A Taiwanese Boy With Congenital Generalized Lipodystrophy Caused by Homozygous Ile262fs Mutation in the *BSCL2* Gene

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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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Congenital generalized lipodystrophy (CGL) is a rare autosomal recessive disorder that is characterized by near-complete absence of adipose tissue, which has been reported in over 300 patients [1]. This condition in affected individuals is usually recognized soon after birth because of the appearance of prominent musculature and hirsutism. Patients show extreme hypertriglyceridemia, hyperinsulinemia and hepatomegaly because of hepatic steatosis. More associated features include voracious appetite, accelerated linear growth, advanced bone age, acanthosis nigricans, and acromegaloid features [2,3]. Mutations that involve three

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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%)

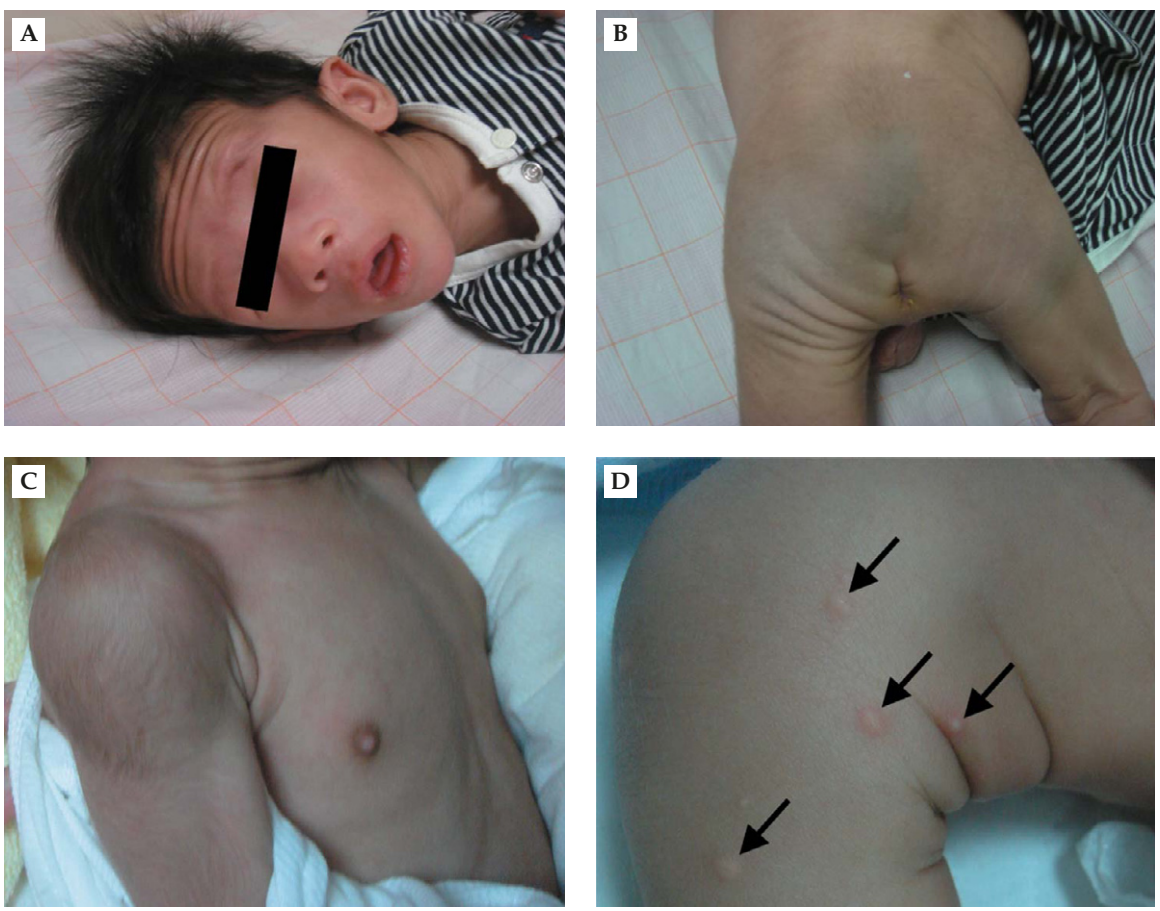

Figure 1. *Clinical features of this patient with (A) typical pinched face; (B) lack of subcutaneous fat including buttocks; (C) prominent musculature and hirsutism; and (D) eruptive xanthomas (arrows) on right knee.*

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.

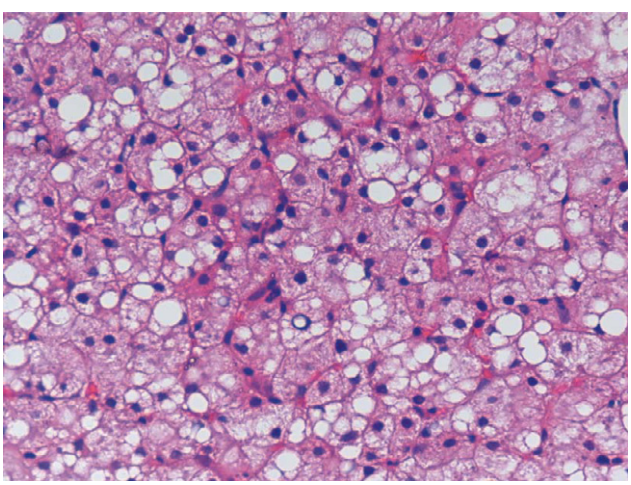

Figure 2. *Liver biopsy: grade 1 portal and lobular inflammatory activity, stage 1 fibrosis, severe hepatic steatosis (>66%) and periportal necrosis (hematoxylin and eosin, original magnification, 400×)*

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

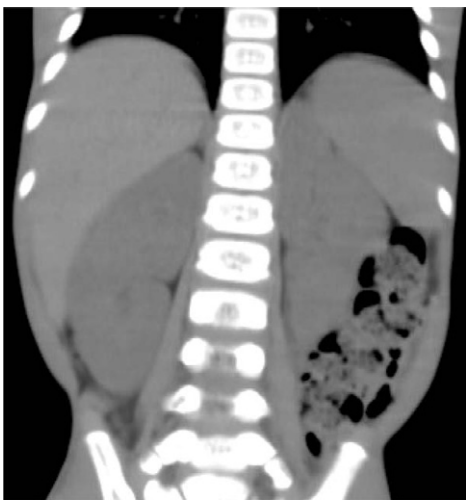

Figure 3. *Computed tomography revealed enlargement of kidneys at the age of 1 year 8 months, whereas hepatomegaly diminished. The expected length according to his height (84 cm) was 4.5–6.7 cm (mean = 5.6 cm) [12].*

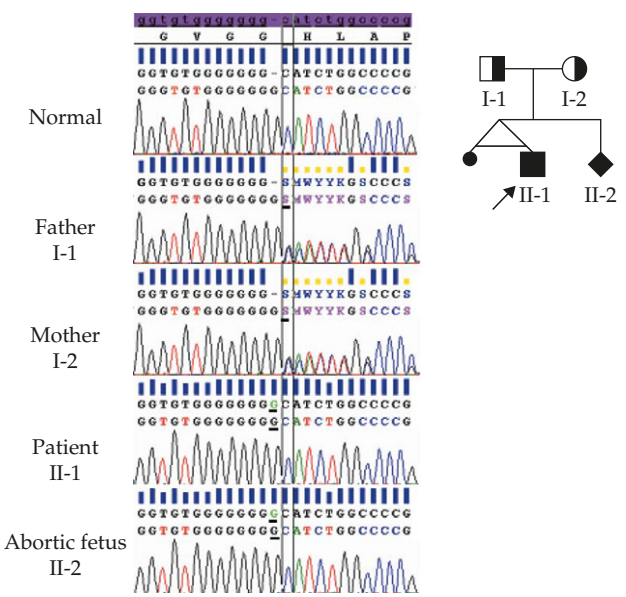

Figure 4. *Sequence of the BSCL2 gene from congenital generalized lipodystrophy cases, including the patient and the next pregnancy which was prenatally diagnosed by chorionic villus sampling and artificially aborted. A homozygous G insertion between nucleotides 782 and 783 in exon 7 was seen in both CGL cases. The heterozygous G insertion was noticed in both the parents (the S is a mix of the normal sequence C and the inserted G).*

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

Table. Clinical characteristics and genetic alterations of congenital generalized lipodystrophy cases from Asia

Patient	Ethnicity	Sex	Onset	Cardiomyopathy	Mental retardation	Steato-hepatitis	Nephromegaly	Causative Gene	Status	Nucleotide alteration(s)	Amino acid change	Ref
1	Taiwan	M	Infancy	–	–	+	+	*BSCL2*	Hom	783insG	Ile262fs	*
2	Taiwan	M	NA	NA	+	+	NA	*BSCL2*	Het	G565T, 783insG	E189X, Ile262fs	[13]
3	India	M	Infancy	–	–	NA	NA	*BSCL2*	Hom	NA	F213fsX231	[9]
4	India	F	Infancy	+	–	NA	–	*BSCL2*	Hom	11 bp deletion in exon 6	H217fsX272	[14]
5	Japan	M	Infancy	–	–	+	NA	*BSCL2*	Hom	C823T	R275X	[15]
6	Japan	F	Infancy	–	–	–	NA	*BSCL2*	Hom	C823T	R275X	[15]
7	Japan	F	Infancy	–	–	+	NA	*BSCL2*	Hom	C823T	R275X	[15]
8	Japan	M	Infancy	–	–	–	NA	*Other loci*	NA	NA	NA	[15]
9	Japan	M	Infancy	NA	NA	+	NA	*BSCL2*	Hom	C823T	R275X	[16]
10	Japan	F	Infancy	NA	NA	+	NA	*BSCL2*	Hom	A560G	Y187C	[16]
11	China	M	Infancy	+	+	+	NA	*BSCL2*	Hom	G565T	E189X	[17]
12	China	M	Infancy	+	NA	+	NA	*BSCL2*	Hom	G565T	E189X	[18]

*Our CGL case in the present study; †Other loci that is neither *BSCL2* nor *AGPAT2*. Het = Compound heterozygote; Hom = homozygous; NA = not available; + = present; – = absent; F = female; M = male; Ref = reference.

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.

Acknowledgments

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BSCL2 基因上的 Ile262fs 同型突變在一台灣先天性全身脂肪失養症男童

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先天性全身脂肪失養症是一罕見的染色體隱性遺傳疾病，特徵為出生後以及嬰兒早期皮下脂肪開始近乎全身缺少。第二型先天性全身脂肪失養症較第一型嚴重，較早發病，皮下脂肪缺少的範圍較廣，血清生化值的變化較大，易發生較嚴重的智能障礙以及較嚴重的心肌病變，目前所知 *BSCL2* 基因（Berardinelli-Seip congenital lipodystrophy 2 基因）上的突變為導致第二型疾病的原因。本文報告一 3 個月大的台灣男童，初期臨床表現為皮下脂肪缺乏，肌肉明顯，全身性的黃色脂肪瘤和極度的高三酸甘油脂血症。頭部的核磁共振掃描顯示眼眶和頭皮等處的機械性脂肪組織缺乏。理學檢查發現肝臟腫大，肝臟切片的病理檢查結果為嚴重的脂化和肝門周圍壞死。但是心臟超音波的報告中並沒有顯示出心肌病變，也沒有影響日常生活的顯著智能障礙。約 1 年後腹部的電腦斷層發現新產生的腎臟腫大。他在 *BSCL2* 基因第七外序列上有一個同型突變 — 在核苷酸 783 位置插入了一個鳥嘌呤（G，guanine），或 Ile262fs 突變。我們回顧了日本，印度，中國，台灣 CGL 個案的基因型，揭示了 *BSCL2* 是在亞洲病例中造成先天性全身脂肪失養症主要的突變基因。

關鍵詞：*BSCL2* 基因，先天性全身脂肪失養症，肝炎，腎臟腫大

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