A Novel Mutation of Notch homolog protein 2 gene in a Chinese Family with Hajdu-Cheney Syndrome

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Hajdu-Cheney syndrome (HCS) is a rare disorder which is characterized by developmental delay, craniofacial anomalies, congenital heart defects, hearing deficit, polycystic kidneys, and bone abnormalities, including progressive osteoporosis, acroosteolysis, wormian bones, and abnormal bone fractures.[1] Truncating mutations in Notch homolog protein 2 gene (*NOTCH2*) are the principal cause of HCS. Here, we described the clinical manifestations, laboratory examinations, and molecular genetic analysis and evaluation of immunological function in a Chinese family with a novel mutation in *NOTCH2*.

Patient 1 (son) was a 4-year-old Chinese boy. He was diagnosed with patent ductus arteriosus (PDA) and pneumonia 4 days after he was born. At 1 year old, he presented with the symptoms of acroosteolysis which was not taken seriously. At 1 year and 9 months old, he was diagnosed with pulmonary hypertension and ventricular septal defect. He received transcatheter occlusion of PDA immediately. At 3.5 years old, his pulmonary artery pressure was 90 mmHg after mild exercise and decreased to 68 mmHg after taking bosentan for 2 months. He had repeated infections, about three times a year since he was born. At 4 years old, he presented with a large anterior fontanelle, low-set ears, bushy eyebrows, synophrys, shallow orbit, mild proptosis, hypertelorism, flat nasal bridge, micrognathia, downslanted palpebral fissures, short neck, stubby fingers, and joint hypermobility [Figure 1a and 1c]; and his immunoglobulin E (IgE) increased (no exact data), but without allergic symptom.

The patient had normal intelligence with a normal height of 100 cm and a little lower weight of 13 kg.[2] Skull radiographs detected wormian bones [Figure 1g and 1h]. No acroosteolysis or brachydactyly of hands was observed [Figure 1e]. His T-Score was −5 (normal value > −1), suggesting that his bone mineral density was far below the expected values for his age.

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Because of his recurrent infection and elevated IgE level, Igs test, IgE radioallergosorbent test (RAST), and lymphocyte subset test were done to evaluate his immunological function. Igs were normal except for elevated level of serum IgE (13,700 U/L; normal value <60 U/L). All of his specific IgE values were 0 in IgE RAST. All lymphocyte subsets including the percentage and absolute count of T, B, and natural killer (NK) cells were normal. The patient's father had similar clinical manifestations, while his mother and his 5-year-old sister were healthy.

Patient 2 (father) was a 26-year-old Chinese man. He was also diagnosed with PDA when he was born but had never received operation. He had recurrent diarrhea for unknown reason every 3 months when he was a child. At 7 years old, he began to present facial abnormities mentioned above [Figure 1b]. At the same time, his teeth turned to fall, his hearing gradually decreased, and his fingers became short and thick [Figure 1d]. At 20 years old, he felt headache and backache once in a while but never received treatment.

This patient's parents, elder and younger sisters were all healthy. His height was 158 cm and weight was 45 kg, which were both far lower than the average levels.[3] Skull radiographs also detected wormian bones [Figure 1i and 1j]. Anteroposterior radiographs of the hands showed obvious acroosteolysis and osteoporosis [Figure 1f]. Immunological results were normal except for elevated level of serum IgE

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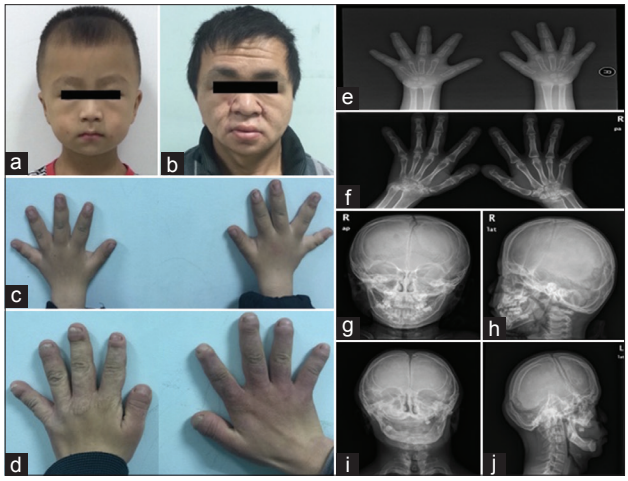

Figure 1: Photographs of the faces in patient 1 (son, a) and patient 2 (father, b) show large anterior fontanelle, bushy eyebrows, synophrys, shallow orbit, mild proptosis, hypertelorism, flat nasal bridge, thin upper lip, micrognathia, downslanted palpebral fissures, and short neck. Photographs of the hands in patient 1 (c) and patient 2 (d) show that most of fingers are short and thick (predominately father's hands). (e and f) Anteroposterior radiographs of the patients' hands show osteoporosis in both father and son, and obvious acroosteolysis in all father's fingers. (g-j) Skull radiographs show that the son had wormian bones in the lambdoidal and coronal sutures (g and h), and the father had wormian bones in the sagittal, coronal, and lambdoidal sutures as well as severe dentition abnormality (i and j).

(5600 U/L). All specific IgE values were 0 in IgE RAST. The lymphocyte subsets including the percentage and absolute count of T, B, and NK cells were also normal.

To detect exact mutation, we performed targeted gene capture combined with next-generation sequencing. The results showed that both patients were a heterozygote for a novel insertion mutation c.6404_6405insTT (p.S2136X) in exon 34 of *NOTCH2*. This mutation of *NOTCH2* was not detected from the mother and sister of patient 1 and 50 unrelated healthy Chinese individuals.

Two patients with *NOTCH2* mutation in this case had most of manifestations reported in the previous study.[4] Immunological features including recurrent infections and elevated level of serum IgE had never been reported in previous studies. However, in this case, both patients had extremely high IgE levels with no allergic symptoms, negative allergen-specific IgE levels, and normal percentage and absolute count of T, B, and NK cells; no evidence supported that their high IgE levels were caused by allergy or other related diseases.

In conclusion, we reported the clinical and radiologic findings of the HCS family with a novel insertion mutation in exon 34 of *NOTCH2*. Immunological features in HCS such as IgE level should be paid more attention by the clinicians to find out whether it is another common characteristic of HCS or only an individual case.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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