A TAIWANESE BOY WITH CONGENITAL GENERALIZED LIPODYSTROPHY CAUSED BY HOMOZYGOUS ILE262FS MUTATION IN THE BSCL2 GENE

Hsiu-Hui Huang,1 Tai-Heng Chen,2,3 Hui-Pin Hsiao,7,8 Chia-Tsuan Huang,1 Cheng-Chu Wang,5 Yü-Huei Shiao,5 and Mei-Chyn Chao4–6

1Department of Family Medicine, 2Division of Pediatric Emergency, Department of Emergency, Divisions of 3Pediatric Neurology and 4Pediatric Genetics, Endocrinology and Metabolism, Department of Pediatrics, and 5Genetic Counseling Center, Kaohsiung Medical University Hospital, and Departments of 6Medical Genetics, and 7Pediatrics College of Medicine, Kaohsiung Medical University, and 8Department of Pediatrics, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung, Taiwan.

Congenital generalized lipodystrophy (CGL) is a rare autosomal recessive disease that is characterized by a near-complete absence of adipose tissue from birth or early infancy. Mutations in the BSCL2 gene are known to result in CGL2, a more severe phenotype than CGL1, with earlier onset, more extensive fat loss and biochemical changes, more severe intellectual impairment, and more severe cardiomyopathy. We report a 3-month-old Taiwanese boy with initial presentation of a lack of subcutaneous fat, prominent musculature, generalized eruptive xanthomas, and extreme hypertriglyceridemia. Absence of mechanical adipose tissue in the orbits and scalp was revealed by head magnetic resonance imaging. Hepatomegaly was noticed, and histological examination of a liver biopsy specimen suggested severe hepatic steatosis and periportal necrosis. However, echocardiography indicated no sign of cardiomyopathy and he showed no distinct intellectual impairment that interfered with daily life. About 1 year later, abdominal computed tomography revealed enlargement of kidneys. He had a homozygous insertion of a nucleotide, 783insG (Ile262fs mutation), in exon 7 of the BSCL2 gene. We reviewed the genotype of CGL cases from Japan, India, China and Taiwan, and found that BSCL2 is a major causative gene for CGL in Asian.

Key Words: BSCL2 gene, congenital generalized lipodystrophy, hepatitis, nephromegaly

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Address correspondence and reprint requests to: Dr Mei-Chyn Chao, Division of Pediatric Genetics, Endocrinology and Metabolism, Department of Pediatrics, Kaohsiung Medical University Hospital, 100 Tzoyu 1st Road, Kaohsiung 807, Taiwan.
E-mail: mcchao@kmu.edu.tw

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different genes (AGPAT2, BSCL2, and CAVEOLIN1) have been identified to underlie this rare disorder, with the first two accounting for about 95% of reported cases [4–7]. CGL due to BSCL2 mutation, designated CGL2, appears to be a more severe disease than that due to AGPAT2 mutation, designated CGL1, with increased prevalence of cardiomyopathy and mild mental retardation [8–10]. Both CGL1 and CGL2 subtypes demonstrate a near-total absence of metabolically active adipose tissue within subcutaneous, intra-abdominal, bone marrow, and intrathoracic sites [10]. However, mechanical adipose tissue in palms, soles, orbits, scalp, and periarticular regions is absent in CGL2 but not in CGL1 [11].

In the present study, we report the clinical phenotype and genetic alterations of a Taiwanese patient with CGL2 and a homozygous Ile262fs mutation in the BSCL2 gene. The cause of nephromegaly in CGL is discussed, and clinical characteristics and genetic alterations in Asian CGL cases are briefly reviewed.

CASE PRESENTATION

A 3-month-old boy was born at term to non-consanguineous Taiwanese parents. He was expected as one of twins, but the other twin died in utero at gestational age 12 weeks. At birth, our patient was referred to our Genetic Counseling Center, where a lack of subcutaneous fat, prominent musculature and generalized eruptive xanthomas were seen (Figure 1). Hepatomegaly with palpable liver at 3 cm below the right costal margin was noticed on physical examination. Biochemical investigations revealed normal liver function (GOT = 44 IU/L, GPT = 34 IU/L), extreme hypertriglyceridemia (7,289 mg/dL), hyperinsulinemia (82.6 μIU/mL), and low serum leptin (0.84 ng/mL). The patient had a normal 46,XY karyotype. Absence of mechanical adipose tissue in the orbits and scalp was revealed by head magnetic resonance imaging. Histological examination of a liver biopsy specimen suggested severe hepatic steatosis (>66%)

![Figure 1. Clinical features of this patient with (A) typical pinched face; (B) lack of subcutaneous fat including buttocks; (C) prominent musculature and hirsutism; and (D) eruptive xanthomas (arrows) on right knee.](image-url)
and periportal necrosis (Figure 2). In addition to a special dietary formula that contained medium to long chain fatty acids, medical treatment with fenofibrate, titrated from 50 mg per day, was given. The eruptive xanthomas gradually diminished and the serum was less lipemic with 217 mg/dL triglycerides. His voracious appetite markedly decreased.

The patient was evaluated every 3 months. He showed neither distinct intellectual impairment nor profound developmental delay that interfered with daily life. Echocardiography indicated no sign of cardiomyopathy and bone age was compatible with his chronologic age. However, abdominal computed tomography (CT) revealed enlargement of kidneys at the age of 1 year 8 months (Figure 3) [12]. Before the age of 17 months, CT scan and periodically performed abdominal sonography had only revealed improving hepatomegaly with normal kidney size.

For the genetic analysis, sequencing of the BSCL2 gene revealed a homozygous insertion of a nucleotide, 783insG (Figure 4), in exon 7 of the BSCL2 gene. This resulted in a frameshift of codon 262, and was presumed to be followed with 11 amino acid residues with a premature stop codon at 273(I262fsX273). His mother’s second pregnancy was prenatally diagnosed with the same homozygous BSCL2 mutation by chorionic villus sampling, and was terminated at gestational age 16 weeks. Both the parents, although not phenotypically affected, had a heterozygous 783insG mutation.

**DISCUSSION**

CGL is an autosomal recessive disorder that is clinically characterized by near-complete absence of adipose tissue. It was first genetically mapped to chromosome 9q34, and is now designated as CGL1.
and caused by mutations in AGPAT2 gene. Homozygosity mapping in CGL families from Lebanon and Norway has identified a second locus on chromosome 11q13, now designated CGL2, which results from BSCL2 mutations and have been reported in Europe, the Middle East, and Asia. Our CGL case was found to be homozygous for the mutation 783insG (Ile262fs) in exon 7 of BSCL2. His parents, although not phenotypically affected, both carry one abnormal allele that bears the same frameshift mutation (783insG) (Figure 4). Wu et al reported another Taiwanese CGL patient who has two abnormal alleles that bear one frameshift (783insG) mutation inherited from the maternal side, and one transition (G565T) mutation from the paternal side [13]. As described, mutations for CGL patients can be homozygous or compound heterozygous, and most of the BSCL2 mutations are nonsense or frameshift mutations that are expected to cause loss of function of the protein [9]. Reports from Japan, India, China and Taiwan [9,13–18] indicate that BSCL2 is a major causative gene for CGL in Asian (Table). However, nearly 50% of CGL cases around the world have no sequence mutation in either AGPAT2 or BSCL2 [19].

CGL2 is a more severe phenotype than CGL1, with earlier onset, more extensive fat loss and biochemical changes, more severe intellectual impairment, and more severe cardiomyopathy. Our patient had all the characteristic clinical features for CGL2 except for mental retardation and cardiomyopathy. It is notable that the correlation between BSCL2 mutation and intellectual competency has varied according to previous reports (Table). More recent studies have emphasized the phenotypic and genetic heterogeneity among and within ethnic groups with CGL.

Nephromegaly has been reported with CGL, but the cause remains unclear. In some cases, there is a tendency for lipid deposition in the kidneys [20]. However, CT of the enlarged kidneys in our present case did not suggest lipid density. Furthermore, it is notable that nephromegaly in our case was not noted in early infancy, but developed 1 year later while serum lipid level was much lower. Tsau et al hypothesized that nephromegaly results from hyperplasia and/or hypertrophy induced by long-term high levels of hepatocyte growth factor stimulation [21]. The level of plasma hepatocyte growth factor, the endogenous response to compensate for liver injury, has been reported to be greater in patients with more severe hepatitis, which is consistent with our case. In our

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patient, severe neonatal steatohepatitis was validated by histological analysis at the age of 3 months, and we assumed that this was the possible cause of enlargement of kidneys at the age of 1 year 8 months.

In summary, the CGL case reported here had a homozygous 783insG mutation in the BSCL2 gene, which contributes to the formation of CGL in Taiwan. As verified in our case, CGL2 is a more severe phenotype than CGL1. However, the absence of mental abnormality in the present case of CGL2 implies that intellectual ability is not a typical distinguishing characteristic of CGL1. Nephromegaly reported with CGL is possibly caused by severe neonatal steatohepatitis. Our brief review indicates that BSCL2 is a major causative gene for CGL in Asian.

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高雄医学大学附设医院 1  家庭医学部 2  急诊部小兒急診科 5  小兒科部小兒神經科
4 小兒遺傳及內分泌新陳代謝科 5 遺傳諮詢中心

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