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Case Report

Tocilizumab effectively reduces flares of hyperimmunoglobulin D syndrome in children: Three cases in China

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ABSTRACT

Hyperimmunoglobulin D syndrome (HIDS) is a rare but severe autoinflammatory disease with a poor prognosis if not diagnosed and treated early. Here, we report three cases of HIDS in children with typical clinical manifestations and a clear genetic diagnosis. Patient 1 experienced recurrent fever flares with a maculo-papular skin rash. Patient 2 presented with periodic fever, cholestasis, lymphadenopathy, aphthous stomatitis, arthralgia, and abdominal pain and underwent surgery for intestinal obstruction. Patient 3, a sibling of patient 2, presented with periodic fever and underwent a surgical procedure for intussusception. All three patients were administered interleukin (IL)-6 receptor antagonist (tocilizumab). The results showed that tocilizumab effectively reduced inflammatory flares. Early diagnosis and tocilizumab treatment are effective at improving the prognosis of HIDS patients.

1. Introduction

Hyperimmunoglobulin D syndrome (HIDS) is a rare autoinflammatory disease with early onset after birth. The clinical features of HIDS include recurrent periodic fever, rash, abdominal pain, diarrhea, aphthous stomatitis, arthralgia, lymphadenopathy, and elevated serum polyclonal immunoglobulin D (IgD) [1,2]. HIDS is categorized as classic or variant type. Classic HIDS is caused by homozygous or compound heterozygous mutations in the mevalonate kinase (MVK) gene, whereas variant HIDS meets the clinical criteria of HIDS; however, no MVK gene mutation has been found, and there is no clear underlying genetic variant [2].

At present, the goals of HIDS treatment are to reduce symptoms, improve patient quality of life, and avoid unnecessary antibiotics and surgical treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line drugs used to treat HIDS and relieve fever. Other treatments include glucocorticoids; biological agents, such as interleukin 1(IL-1) receptor antagonists; interleukin 6 (IL-6) receptor antagonist (tocilizumab); tumor necrosis factor α receptor antagonists; and stem cell transplantation [3–7].

To date, several HIDS cases have been reported worldwide, mostly among Caucasian populations [8–13]. These cases have rarely been described in China, barring three Chinese articles involving three patients [14–16]. With the approval of the hospital ethics committee (approval number: 2023-115A01) and the permission of each participant's legal guardian, we reported three cases of HIDS in China and retrospectively analyzed the clinical characteristics, genetic variants, and therapeutic interventions. Our case series included a new genetic variant of the MVK gene and detailed clinical features of HIDS in a Chinese patient cohort. The detailed clinical and laboratory data of the three patients are shown in Table 1, the specific event history is presented in Fig. 1, and the pedigrees of the three patients are displayed in Fig. 2.

2. Case presentation

Patient 1 (P1; male) was born at 39^{+5} weeks of gestation with a birth weight of 3.1 Kg to a 28-year-old Chinese mother. His parents had no family history of consanguinity or hereditary diseases. At 36 weeks of maternal pregnancy, routine prenatal examinations revealed infection with Group B *Streptococcus* (GBS). Cefazolin was administered as an anti-infection agent. P1 was delivered naturally with a normal Apgar score; however, the amniotic fluid was grade III turbid at birth, and P1 was admitted to the neonatal department for further treatment. During

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Table 1
Clinical features, biochemical detection index and therapy of HIDs patients ($n = 3$).

	patient 1	patient 2	patient 3
Country of birth	China	China	China
Gender	Male	Female	Male
Ethnicity	Han	Han	Han
birth weight (Kg)	3.1	2.0	1.8
Age at onset	8 days	3 days	4 days
Age at diagnosis	6 months	30 months	12 months
Clinical features	recurrent fever rash mild delay in movement cough lymphadenopathy hepatomegaly splenomegaly	recurrent fever cholestasis diarrhea abdominal pain rash cough pneumonia Joint swelling arthralgia Bloody stool chronic superficial gastritis and colitis	fever bloody stool intussusception abdominalgia
Biochemical detection index			
Hb (110-140 g/dl)	82 ↓	104 ↓	92 ↓
Red blood cell count(4–4.5 × 10^12/L)	3.79 ↓	4.54 ↑	5.26 ↑
White blood cell count (4.8–14.6 × 10^9/L)	16.6 ↑	22.6 ↑	21.35 ↑
neutrophils (0.8–6.4 × 10^9/L)	8.57 ↑	12.93 ↑	13.32 ↑
platelet count (100–300 × 10^9/L)	513 ↑	459 ↑	676 ↑
hsCRP (0–8.2 mg/L)	51.65 ↑	35.3 ↑	12.65 ↑
ESR (0–15 mm/h)	65 ↑	92.0 ↑	35 ↑
IL-6(0–8.88 pg/ml)	4.63–176 ↑	4–674 ↑	not done
IL-8(0–15.71 pg/ml)	8.92	1.74	not done
IL-12p70 (0–6.90 pg/ml)	1.68	1.25	not done
IgG (5–10.6 g/L)	4.8	14.8 ↑	not done
IgA (0.14–1.14 g/L)	0.99	1.63 ↑	not done
IgM (0.4–1.28 g/L)	1.74	2.21 ↑	not done
IgE (0–200 IU/ml)	1070 ↑(after therpy , 455)	14	52
IgD(<132.1 mg/L)	<13.2	<13.2	<13.2
Urinary mevalonate	negative	negative	negative
Drug therapy	ibuprofen, antbiotics, tocilizumab, IVIG	ibuprofen, antbiotics, tocilizumab, IVIG, canakinumab, glucocorticoid, methotrexate	ibuprofen, antbiotics, tocilizumab

hospitalization, an increase in the hypersensitive C-reactive protein (hsCRP) level was observed (12–21 mg/L, reference value: 0–8.2 mg/L) after a 6-day course of intravenous penicillin drip. At the second week after birth, the infant experienced recurrent fever with a peak temperature of 38.7 °C, shortness of breath, foaming at the mouth, and an increase in hsCRP level to 87 mg/L. After receiving anti-infection treatment, the fever subsided, but his hsCRP level remained elevated (26 mg/L). After discharge from the hospital, recurrent fever occurred every 1–2 weeks and subsided with antibiotics. At 6 months of age, P1 was admitted to our hospital for 2 days with fever and cough. Physical examinations revealed lymphadenopathy, hepatomegaly, and splenomegaly. Scattered congestive maculopapules appeared on the forehead and upper limbs. Laboratory examination revealed increased acute inflammatory phase markers, as follows: hsCRP 75 mg/L; erythrocyte sedimentation rate (ESR) 27 mm/h (reference value: 0–15 mm/h); white blood cell count, 16.6 × 10^9/L (reference value: 4.8–14.6 × 10^9/L); neutrophil count, 72% (reference value: 34%–58%); IgD, <13.2 mg/L (reference value: ≤132.1 mg/L); immunoglobulin (Ig) G, 4.8 g/L (reference value: 5.0–10.6 g/L); IgA, 0.99 g/L (reference value: 0.34–1.38 g/L); IgM, 1.74 g/L (reference value: 0.44–1.44 g/L); IgE, 1070 IU/mL (reference value: 0–100 IU/mL); and normal complement C3 and C4 (Table 1). Chest radiography indicated bronchopneumonia and increased specific milk protein IgE, while urine gas chromatography–mass spectrometry (GS-MS) analysis revealed a small amount of mevalonate. After treatment with antibiotics and aerosolized water for 3 days, the fever subsided, and re-examination revealed that the urine was negative for mevalproic acid (Table 1). Whole-exon gene sequencing revealed the MVK (NM 000431.4) compound heterozygous variants c.656G > A (p.Gly219Glu) and c.863C > T (p. Pro288Leu) inherited from the mother, and c.75C > T (p. Gly 25 =) inherited from the father (Table 1; Fig. 2A). Based on the clinical manifestations and genetic variants, P1 was diagnosed as HIDS with a normal serum IgD level. Considering the lack of an IL-1 receptor antagonist in mainland China, 12 mg/kg tocilizumab was administered every 2 weeks as an anti-inflammatory treatment. It was gratifying to note that the use of tocilizumab significantly reduced and interrupted the fever flares. At 2 years of age, P1 weighed 10 kg and had a height of 82 cm. His motor and mental development were normal. The levels of ESR, hsCRP and IgD were normal. His rash had reduced, and the sizes of the liver and spleen were normal.

Patient 2 (P2; female) was delivered via cesarean section owing to premature rupture of membranes and breech presentation at 32^{+3} weeks gestation. There was no history of hereditary disease or consanguinity in the family, but her mother had a history of gestational diabetes during her pregnancy. Bilateral ovarian cysts, umbilical cord edema and placental enlargement were discovered during the cesarean section. The birth weight was 2.0 Kg. Fever occurred 3 days after birth, and neonatal infection was considered. Radiography indicated neonatal pneumonia, and increased hsCRP and white blood cell levels were noted. Antibiotic and ventilator-assisted ventilation were administered, and the fever subsided. At the age of 2 months, Patient 2 was diagnosed with cholestasis and biliary atresia and underwent Kasai portoenterostomy at the local hospital. Patient 2 recovered well after surgery. At the age of 5 months, fever occurred repeatedly every 3–5 weeks and was accompanied by rash, diarrhea, and recurrent cough. P2 was hospitalized multiple times for pneumonia and diarrhea accompanied by fever. At the age of 24 months, the frequency of fever increased to once every 2 weeks, and two febrile convulsions occurred. Electroencephalogram (EEG), head magnetic resonance imaging (MRI), serum IgD and urine mevalamic acid were normal. ESR and hsCRP levels increased. Fever was managed and temporarily alleviated, yet it tended to recur easily despite treatment with ibuprofen and antibiotics. When P2 was 30 months old, she experienced swelling and pain in both the knee and left ankle joints with limited movement. Physical examination revealed a body weight of 12.8 kg and height of 85 cm. The pharynx was congested with enlarged lymph nodes in the neck (1.5 cm × 1.5 cm). Both knees

were swollen and tender with a negative floating patellar test. The left ankle joint was slightly swollen and tender. Abdominal and cervical ultrasound revealed enlarged bilateral cervical lymph nodes and splenomegaly. Chest computed tomography (CT) revealed bronchopneumonia. MRI revealed mild synovial inflammation in the sacroiliac joints and mild synovial inflammation in the knee joints, with a small amount of fluid in the joint cavity and superior patellar capsule. The peripheral blood analysis revealed the following results: white blood cells, 22.6 $\times$ 10^9/L; neutrophil ratio, 65%; hemoglobin (Hb), 104 g/L; hsCRP, 35.3 mg/L; IgD, <13.2 mg/L; IgG, 14.80 g/L (reference value: 3.82–10.58 g/L); IgA, 1.63 g/L (reference value: 0.14–1.14 g/L); IgM, 2.21 g/L (reference value: 0.4–1.28 g/L); IgE, 14 IU/mL (reference value: 0–60 IU/mL); complement C3, 1.71 g/L (reference value: 0.8–1.5 g/L); and complement C4, 0.29 g/L (reference value: 0.13–0.43 g/L). Urinary GS-MS revealed no mevalonate (Table 1). Detection of cytokine levels indicated increased IL-6 levels but normal with IL-12p70 and IL-8 (Table 1). After admission, P2 exhibited symptoms of diarrhea, bloody stool with mucus, and intermittent abdominal pain without fever. Subsequent gastroscopy and colonoscopy examination revealed chronic superficial gastritis and colitis. Whole-exon gene sequencing revealed compound heterozygous variants c.442G > A (p.Ala148Thr) from the father and c.925G > A (p.Gly309Ser) from the mother in the MVK (NM 000431.4) gene (Table 1; Fig. 2B). P2 was diagnosed with HIDS with normal serum IgD. Tocilizumab was administered once every 2 weeks for 4 weeks at 12 mg/kg, but fever flares occurred, and arthralgia persisted. Later, after we added 1 mg/kg prednisone, the arthralgia and fever were relieved; however, during the process of prednisone reduction, the fever recurred, and the patient's abdominal pain and vomiting returned. Patient 2 was diagnosed with intestinal obstruction by gastrointestinal angiography and abdominal CT. The surgical diagnosis was adhesive intestinal obstruction accompanied by edema of the intestinal wall and enlargement of mesenteric lymph nodes. Later, she underwent surgical treatment for intestinal adhesiolysis. Canakinumab (4 mg/kg) was subcutaneously injected twice every 4 weeks outside the hospital but was ceased after the second injection owing to lung infection. After infection control, 12 mg/kg tocilizumab was administered every 2–4 weeks, resulting in an extended period without fever, alleviation of joint swelling, or pain relief; however, a low dose of prednisone was still needed, and methotrexate was added to control the arthralgia. At present, P2 is 5 years old, and she is receiving oral prednisone and methotrexate and intravenous infusion of tocilizumab every 2–4 weeks.

Patient 3 (P3; Male) is P2's brother. P3 was delivered at the 30th week of pregnancy due to premature rupture of membranes by induced labor, with a birth weight of 1.8 kg. Four days after birth, P3 developed a fever and recovered after antibiotics. Recurrent fever occurred 3 months after birth (interval of 4–8 weeks) and increased in frequency after his age of 12 months (interval of 2–3 weeks). The levels of ESR, hsCRP and interleukin-6 increased during the onset of fever (Table 1), and fever can be controlled by ibuprofen and antibiotics. No mevalonate was detected. However, abdominal pain and Jam-like bloody stool appeared when the patient was 1.8 years old, and a diagnosis of intussusception was confirmed by gastrointestinal ultrasound examination. After the failure of air pressure enema treatment, P3 underwent surgical resection for intussusception. The MVK gene analysis revealed the same compound heterozygous variants as P2, c.442G > A (p.Ala148Thr) and c.925G > A (p.Gly309Ser) (Table 1; Fig. 2B), and P3 was diagnosed with HIDS. According to the treatment experience of his sister (P2), P3 promptly began receiving tocilizumab treatment at a dosage of 12 mg/kg every 2–4 weeks. By the time he was 2.7 years old, this treatment effectively controlled the inflammation without causing arthralgia or abdominal pain.

3. Discussion

HIDS is a rare autoinflammatory disease. Here, we reported three patients with HIDS and identified a new genetic variant of the MVK gene, the local variant c.656G > A (p.Gly219Glu), which has possible pathogenic implications. Furthermore, tocilizumab had a positive impact on alleviating fever flares in HIDS patients.

Mevalonate kinase deficiency (MKD) includes hyper-IgD syndrome (HIDS) and mevalonate aciduria (MA), which are caused by genetic mutations in MVK [11,17]. According to the Infevers website (https://infevers.umai-montpellier.fr/web/search.php?) for auto-inflammatory disease registration, >200 mutation sites in the MVK gene were identified. Among them, c.655G > T (p.Gly219Trp) in MVK gene, was identified as a pathogenic agent [12,13]. Since both the genetic loci of c.655G > T (p.Gly219Trp) and c.656G > A (p. Gly219Glu) encode the 219th protein of MVK, c.656G > A (p. Gly219Glu), which was frstly found in this study, was most likely to be a pathogenic site. Of the five MVK gene variants identified in the three patients in this study, c.75C > T (p.Gly25=), c.442G > A (p.Ala148Thr) and c.925G > A (p.Gly309Ser) had been confirmed to be pathogenic and associated with HIDS [18–20]. While the c.863C > T (p. Pro288Leu) was uncertain but may be likely pathogenetic and requires further verification [21]. In this study, P1's

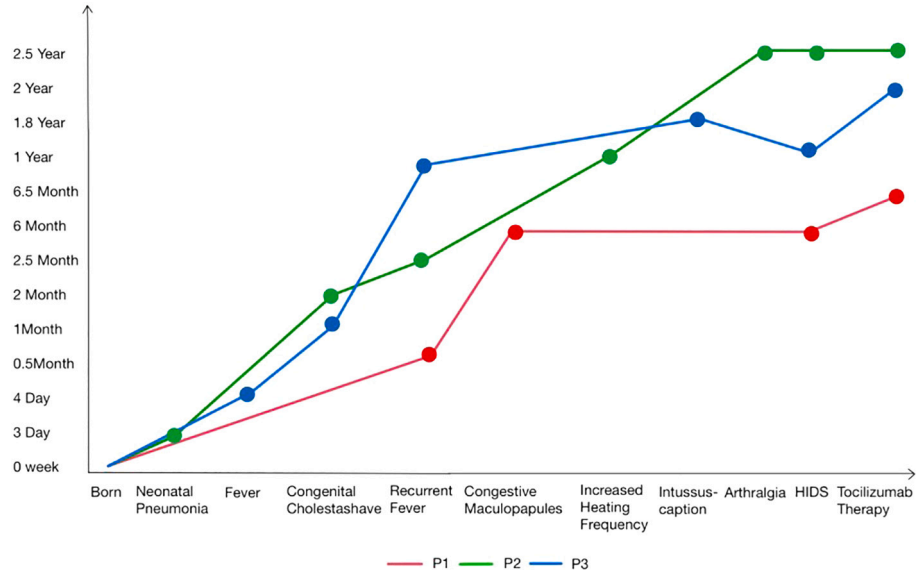

Fig. 1.. Time chart of clinical presentations and treatment process.

sister and P1's mother were carriers of the MVK genetic variants c.656G > A (p. Gly219Glu) and c.863C > T (p. Pro288Leu) (Fig. 2A), and they did not show any clinical manifestations of HIDS, with normal serum IgD and urinic mevalonate. Therefore, the probability of pathogenic variants of P1 were inferred from high to low as: c.656G > A (p. Gly219Glu) and c.75C > T (p.Gly25=); or c.863C > T (p. Pro288Leu) and c.75C > T (p. Gly25=); or even a combinition of c.656G > A (p. Gly219Glu), c.863C > T (p. Pro288Leu) and c.75C > T (p.Gly25=), which need to be further verified. P2 and P3 are siblings with compound biallelic MVK mutations, local loci of c.442G > A (p.Ala148Thr) and c.925G > A (p.Gly309Ser), which had been identified as pathogenic with HIDS in previous researches [19,20].

HIDS is characterized by elevated inflammatory marker levels and involvement of multiple systems. The mutation of the MVK biallelic gene can interfere with the MVK synthesis pathway, which is the key enzyme in the mevalonate biosynthesis pathway. This interference leads to insufficient activity and inhibits the synthesis of cholesterol and nonsteroidal isoprenoids [11,17,22]. Studies on HIDS patients and mouse models with MVK gene mutations have shown that the release of the proinflammatory cytokine IL-1 in peripheral blood or signal transduction drive an increase in circulating IL-1β levels [22–24]. Therefore, IL-1 receptor antagonists, such as canakinumab and anakinra, are the best therapies for patients with HIDS. Ozlem et al. reported a case in which an adult male HIDS patient presented with recurrent fever and arthritis and successfully responded to canakinumab but not to anakinra [25]. However, some HIDS patients may not respond to IL-1 receptor antagonists but may instead respond to the IL-6 receptor (IL-6R) antagonist tocilizumab, the tumor necrosis factor α receptor antagonist etanercept or stem cell transplantation [3–7,26,27]. Moreover, adverse drug reactions such as infections may be another aspect of deactivation with IL-1 receptor antagonists [28–32]. Sanz et al. reported the case of a 22-year-old woman who was diagnosed with MKD. After receiving canakinumab treatment, she developed paradoxical purulent hidrosis caused by canakinumab, but her condition was controlled by anakinra and ustekinumab [31]. Since IL-6 is a major pro-inflammatory cytokine and play a key role in immune activation and inflammation [33], IL-6 inhibition may be a compelling strategy for controlling inflammatory diseases. The humanized IL-6R antibody, tocilizumab, has been developed and approved for use in asrheumatoid arthitis (RA), a chronic autoimmune disorder, and other rheumatologic conditions [34,35]. However, adverse events due to tocilizumab have been reported by recent data, the most common of which are infection and abnormal laboratory findings including neutropenia, thrombocytopenia, dyslipidemia, and transaminase (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) elevations [35]. In addotion, gastrointestinal perforation is an uncommon but serious side-effect in tocilizumab therapy due to the impaired IL-6 signaling, which also plays a role in maintaining intestinal health [35,36]. In this study, P1 and P3 manifested recurrent fever, elevated inflammatory indices and no joint swelling or arthralgia and showed good responses to tocilizumab. For P2, in addition to her recurrent fever, she also exhibited multiple system involvement, abdominal symptoms, arthritis, infections, etc. Initially, tocilizumab and canakinumab failed to effectively control her fever, joint swelling and arthralgia. Last, tocilizumab, prednisone and methotrexate stabilized her condition without causing fever or arthritis.

There are limited data on the use of tocilizumab for the treatment of HIDS. The rationale for using tocilizumab is closely correlated with the elevation of IL-6 during acute episodes of HIDS, during which time hsCRP and serum phospholipase A2 (PLA2) levels increase significantly. PLA2 has been found to spread tissue damage through membrane digestion and release cytotoxic fatty acids, leading to clinical manifestations of inflammatory reactions such as HIDS, arthritis, and vasculitis. An IL-6 receptor antagonist (tocilizumab) was reported in several case reports on HIDS [4,5]. Due to the limited availability of IL-1 receptor antagonists, the three HIDS patients we reported were treated with tocilizumab, which effectively reduced inflammatory flares. According to previous reports, hematopoietic stem cell transplantation is also an effective method for treating severe HIDS [6,7]. However, severe symptoms related to transplantation may be life-threatening [37]. Moreover, there may be recurrence after transplantation [38]. However, additional materials are needed to determine the effectiveness of hematopoietic stem cell transplantation and to evaluate the severity of the patient's condition, presence of genetic mutations, and donor compatibility.

Additionally, the reference values for the laboratory tests in this paper are listed according to the reference ranges of the test data from our hospital's laboratory. There are also references in the literature regarding the reference ranges of IgD levels for different ages, and these ranges may vary among different populations [39].

4. Conclusion

The three cases of HIDS in children reported here in China exhibited typical clinical manifestations with definite genetic diagnosis. Tocilizumab may be an option when anti-IL-1 receptor antagonists are unavailable or ineffective. Moreover, the greater the effect of IL-6 blockade is, the more effective the agent is.

The limitations of this study include the lack of additional protein expression information and functional verification of the gene mutations. In addition, comprehensive analyses of the changes in peripheral blood cytokines (such as IL-6, IL-1, and IL-1β) are lacking.

Ethics statement

The studies involving human participants were reviewed and approved by the hospital ethics committee (approval number: 2023-115A01) of Guangzhou Women and Children's Medical Center. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

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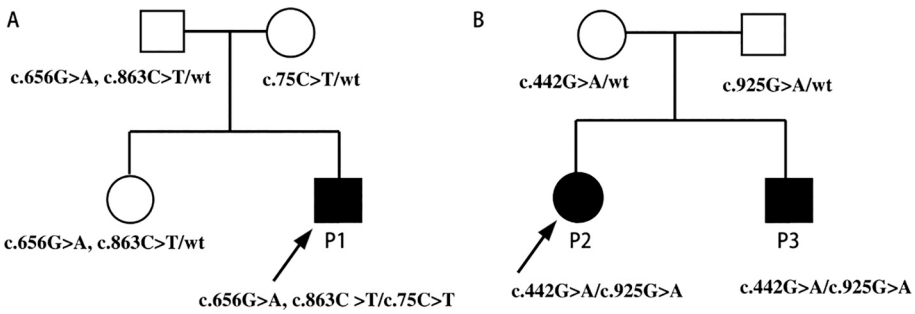

Fig. 2.. The pedigree of three patients with HIDS.

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CRediT authorship contribution statement

Chenxi Li: Writing – original draft. **Xiangyuan Chen:** Writing – review & editing, Data curation, Conceptualization. **Xilong Tang:** Writing – review & editing, Supervision. **Huasong Zeng:** Supervision, Conceptualization. **Juan Zhou:** Data curation, Conceptualization.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Data availability

The authors acknowledge that the data presented in this study must be deposited in an appropriate way before publication. The original contributions presented in the study are included in the article/supplementary material (DOI:10.17632/wgs5dr34f4.1); further inquiries can be directed to the corresponding author.

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