure and potassium level before and after treatment with epithelial sodium channel (ENaC) inhibitors in pediatric patients with Liddle syndrome. (a) Reduction in systolic and diastolic blood pressure; (b) significant increase (improvement) in potassium level.

of the distal nephron, and consists of 3 partly homologous subunits (α -ENaC, β -ENaC, and γ -ENaC).¹⁵ Mutations in ENaC genes impair expression of proline-rich regions (PY motif), resulting in loss of regulatory binding sites for Nedd4-2, an ubiquitin ligase associated with breakdown of ENaC.^{16,17} Therefore, uncontrolled ENaC is constitutively activated with increased Na⁺ reabsorption and subsequent intravascular volume expansion, resulting in high BP.^{18,19} Hypokalemia is secondary to excess Na⁺ reabsorption promoting extrusion of K⁺ via the Na⁺/K⁺ ATPase pumps.²⁰ Renin and aldosterone are suppressed by both the elevated sodium level and the volume expansion.⁵ This molecular mechanism explains the typical clinical manifestations observed in LS patients.

Pediatric LS is mainly affected by pathogenic variants in *SCNN1B* and *SCNN1G* (located on chromosome 16p), which encode the β and γ subunits of ENaC, respectively. In the pediatric LS literatures, 25 ENaC gene pathogenic variant sites have been reported, consisting of 19 *SCNN1B* variants and 6 *SCNN1G* variants (including this study). These pathogenic variants either cause a missense variant of a key residue in the PY motif or generate a nonsense or frameshift (deletions and insertions) variant that truncates the cytoplasmic carboxyl terminus with loss of the PY motif.²¹

SCNN1G pathogenic variants are relatively infrequent in the spectrum of ENaC variants. To date, only 9 different pathogenic variants have been identified in *SCNN1G* (5 in pediatric LS). In particular, *SCNN1G* missense variants are quite rare. Hiltunen *et al.* described the first missense variant located in the extracellular domain of γ -ENaC associated with increased ENaC activity and LS.²² Then, in 2018, Lata *et al.* reported a missense variant (c.1874C>G, p. Pro625Arg) of a key residue in the PY motif in a white male, who presented with hypertension and hypokalemia at 13 years of age.²³ The present study identified the second missense variant (c.1874C>T, p. Pro625Leu) in the same nucleotide position, changing cytosine to thymine. A predicted likely pathogenic *SCNN1G* variant may locate in the key residue in the PY motif, resulting in LS.

Among LS patients, phenotypic heterogeneity is very common, especially in children. In this family, the proband's grandmother, father, and younger brother all presented with typical LS symptoms, such as severe hypertension, hypokalemia, hyporeninemia, and hypoaldosteronism. However, the proband manifested only early-onset hypertension with low-normal levels of potassium, plasma aldosterone concentration, and PRC. According to the literature review (Table 2), phenotypic heterogeneity in pediatric LS is mainly reflected in the following aspects. Early-onset hypertension is the most common (88.89%) clinical feature of pediatric LS, with a median maximum BP of 153/100 mm Hg before management. Overall, 78% of pediatric cases had hypokalemia (median minimum potassium level: 3.2 mmol/l). Hyporeninemia were observed in 72.55% and 86.27% of pediatric pathogenic variants carriers, respectively. Tetti *et al.* reported that, in 200 LS patients diagnosed by genetic testing, 92.4% had hypertension, 71.8% had hypokalemia, and 58.2% had hypoaldosteronemia.²⁴ In 54

genetically confirmed LS probands, 100% had hypertension, 94% had hypokalemia, 84% had hypoaldosteronism, and 94% had hyporeninemia.²⁵ Thus, pediatric LS patients are more likely to be normotensive. LS patients lacking a family history have also been noted. Cui *et al.* reported that *de novo* pathogenic variants accounted for 50% of cases,²⁶ and Yang *et al.* found that 86% index cases with LS had a family history.²⁵ Consistent with our review in this study, only 4 (10%) pediatric cases were isolated with *de novo* pathogenic variants.^{13,26,27} Although a family history of childhood hypertension is a clue for pediatric LS, physicians should consider the isolated LS individual with a *de novo* pathogenic variant.

It is helpful for early diagnosis to define the molecular basis of LS in childhood (Supplementary Figure S1 online). Usually, genetic diagnosis occurs at a later age than the onset of hypertension.²⁵ In pediatric cases of LS, the median ages at genetic diagnosis and hypertension onset are 14 and 12.75 years, respectively. Actual age at genetic diagnosis should be much later, because not all LS children included in this study were probands. Misdiagnosis or underdiagnosis without genetic confirmation misses the best opportunity for early control of disorders in pediatric patients with LS.

Comprehensive management (Supplementary Figure S1 online) for LS patients consists of a healthy lifestyle (low-sodium diet, with <2 g of NaCl/day, not smoking, and getting more exercise) and treatment with ENaC antagonists.^{28,29} Patients with LS do respond to treatment with ENaC inhibitors, such as amiloride and triamterene. ENaC inhibitors can improve arterial hypertension and hypokalemia, because they reverse the pathological volume expansion and excessive sodium reabsorption.³⁰ In contrast, mineralocorticoid receptor antagonists are not helpful in the management of LS, because Na⁺ reabsorption is independent of mineralocorticoid receptor activation.³¹ Hence, the lack of response to mineralocorticoid receptor antagonists should increase suspicions about LS.³²

We acknowledge several limitations of this study. We did not conduct electrophysiological measurements of the amiloride-sensitive sodium current. The systematic review data lacked information on long-term prognosis, thus we could not evaluate management efficacy.

In conclusion, we identified a novel and predicted likely pathogenic *SCNN1G* missense variant in a pediatric LS proband in a Chinese family. This discovery expands the genetic spectrum of *SCNN1G* pathogenic variants and demonstrates the PY motif of γ -ENaC to be a potential mutant region. We recommend that LS should be considered in children with early-onset hypertension, regardless of potassium level, plasma aldosterone concentration, or PRC, and even in the absence of a family history. Furthermore, once a genetic diagnosis of LS is confirmed, at-risk family members should be screened for the same variant to allow early identification. For pediatric patients with LS, it is crucial to make a precise diagnosis as early as possible, because tailored therapy can prevent the development of hypertensive end-organ damage and decrease the morbidity and mortality associated with long-term and uncontrolled hypertension.³³

SUPPLEMENTARY MATERIAL

Supplementary data are available at *American Journal of Hypertension* online.

Supplemental Figure S1. Flow chart for diagnosis and treatment of Liddle syndrome. ACTH, adrenocorticotropic hormone; AME, apparent mineralocorticoid excess; CAH, congenital adrenal hyperplasia; COX2, cyclooxygenase-2; DOC, deoxycorticosterone; ENaC, epithelial sodium channel; GRS, glucocorticoid-resistance syndrome; GS, Geller syndrome; K, potassium level; N, normal; NASIDs, nonsteroidal anti-inflammatory drugs.

FUNDING

This work was supported by CAMS Innovation Fund for Medical Sciences (2016-I2M-1-002), the National Key Research and Development Program of China (2016YFC1300100), National Natural Science Foundation of China (81600305), Beijing Nova Program (Z171100001117026), PUMC Youth Fund and the Fundamental Research Funds for the Central Universities (3332015205 and 3332019134), and PUMC Graduate Innovation Fund (2018-1002-01-14).

DISCLOSURE

The authors declared no conflict of interest.

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