ORIGINAL ARTICLE

WILEY

# Neurophenotype and genetic analysis of children with Aicardi-Goutières syndrome in China

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Received: 29 November 2023
Accepted: 27 March 2024

## ABSTRACT

**Importance:** Aicardi–Goutières syndrome (AGS) is a rare genetic disorder mainly affecting the central nervous system and autoimmunity. However, research on AGS among Chinese patients is limited.

**Objective:** To summarize the neurologic phenotypes and genetic causes in pediatric AGS patients, providing insights for early recognition and diagnosis in the Chinese population.

**Methods:** Clinical features and neuroimaging results of the patients diagnosed with AGS from Beijing Children's Hospital between January 2018 and January 2022 were collected. Whole exome sequencing was used for genetic analysis.

**Results:** A total of 15 patients was included, all presenting with various neurological symptoms, including developmental delay (100%), motor skill impairment (100%), language disability (78.6%), dystonia (93.3%), microcephaly (73.3%), sleep disorders (26.7%), regression (20.0%), vessel disease (6.7%), and epilepsy (6.7%). Neuroimaging revealed intracranial calcification (86.7%), cerebral atrophy (73.3%), and leukodystrophy (73.3%). Seven genes were identified, with *TREX1* being the most common (40.0%, 6/15), followed by *IFIH1* (20.0%, 3/15). Variant c.294dupA (p.C99Mfs*3) was detected in four unrelated patients, accounting for 66.7% (4/6) patients with the *TREX1* variant. A literature review showed that *TREX1* gene mutations in 35.6% (21/59) of AGS patients among the Chinese population.

**Interpretation:** Neurological symptoms are the most prevalent and severe presentation of AGS. Diagnosis may be considered when symptoms such as developmental delay, dystonia, microcephaly, brain calcification, and leukodystrophy emerge. *TREX1* mutations are predominant in the Chinese population.

## KEYWORDS

Aicardi-Goutières syndrome, Developmental delay, Leukodystrophy, Neurophenotype, Whole exome sequencing

DOI: 10.1002/ped4.12428

# INTRODUCTION

First described in 1984, Aicardi–Goutières syndrome (AGS) is characterized by early onset leukoencephalopathy, brain calcification, cerebral atrophy, and cerebrospinal fluid (CSF) pleocytosis.[1] Over time, a broader spectrum of clinical features has been identified, ranging from skin lesions and neurological disorders to autoimmune diseases. AGS is genetically linked to variants in nine specific genes: *TREX1*,[2] *RNASEH2B*, *RNASEH2C*, *RNASEH2A*,[3] *SAMHD1*,[4] *ADAR*,[5] *IFIH1*,[6] *LSM11*, and *RNU7-1*.[7] Mutations in these genes can explain about 95% of patients with AGS.[8,9] All genes are involved in nucleic acid metabolism signaling pathways, with mutations leading to persistent activation of type I interferon signaling. The term "type I interferonopathies" was proposed in 2011 to describe a group of monogenic phenotypes associated with a pathological upregulation of type I interferon signaling, including AGS.[10]

AGS is a systemic disease that affects multiple organs, including the central nervous system (CNS), skin, joints, liver, kidney, blood system, lung, and thyroid.[9,11] Neurological manifestations are the most prevalent in AGS and are often associated with severe disease and poor prognosis. These neurological features encompass acute loss of neurological function, developmental delay, regression, dystonia, epilepsy, sleeping disorder, and microcephaly. Neuroimaging studies have revealed brain atrophy, calcification, and leukodystrophy.[12]

Although AGS has been described for decades, research on AGS patients in China remains limited, primarily comprising sporadic case reports with small sample sizes. Moreover, the broad spectrum of phenotypes often results in delays in diagnosis and treatment. Early diagnosis and intervention for AGS patients can improve prognosis. The aim of this study is to summarize both the clinical and molecular diagnostic findings in 15 cases of pediatric AGS patients. Search for the neurologic phenotypes and genotype association of AGS in the Chinese population, providing clues for clinical identification and diagnosis of AGS.

# METHODS

## Ethical approval

This study has been approved by the Ethical Committee of Beijing Children's Hospital, Capital Medical University ([2024]-E-059-R). Informed consent was signed by all participants or their legal guardians in this study.

## Patients and data collection

A retrospective review of clinical charts was conducted for pediatric patients who were admitted to the Department of Neurology at Beijing Children's Hospital from January 2018 to January 2022. The data was acquired from The FUTang Updating medical REcords (FUTURE) Database.[13] Patients with clinically and genetically diagnosed AGS were included in this study. The patient's family history, clinical presentation, neuroimaging results, genetic test results, therapy options, and prognosis were systematically reviewed.

## Whole exome-sequencing and variants interpretation

A total of 3–5 mL peripheral blood was taken from the patients and their parents (if available). Genomic DNA was extracted from peripheral blood using the Solpure Blood DNA Kit (Magen) and then fragmented by the Q800R Sonicator (Qsonica) to generate 300–500 bp insert fragments. Libraries were prepared by the Agilent Sureselect Human All Exon v5 kit (Agilent Technologies) and were sequenced on HiSeq 2000 (Illumina). The coverage depth was 80–100×, with over 99% of the target regions. NextGENe (SoftGenetics) was used for raw data alignment. Variants interpretation followed the American College of Medical Genetics guidelines.[14,15] The identified variants were classified into "Pathogenic (P)," "Likely Pathogenic (LP)," "Variants of Uncertain Significance (VUS)," "Likely Benign (LB)," or "Benign (B)." Sanger sequencing was performed to verify the variants found by Whole exome-sequencing (WES).

# RESULTS

## Demographics and clinical features

The clinical characteristics of the patients are summarized in Table 1, which includes a total of 15 patients (eight males and seven females) from unrelated families who received clinical and genetic diagnoses of AGS. Age at onset ranged from 3 days to 3 years old, with an average of 8.8 months. Among the cases, 10 were classified as infantile-onset AGS (before 1 year old), while five were categorized as late-onset AGS (over 1 year old), and no cases had a prenatal onset. All patients had healthy parents and no reported family history of autoimmune diseases.

The CNS was the most commonly affected organ system, with all patients exhibiting varying degrees of developmental delay and motor disorders. Dystonia was observed in

**TABLE 1** Demographic, neurological, and genetic features of the 15 pediatric patients with Aicardi-Goutières syndrome

| Patient ID | Sex | Age at onset | Gene | Variant | Zygosity | Origin | Initial symptoms | DD | Dystonia | ES | IC | CA | Leukoence-phalopathy | Micro-cephaly |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 1 y | *TREX1* | c.294dupA (p.C99Mfs*3); c.−26-1G>A† | Het | Inherited | Chilblain-like rash | + | + | − | + | − | − | − |
| 2 | F | 1 y | *TREX1* | c.294dupA (p.C99Mfs*3); c.340C>T (p.R114C) | Het | Inherited | DD | + | + | − | + | − | + | − |
| 3 | F | 3 d | *TREX1* | c.292C>G (p.Q98E)† | Het | *De novo* | Cerebral infarction | + | + | − | − | + | + | + |
| 4 | M | 4 m | *TREX1* | c.294dupA (p.C99Mfs*3); c.−26-1G>A† | Het | Inherited | DD | + | + | − | + | + | + | + |
| 5 | F | 1 y | *TREX1* | c.302A>G (p.D101G)†; c.536T>C (p.L179P)† | Het | Inherited | Fever, seizures | + | − | + | − | + | + | − |
| 6 | M | 3 m | *TREX1* | c.294dupA (p.C99Mfs*3) | Het | Unknown‡ | DD | + | + | − | + | + | + | + |
| 7 | M | 8 m | *IFIH1* | c.2159G>A (p.R720Q) | Het | *De novo* | DD | + | + | − | + | + | − | + |
| 8 | M | 6 m | *IFIH1* | c.2336G>A (p.R779H) | Het | *De novo* | DD | + | + | − | + | + | + | + |
| 9 | M | 6 m | *IFIH1* | c.2922C>G (p.H974Q)† | Het | Inherited | DD | + | + | − | + | + | + | + |
| 10 | M | 14 m | *RNASEH2A* | c.229delG (p.E77Kfs*37)†; c.857G>T (p.R286L)† | Het | Inherited | Regression | + | + | − | + | + | + | − |
| 11 | F | 5 m | *RNASEH2A* | c.370C>T (p.L124F)†; c.872G>A (p.R291H)† | Het | Inherited | DD | + | + | − | + | + | + | + |
| 12 | F | 4 m | *RNASEH2B* | c.172C>T (p.Q58*); c.263C>G (p.A88G) | Het | Inherited | DD | + | + | − | + | + | − | + |
| 13 | F | 3 m | *RNASEH2C* | c.218_219delTG (p.V73Gfs*32)†; c.434G>T (p.R145L)† | Het | Inherited | DD | + | + | − | + | − | − | + |
| 14 | F | 3 y | *SAMHD1* | c.428G>A (p.R143H) | Hom | Inherited | Papule-like rash | + | + | − | + | − | + | + |
| 15 | M | 9 m | *ADAR* | c.3019G>A (p.G1007R) | Het | *De novo* | DD | + | + | − | + | + | + | + |

†The variant is novel.

‡Patient 6 received individual whole exome sequencing, and the genotypes of his parents were unknown.

Abbreviations: CA, cerebral atrophy; d day; DD, developmental delay; ES, epileptic seizures; F, female; Het, heterozygous; Hom, homozygous; IC, intracranial calcification; M, male; m, month; y, year.

14 patients (93.3%), microcephaly in 11 patients (73.3%), and language delay in 11 out of 14 patients (78.6%). Three patients (Patients 5, 10, and 15) had a history of normal development but experienced developmental regression after respiratory or gastrointestinal infections. Patient 5 presented with epileptic seizures, and the electroencephalogram results showed generalized spike-and-slow-wave discharges in bilateral leads, along with irregular slow waves in the bilateral posterior-temporal leads. Patient 3 showed neonatal cerebral infarction 3 days after birth manifesting as reduced responsiveness and seizures. All patients underwent a Developmental Quotient (DQ) assessment, with DQ scores ranging from 33 to 75. Four patients (26.7%) presented with sleep

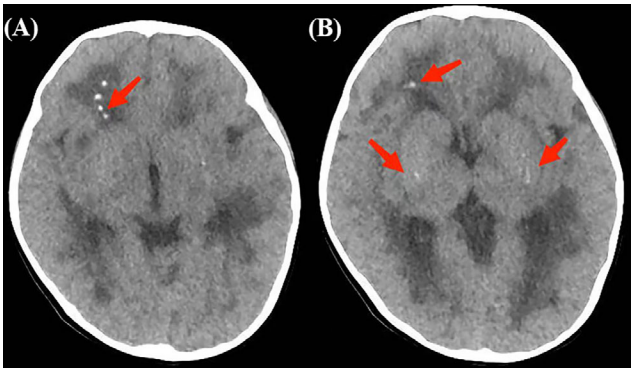


**FIGURE 1** Computed tomography findings in Patient 15. Computed tomography showed spot calcification (red arrows) of basal ganglia (A), frontal lobes, and parietal lobes (B).

disorders, mostly characterized by sleepiness. Patient 11 exhibited sleep-wake cycle disturbance, with episodes of continuous sleep lasting 2–3 days followed by periods of wakefulness lasting 2–3 days, occurring approximately once a month.

Non-neurological symptoms were observed in a minority of cases, including skin lesions in four patients, recurrent (sterile) fevers in three patients, increased liver function in two patients, large vessel disease in one patient, and joint contracture in one patient.

All patients had normal levels of white blood cells, red blood cells, neutrophil and lymphocyte counts, ammonia, lactic acid, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Five patients were tested for antinuclear antibodies, anti-double-stranded DNA, antineutrophil cytoplasmic antibodies, rheumatoid factors, and thyroid function tests, all of which returned normal results. Three patients (Patients 5, 10, and 11) with recurrent fever received a CSF test and only Patient 11 showed elevated white blood cells, monocytes, and CRP levels.

### Neuroimaging findings

All patients received brain computed tomography (CT) and magnetic resonance imaging (MRI). Intracranial calcification was observed in 13 patients (86.7%), with seven showing limited calcification in the basal ganglia and six exhibiting calcification in both the basal ganglia and white matter. The calcifications typically appeared as spot-like lesions, predominantly bilateral in the basal ganglia and unilateral in the white matter (Figure 1). Cerebral atrophy manifested in 11 patients (73.3%), characterized by bilateral ventriculomegaly. White matter involvement was observed in 11 patients (73.3%), predominantly affecting bilateral and affected cortex and deep white matter. Leukoencephalopathy mainly occurred in the frontal lobe, but the white matter at the centrum semiovale and lateral ventricles were also affected. Brain cysts were found in two patients and delayed myelination of the white matter was found in another two patients (Figure 2). Moreover, six patients received spinal MRI, and 3 patients received brain magnetic resonance angiography and magnetic resonance venography; all results were normal.

### Genetic findings

Nineteen variants were identified in seven AGS-associated genes, including *TREX1* in 6 patients (40.0%), *IFIH1* in three patients (20.0%), *RNASEH2A* in two patients (13.3%), and *RNASEH2B*, *RNASEH2C*, *SAMHD1*, and *ADAR* each in one patient (6.7%), respectively (Table 1). Four variants were *de novo*, and 14 were inherited. There were two recurrent variants in *TREX1*, including c.294dupA (p.C99Mfs*3) in four patients and c.–26-1G>A in 2 patients, respectively. Eleven variants were novel, including eight missense variants, two frameshift variants, and one splicing variant.

### Treatment and follow-up

Two patients with *TREX1* mutations with rashes were treated with hormones (7.5 mg/d) and tofacitinib (5 mg/d). While the rashes subsided after one month of treatment, there was no significant improvement in muscular tension, motor skills, or language development during the 8- and 6-month follow-ups, respectively. The remaining 13 patients did not undergo any immunotherapy due to normal inflammatory indicators such as CRP and ESR. All patients received rehabilitation treatment for language and motor skills. Despite being followed up for 5–50 months (average 21 months), all patients exhibited persistent language and motor developmental delays.

### Literature review

To get comprehensive insights into AGS in China, we searched PubMed using the term "AGS AND China," and Wanfang/CNKI databases using the term "AGS" from January 1984 to May 2023. After excluding incomplete clinical data, basic studies, and review articles, 24 articles with data on 44 patients were identified.[16–39] Adding our 15 patients, a total of 59 Chinese patients were diagnosed with AGS. We summarized the genetic mutations in these children. Among the 59 patients, 21 (35.6%) had mutations in *TREX1*, followed by 13 (22.0%) in *RNASEH2C* and *IFIH1* each, four (6.8%) in *RNASEH2A* and *ADAR* each, and two (3.4%) in *RNASEH2B* and *SAMHD1* each.

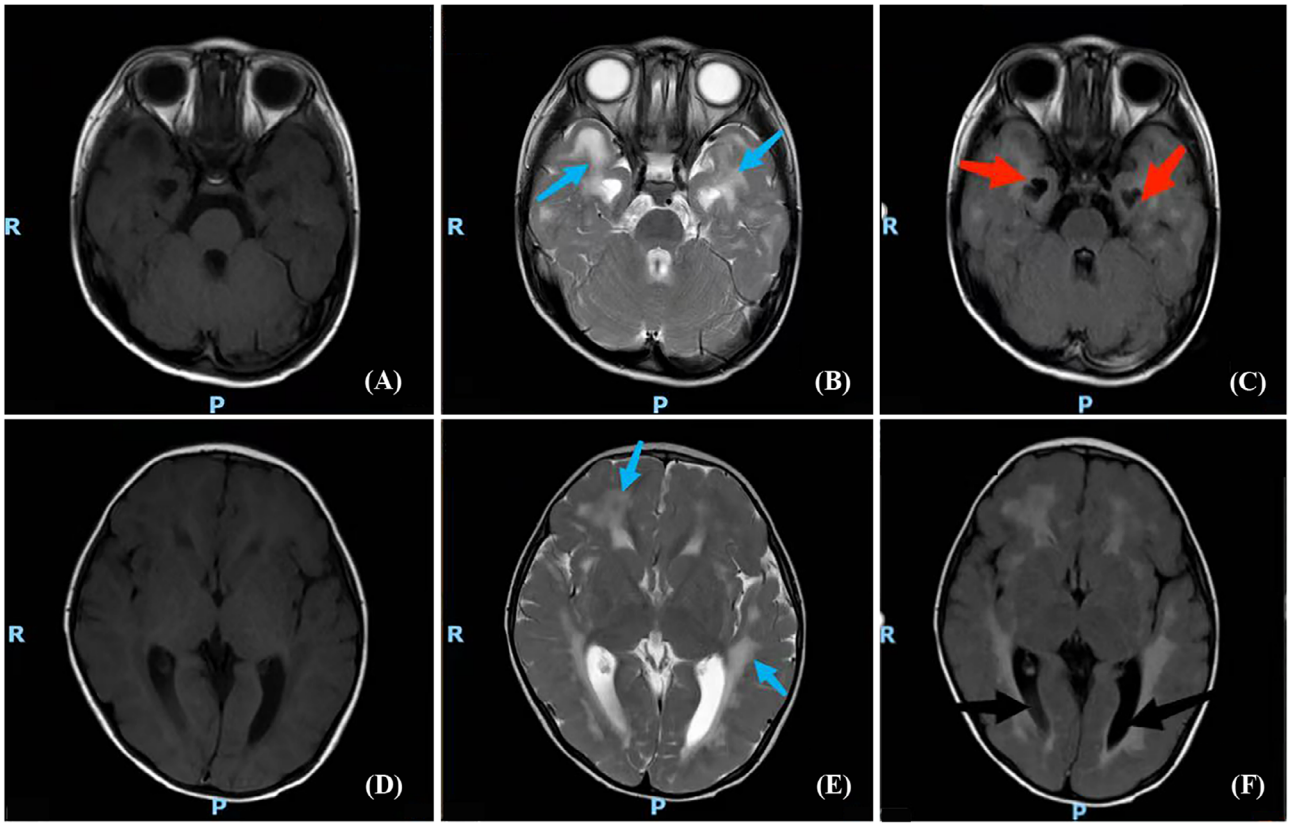


**FIGURE 2** Magnetic resonance imaging (MRI) findings in Patient 6. Brain MRI showed bilateral white matter involvement in the cerebral hemisphere (blue arrows), ventriculomegaly (black arrows), and subependymal cyst in the temporal horn (red arrows). (A) and (D) showed axial T1-weighted images. (B) and (E) showed axial T2-weighted images. (C) and (F) showed Flair-weighted images.

## DISCUSSION

In this study, we summarized the clinical manifestations and underlying genetic factors in 15 Chinese patients diagnosed with AGS. Neurological symptoms constituted the primary clinical features, including a spectrum of developmental delays, dystonia, and intracranial calcification. Genetic analysis revealed that all patients exhibited mutations involving seven pathogenic genes, in which the most prevalent subtype was associated with mutations in the *TREX1* gene.

AGS can be classified based on the time of onset: prenatal-onset, infantile-onset, and late-onset AGS (>12 months). The developmental milestones of AGS patients vary widely, ranging from quadriplegia and severe intellectual disability to spastic paraplegia and preserved cognitive function. The age of onset and disease progression in AGS were associated with specific affected genes. In this study, six patients with *TREX1* mutations had an average onset age of 7 months, which was earlier than the overall average onset age of all patients (8.8 months). Notably, the patient with *SAMHD1* mutation had the latest onset age at 3 years old. The average DQ score of the six patients with *TREX1* mutations was 44.5, while the average DQ score of 62.1 for the other nine patients. The patient with *ADAR* mutation achieved a DQ score of 75, representing the most favorable developmental milestone. Compared to AGS patients with a mutation in other genes, patients with *TREX1* mutation were more inclined to have an earlier onset age and poorer developmental milestones. This aligns with the previous report.[40,41]

AGS typically presents severe neurological symptoms such as developmental delay, moto regression, dystonia, intracranial calcification, and brain atrophy. The neurological symptoms observed in our patients were consistent with the previous reports.[42] In this study, white matter abnormality was found in 83.3% (5/6) patients with *TREX1* mutations, and the two patients who had brain cysts also carried *TREX1* mutations, indicating that white matter abnormality and deep white matter cysts were associated with mutations in *TREX1*.[42]

A total of nine genes have been associated with AGS. Crow et al.[9] conducted a large cohort of AGS in Europe and found that the most common mutation was in *RNASEH2B* (36%), followed by *TREX1* (22%), *SAMHD1* (13%), *RNASEH2C*

(12%), *ADAR* (6%), *RNASEH2A* (5%), *IFIH1* (3%). A study conducted in Arabia revealed that *RNASEH2B* was also the most common mutation (54.2%), followed by *RNASEH2A* (20.8%), *RNASEH2C* (8.3%), *SAMHD1* (8.3%), *TREX1* (4.2%), and *IFIH1* (4.2%).[43] Our study showed that *TREX1* (40.0%) was the most frequent gene, followed by *IFIH1* (20.0%). Among 59 Chinese children, *TREX1* (35.6%) was also the most frequent gene, followed by *RNASEH2C* (22.0%) and *IFIH1* (22.0%). These results suggested a different predominant type of AGS between ethnicities.

*TREX1* and *ADAR* were reported to have two inherited patterns: autosomal recessive and autosomal dominant.[11] Dominant TREX1-related AGS were all reported to be missense mutations, and mostly *de novo*. Notably, in our study, Patient 6 presented typical AGS symptoms, and WES revealed a heterozygous c.294dupA (p.C99Mfs*3) mutation in *TREX1*. The c.294dupA mutation has been reported in several AGS patients with homozygous or compound heterozygous conditions, suggesting its involvement in the autosomal recessive pattern.[9,44] In our cohort, c.294dupA was also detected in four unrelated patients, accounting for 66.7% (4/6) of those with *TREX1* variants. Among the 59 Chinese children with AGS, c.294dupA was detected in six out of the 21 patients who had *TREX1* mutations (Table S1). Previous reports have not designated c.294dupA as a hotspot mutation, its prevalence in Chinese AGS patients warrants further investigation. Variant c.194G>A (p.G65D), c.434G>T (p.R145L) in *RNASEH2C* and c.2336G>A (p.R779H) in *IFIH1* are also hotspot variants in the Chinese population (Table S1). A *de novo* heterozygous mutation c.3019G>A (p.G1007R) in *ADAR* was found in Patient 15. This mutation is located in the adenosine deaminase region of the protein and has been reported as a classic dominant negative mutation in several AGS patients with *ADAR* mutation.[5]

AGS cannot be cured currently, and treatments primarily aim to manage systemic and organ inflammation to reduce the progression of organ damage. The treatment for AGS mainly targets type I interferon signaling pathways.[45,46] Two of our patients were treated with tofacitinib and glucocorticoids, resulting in significant improvement of skin lesions. However, neurological function showed limited improvement. Neurological damage in AGS is irreversible, therefore, early diagnosis and treatment are essential.

In summary, the diagnosis of AGS depends on clinical features and genetic testing. Key neurological features include developmental delay, dystonia, microcephaly, brain calcification, and leukodystrophy. In the Chinese population, *TREX1* mutations are the most prevalent genetic anomaly, providing a start for further genetic investigation into AGS among Chinese children.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

**How to cite this article:** Zhang S, Zhang W, Ding C, Ren X, Fang F, Wu Y. Neurophenotype and genetic analysis of children with Aicardi-Goutières syndrome in China. *Pediatr Investig*. 2024;8:193–200. https://doi.org/10.1002/ped4.12428