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## Cardiomyopathy in Congenital and Acquired Generalized Lipodystrophy:

### A Clinical Assessment

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### Abstract

Lipodystrophy is a rare disorder characterized by loss of adipose tissue and low leptin levels. This condition is characterized by severe dyslipidemia, insulin resistance, diabetes mellitus, and steatohepatitis. Another phenotypic feature that occurs with considerable frequency in generalized lipodystrophy is cardiomyopathy. We report here the cardiac findings in a cohort of patients with generalized congenital and acquired lipodystrophy, and present a literature review of the cardiac findings in patients with generalized lipodystrophy.

We studied 44 patients with generalized congenital and acquired lipodystrophy, most of them enrolled in a clinical trial of leptin therapy. Patients underwent electrocardiograms and transthoracic echocardiograms to evaluate their cardiac status. We followed these patients for an extended time period, some of them up to 8 years.

Evaluation of our cohort of patients with generalized lipodystrophy shows that cardiomyopathy is a frequent finding in this population. Most of our patients had hypertrophic cardiomyopathy, and only a small number had features of dilated cardiomyopathy. Hypertrophic cardiomyopathy was more frequent in patients with seipin mutation, a finding consistent with the literature. The underlying mechanism for cardiomyopathy in lipodystrophy is not clear. Extreme insulin resistance and the possibility of a “lipotoxic cardiomyopathy” should be entertained as possible explanations.

## INTRODUCTION

Lipodystrophy is a rare disorder characterized by loss of adipose tissue and low leptin levels. The etiology may be congenital or acquired and the involvement may be generalized or partial. Leptin is a newly discovered adipocyte-derived hormone that is important in overall energy regulation. In obesity, leptin levels are high and there is a relative state of leptin resistance. In lipodystrophy, the loss of fat cells leads to low leptin levels and metabolic consequences that can be corrected with exogenous leptin administration.

Patients with generalized lipodystrophy have a phenotype characterized by nearly complete loss of adipose tissue and a muscular appearance. This condition can have a genetic or acquired etiology. The congenital generalized forms are caused by mutations in the AGPAT2[1], seipin (also known as BSCL2),[18] LMNA,[5] caveolin-1,[13] and rarely the

PTRF gene.[8] The acquired generalized forms can be associated with panniculitis and autoimmune diseases such as juvenile dermatomyositis, but most often are idiopathic.

Regardless of the etiologic basis of the generalized lipodystrophy, these patients have a metabolic condition characterized by severe dyslipidemia, insulin resistance, diabetes mellitus, and steatohepatitis. These metabolic abnormalities are significantly ameliorated by administration of leptin.[6]

Other phenotypic features in patients with generalized lipodystrophy occur with considerable frequency. One feature is cardiomyopathy. Case reports have described cardiomegaly or left ventricular (LV) hypertrophy in the setting of generalized congenital lipodystrophy, and less frequently in acquired generalized lipodystrophy. [3-5,9,12,14,16,20,21,24,26,27] Patients with partial lipodystrophy may have accelerated vascular disease, but they do not appear to have features of cardiomyopathy as described in patients with generalized lipodystrophy.

We studied 44 patients with generalized congenital and acquired lipodystrophy, most of them enrolled in a clinical trial of leptin therapy. Patients underwent electrocardiograms (ECGs) and transthoracic echocardiograms to evaluate their cardiac status. We followed these patients for an extended time period, some of them up to 8 years.

We also reviewed 48 cases reported in the literature that discuss a possible association between cardiomyopathy and generalized lipodystrophy. Many patients with generalized lipodystrophy had evidence of cardiac hypertrophy, as measured by different echocardiographic parameters. A much smaller number of patients had true cardiac dysfunction, although some patients were observed to develop severe congestive heart failure. The literature is confusing in that some patients were reported before genetic testing, and other patients have been repeatedly reported in different publications. In fact, 2 of the lipodystrophy patients reported in the literature have been followed by us at the National Institutes of Health (NIH) over a long period of time.

We conducted the present study to define further the cardiac abnormalities in our group of lipodystrophy patients and to compare these findings with findings previously reported in the literature.

## **PATIENTS AND METHODS**

### **Cardiomyopathy**

Cardiomyopathies are defined according to the World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies, as diseases of the myocardium associated with cardiac dysfunction. They are classified as dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy.[22]

Dilated cardiomyopathy is characterized by dilatation and impaired contraction of 1 or both ventricles, leading to decreased systolic function. Hypertrophic cardiomyopathy is characterized by increased left and sometimes right ventricular mass. Hypertrophic cardiomyopathy can be primary, either genetic or acquired in origin, or secondary to an identifiable cause, such as hypertension or aortic stenosis.

### **Patient Population**

Forty-four patients with congenital and acquired generalized lipodystrophy were evaluated at the Clinical Center of the NIH between 1999 and 2009. Most of the participants were

enrolled in a clinical trial of leptin therapy approved by the Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases. Informed consent was obtained from each patient or the patient's legal guardian.

Genetic analyses were performed to classify patients by type of lipodystrophy. "Seipin" patients had a mutation in the seipin gene.[18] The "AGPAT" patients had a mutation in the AGPAT2 gene.[1] One congenital lipodystrophy patient had a R133L mutation in the LMNA gene.[5] The term "acquired" lipodystrophy was used for patients who clearly did not have an inherited form of lipodystrophy by clinical history. One patient with an inherited form of lipodystrophy did not have an identifiable mutation and was classified as "unknown." The genetic analyses were mostly performed in the laboratory of Dr. Abhimanyu Garg (University of Texas at Southwestern Medical Center); some were carried out in the laboratories of Dr. Jocelyne Magre (INSERM, Paris, France) and Dr. Robert Hegele (University of Western Canada, Ontario).

### Echocardiograms

Images were recorded using a standardized protocol in which at least 3 beats were acquired in each view in digital format. Two studies were recorded on videotape and were digitized for analysis. Two-dimensional measurements of LV dimensions and wall thickness were made in the parasternal view, just below mitral leaflet tips following American Society of Echocardiography guidelines. [15] LV mass was calculated from wall thickness measurements and indexed to body surface area. The formula for LV mass ( $\text{mass} = 1.04 \times 0.8 [ (\text{wall thicknesses} + \text{LV internal dimension})^3 - (\text{LV internal dimension})^3 ] + 0.6 \text{ g}$ ) is based on a necropsy-validated[7] prolate ellipse model of the left ventricle. LV hypertrophy was defined as LV mass index  $>95 \text{ g/m}^2$  in women and  $>115 \text{ g/m}^2$  in men. Mild, moderate, and severe degrees of hypertrophy were classified according to sex-specific criteria. In women, a LV mass between  $96$  and  $108 \text{ g/m}^2$  was classified as mildly abnormal; between  $109$  and  $121 \text{ g/m}^2$ , as moderately abnormal; and  $\geq 122 \text{ g/m}^2$ , as severely abnormal. In men, a LV mass between  $116$  and  $131 \text{ g/m}^2$  was classified as mildly abnormal; between  $132$  and  $148 \text{ g/m}^2$ , as moderately abnormal; and  $\geq 149 \text{ g/m}^2$ , as severely abnormal. Concentric remodeling was defined as normal LV mass with increased relative wall thickness  $\geq 0.42$ . [15] LV volumes and left atrial volumes were calculated from the Simpson formula using apical 4-chamber and 2-chamber views. Volumes were adjusted to body surface area measurements. Ejection fraction (EF) was calculated as  $(\text{end-diastolic volume} - \text{end-systolic volume}) / \text{end-diastolic volume}$ . An EF  $\geq 55\%$  was considered normal. Mild LV dysfunction was defined by an EF between  $45\%$  and  $55\%$ ; moderate by an EF between  $30\%$  and  $44\%$ , and severe LV dysfunction by an EF  $<30\%$ . A diagnosis of dilated left ventricle was made based on the left-ventricle end-diastolic volume indexed to body surface area. If multiple echocardiograms were available for a given patient, the most recent one was used for analysis. All echocardiograms were overread by a single cardiologist (VS) in a blinded fashion.

### Electrocardiograms

Standard 12-lead ECGs were obtained using the Hewlett Packard Pagewriter XLI 1700A machine. They were analyzed using Pagewriter A.04.01 ECG analysis software (Philips Medical Systems). All ECGs were overread by a single cardiologist (DRR) in a blinded fashion. As with the echocardiograms, we used only the most recent ECG for analysis.

### Statistical Analysis

Data for continuous variables are shown as means  $\pm$  standard deviation.

## RESULTS

We studied 44 patients with congenital and acquired generalized lipodystrophy. The results of the echocardiographic findings are summarized in Table 1.

The cohort included 29 female patients and 15 male, ranging in age from 7 to 69 years (mean,  $23 \pm 14$  yr). The mean age for the AGPAT group was  $23 \pm 12$  years, for seipin was  $17 \pm 7$  years, and for the acquired group was  $28 \pm 20$  years.

One female patient had a history of coronary artery bypass grafting at the age of 45 years. Most of our patients were in a younger age-group and did not have clinical features of ischemic heart disease, such as angina, history of heart attack, or ECG changes suggestive of ischemia. Seven patients were found to have borderline or increased blood pressure, including 1 patient on medical therapy and 1 patient with a history of kidney transplant.

The mean LV mass index was  $104 \pm 21$  g/m<sup>2</sup> in women and  $116 \pm 22$  g/m<sup>2</sup> in men. LV hypertrophy was present in 24 of the 44 (55%) patients (mild in 8 patients, moderate in 9 patients, and severe in 7 patients). Only 4 of the 24 patients with LV hypertrophy (17%) were hypertensive. Of the 20 patients without evidence of increased LV mass, 8 patients had concentric remodeling of the left ventricle, of whom 1 had hypertension. The mean EF was  $66\% \pm 12\%$ . Six patients (14%) had LV dysfunction (4 mild, 1 moderate, 1 severe). One patient had evidence of congenital heart disease (patent ductus arteriosus).

ECGs were available in 37 of the 44 patients. Fourteen patients (38%) had normal ECGs. Three (8%) were borderline or had minor variations such as an RSR' in lead V1 with a normal QRS duration. Twenty patients (54%) had abnormal ECGs. Of those with abnormal ECGs, prolonged QTc intervals (9%), nonspecific T-wave abnormalities (9%), and LV hypertrophy (5%) were the most common abnormalities identified.

### Genotype-Phenotype Correlations

Thirty-one of the 44 patients had congenital generalized lipodystrophy (19 patients had AGPAT2 mutations, 10 had seipin mutations, 1 had LMNA mutation, and 1 patient had an unknown mutation).

Of the 19 patients with generalized lipodystrophy due to AGPAT2 mutations, 3 patients had mild LV hypertrophy, 4 had moderate, 3 had severe, and 9 patients had normal LV mass. ECG abnormalities were seen in 9 of the 17 AGPAT patients with ECGs available for analysis.

Of the 10 patients with seipin mutations, 2 patients had mild LV hypertrophy, 2 had moderate, 4 had severe, and 2 had normal LV mass. ECG abnormalities were seen in 5 of the 7 seipin patients with ECGs available for analysis.

The patient with an unknown mutation had a normal LV mass but concentric remodeling of the left ventricle.

The patient with generalized lipodystrophy caused by a R133L LMNA mutation had one of the most severe cases of cardiomyopathy we have seen in the context of lipodystrophy. He was a 9-year-old boy who was found during his initial visit at the NIH to have dyspnea on exertion and low exercise tolerance. On physical examination he had a 2/6 systolic ejection murmur. His baseline echocardiogram showed normal LV index mass, a dilated left ventricle, and an EF of 35% consistent with dilated cardiomyopathy. He was started on an angiotensin-converting enzyme inhibitor with stabilization of his symptoms. One year later his echocardiogram remained stable.

Thirteen of the 44 patients had an acquired form of generalized lipodystrophy. Of the 13 patients, 3 had mild LV hypertrophy, 3 had moderate, and the other 7 patients had a normal LV mass. ECG abnormalities were seen in 5 of the 11 acquired patients with ECGs available for analysis.

### Pathologic Examination

We examined the hearts of 3 lipodystrophy patients, 1 from heart transplant and 2 from autopsies.

One of the patients was an 18-year-old girl with congenital generalized lipodystrophy secondary to an AGPAT2 mutation. At age 14 years, during a hospitalization for acute pancreatitis, she was found to have LV dysfunction. Echocardiogram done at the NIH at age 18 years showed severe LV hypertrophy, dilated left ventricle, and severe LV dysfunction with an EF of 29%. She progressively became more symptomatic and required heart transplantation at age 19 years for severe heart failure. Pathologic examination of the heart showed biventricular dilation, mild to moderate biventricular myocyte hypertrophy with vacuolated subendocardial myocytes, focal subendocardial fibrosis, and epicardial fibrosis with atrophic fat and scattered lymphocytic infiltrates. The left ventricle displayed increased myocardial trabeculation, but the degree of trabeculation was not enough to make a diagnosis of LV noncompaction. The coronary arteries were normal (the pathologic examination of the heart was performed by Dr. Renu Virmani). The patient died 1 year later from noncompliance with the transplant regimen.

The second patient was a woman with congenital lipodystrophy, caused by an AGPAT2 mutation. At age 30 years, she developed respiratory distress secondary to pneumonia and died unexpectedly, presumably from a cardiac arrhythmia. Her last echocardiogram showed mild LV eccentric hypertrophy and mild LV systolic dysfunction. Pathologic examination of the heart showed mild LV hypertrophy, primarily in the postero-lateral region.

The third patient was a 32-year-old man with congenital lipodystrophy secondary to a seipin mutation. He developed panlobar pneumonia and after a prolonged hospital course died from respiratory failure. His last echocardiogram showed severe LV hypertrophy and normal EF. Pathologic examination showed a 410-g heart, LV patchy perivascular and interstitial fibrosis, and 50% occlusion of the left main coronary artery.

### Literature Review

We performed a PubMed (National Library of Medicine, Bethesda, MD) search of the articles in English describing cardiac abnormalities in the context of acquired and congenital generalized lipodystrophy. We found 12 articles that describe 48 lipodystrophy patients with different degrees of cardiac abnormalities. The cardiac findings ranged from incidentally found asymptomatic cardiomegaly to severe heart failure. In most of these cases, the diagnosis of cardiac abnormalities was made using echocardiography and electrocardiography. Chest X-rays were also used to evaluate for cardiomegaly. In some cases, the cardiac abnormalities were observed only at autopsy.

It is difficult to specify the exact number of patients found to have cardiac abnormalities, because some of the papers describe patients who have been reported previously. Also, in some of the congenital lipodystrophy cases the underlying genetic defect is unknown, mostly because these cases were reported before the genetic analysis was made available.

Table 2 summarizes these 48 patients. After excluding the possible duplicate cases, 23 patients had evidence of hypertrophic cardiomyopathy (2 patients had unknown mutations, 12 had seipin mutations, 7 had AGPAT2 mutations, 1 had a R133L LMNA mutation, and 1

patient had acquired generalized lipodystrophy). The remainder had additional cardiac abnormalities including cardiomegaly, dilated cardiomyopathy, and congestive heart failure. Four patients died of congestive heart failure. One-third of the lipodystrophy patients with cardiac abnormalities were infants below the age of 2 years. The average age for the rest of the patients was about 20 years, similar to our patient population.

### Special Considerations

It is noteworthy that 2 of the patients reported in the literature were also evaluated by our group. Bhayana et al[3] described in 2002 a young girl with congenital generalized lipodystrophy due to a seipin mutation, who was found to have myocardial hypertrophy from a very young age. At 6 months of age, she was noted to have cardiomegaly, a systolic apical ejection murmur, and evidence of ventricular hypertrophy on ECG and 2-dimensional echocardiogram. At 3 years of age, she was found to have concentric hypertrophy of the left ventricle, moderate hypertrophy of the right ventricle, increased intraventricular septal thickness, good myocardial contractility, and no evidence of outflow obstruction. At 5 years of age, the patient developed mild exercise intolerance and occasional palpitations. These symptoms progressed, and at age 10 years the patient had dyspnea with minimal exertion. The ECG showed voltage criteria for LV hypertrophy, and the echocardiogram confirmed concentric ventricular hypertrophy with a gradient across the LV outflow tract.[3] This patient was first seen at our institution at age 14 years. At that point, she was asymptomatic and she was on no cardiac medications. The patient has continued to be followed in our Clinical Center on a yearly basis. She is now aged 17 years and her most recent echocardiogram showed severe LV hypertrophy. However, she is completely asymptomatic from a cardiac point of view and on no cardiac medications.

Rheuban et al[21] described in 1986 3 siblings with congenital generalized lipodystrophy and nonobstructive hypertrophic cardiomyopathy. One of the siblings was a 20-year-old woman who was noted to have a systolic ejection murmur at the apex. She was not hypertensive and her ECG was normal. The echocardiogram showed evidence of nonobstructive hypertrophic cardiomyopathy[21]. This patient was evaluated for the first time at the Clinical Center at age 36 years. Genetic analysis showed that her congenital generalized lipodystrophy was due to an AGPAT2 mutation. The initial echocardiogram done at the NIH showed mild hypertrophic cardiomyopathy and normal EF of 71%. At age 45 years, however, the patient underwent coronary artery bypass grafting because of severe coronary artery disease.

## DISCUSSION

The presence of cardiac abnormalities has been noted in the context of acquired generalized lipodystrophy since 1946[16] and in congenital generalized lipodystrophy since 1959.[23] Since then, multiple articles have described a possible association between cardiomegaly and/or cardiomyopathy and generalized lipodystrophy. Classically, it is believed that the congenital lipodystrophy patients with underlying seipin mutations have a higher prevalence of cardiomyopathy.[2] However, the literature is confusing because some patients are repeated in more than 1 report, and because in a significant number of patients with congenital generalized lipodystrophy, the underlying genetic mutation is not known.

We followed 44 patients with congenital and acquired generalized lipodystrophy and found that more than half of the patients had echocardiographic evidence of LV hypertrophy, as well as ECG abnormalities. In the AGPAT patients, about 53% had evidence of LV hypertrophy, and in the seipin patients, 80% had LV hypertrophy. The seipin patients also tended to have more frequent abnormalities on ECGs. It is noteworthy that the patients with

acquired generalized lipodystrophy also had cardiac hypertrophy, but of a significantly milder nature.

Although cardiomyopathy was a frequent finding in our lipodystrophy patients, we found severe heart failure in only 2 patients. Both patients had evidence of underlying dilated cardiomyopathy. One of the patients had an AGPAT2 mutation and required heart transplant for severe heart failure. The second patient had generalized lipodystrophy secondary to a LMNA mutation. This is in contrast to the lipodystrophy patient reported by Caux et al,[5] who had the same LMNA mutation as our patient but had features of hypertrophic cardiomyopathy and was asymptomatic. The LMNA mutations in general present a complex picture, in that mutations in this system may involve both the phenotypic features of cardiomyopathy, muscular dystrophy, as well as lipodystrophy. The mechanism of these complex phenotypes related to mutations in the LMNA system is unclear.[10]

The underlying etiology of the cardiac abnormalities in lipodystrophy remains unclear. It does not appear to be related to underlying hypertension, because this was uncommon in our patients.

Severe insulin resistance, which was characteristic of our patients,[11,19] may provide the context for the development of hypertrophic cardiomyopathy, given the growth effect of insulin.[3,14,24,27] The long-term effect of severe hyperinsulinemia on cardiac function is not known; however, in other severe syndromic forms of hyperinsulinemia, such as in insulin receptor mutations, cardiomyopathy is not a prominent feature of the disease.

Preliminary research in obese individuals suggests that accumulation of triglycerides in the myocardium can cause a “lipotoxic cardiomyopathy.”[17,25] Lipodystrophy patients have ectopic accumulation of fat in organs like muscle and liver. There is no clear evidence that these patients have ectopic deposition of fat in the myocardium, but the possibility of a lipotoxic cardiomyopathy in lipodystrophy should be entertained as a possible explanation.

It is noteworthy that hypertrophic cardiomyopathy is more frequently seen in patients with seipin mutation, who have overall milder metabolic abnormalities (including lower triglycerides levels and glycated hemoglobin) than in the AGPAT or acquired lipodystrophy groups.

The NIH cohort of patients, for the most part, was enrolled in a clinical trial of leptin therapy, which has a major beneficial effect on insulin resistance, dyslipidemia, and dissipation of ectopic fat. It is possible that some of the effect extends to the heart. We have no direct evidence that correction of these abnormalities is cardioprotective with respect to cardiomyopathy, but it is probably protective with respect to vascular disease.

The current study was observational and the number of patients enrolled was small, therefore it has the limitations inherent to this type of study. However, we do have the advantage of having observed these patients over a long period of time and having performed serial echocardiograms and ECGs.

## Conclusion

Evaluation of our cohort of patients with congenital and acquired generalized lipodystrophy shows that cardiomyopathy, demonstrated by echocardiography and ECG, is a frequent finding in this population. Both congenital lipodystrophy patients with known genetic defects and those having an acquired form seem to develop similar cardiac abnormalities. Most of our patients had hypertrophic cardiomyopathy, and only a small number had features of dilated cardiomyopathy. However, with continued follow-up, it is possible that

the hypertrophic form may transition into the dilated type. Furthermore, hypertrophic cardiomyopathy was more frequent in patients with seipin mutation, a finding consistent with the literature.

Although most of the lipodystrophy patients in the current study had evidence of hypertrophic cardiomyopathy, over the period of time we were able to follow them it was seldom clinically significant and appeared to be stable. Whether this continues to be the case as this population ages, remains to be seen.

The underlying mechanism for cardiomyopathy in lipodystrophy is not clear. We have raised several issues including the possibility of a form of lipotoxicity and a potential relationship to extreme insulin resistance. However, none of these possibilities offers a clear explanation. Cardiac abnormalities do not seem to be related to underlying hypertension, because this was uncommon in our patients. Further observation and evaluation will, we hope, provide more insight into this complex disease.

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## Abbreviations

<b>ECG</b>	electrocardiogram
<b>EF</b>	ejection fraction
<b>LV</b>	left ventricular

**TABLE 1**  
 Echocardiographic Findings in 44 Patients With Lipodystrophy Evaluated at the NIH

Mutation	No. of Patients	Age (yr)	LV Mass (g/m <sup>2</sup> )	LAV/BSA (mL/m <sup>2</sup> )	LV EF (%)	Cardiac Finding
AGPAT2	19	23±12	104±20	26±6	66±13	10 Patients with increased LV mass 4 Patients with LV dysfunction 1 Patient with PDA
Seipin	10	17±7	126±16	31±6	65±7	8 Patients with increased LV mass
LMNA	1	9	110	29	35	Moderate LV dysfunction and dilation, no increased LV mass
Unknown	1	17	71	16	68	Concentric remodeling
AGL	13	28±20	103±20	32±9	68±9	6 Patients with increased LV mass 1 Patient with mild LV dysfunction

Abbreviations: AGL = acquired generalized lipodystrophy, LAV/BSA = left atrial volume indexed to body surface area, PDA = patent ductus arteriosus.

TABLE 2

## Literature Review of Cardiac Findings in Patients With Generalized Lipodystrophy

Study First Author (ref.)	Cases
Lawrence (16)	1 AGL patient, cardiomegaly
Seip* (24)	4 CGL patients, unknown mutation, hypertrophic cardiomyopathy 2 CGL patients, unknown mutation, hypertrophic cardiomyopathy, CHF
Bhayana† (3)	1 CGL patient, seipin mutation, hypertrophic cardiomyopathy
Caux (5)	1 CGL patient, R133L LMNA mutation, hypertrophic cardiomyopathy, valvular disease
Khalife (12)	1 CGL patient, unknown mutation, dilated cardiomyopathy, CHF, severe mitral regurgitation, myocardial infarction, normal coronaries
Van Maldergem* (26)	4 CGL patients, AGPAT2 mutation, hypertrophic cardiomyopathy 11 CGL patients, seipin mutation, hypertrophic cardiomyopathy 2 CGL patients, seipin mutation, CHF 1 CGL patient, unknown mutation, hypertrophic cardiomyopathy, CHF
Rajab (20)	6 CGL patients, unknown mutation, cardiomegaly
Rheuban† (21)	3 CGL patients, AGPAT2 mutation, hypertrophic cardiomyopathy 1 CGL patient, unknown mutation, hypertrophic cardiomyopathy
Bjornstad* (4)	6 CGL patients, unknown mutation, hypertrophic cardiomyopathy 1 AGL patient, hypertrophic cardiomyopathy
Klar (14)	1 CGL patient, unknown mutation, septal hypertrophy
Viegas (27)	1 CGL patient, unknown mutation, CHF
Ishii (9)	1 AGL patient, asymmetrical septal hypertrophy, CHF

Abbreviations: AGL = acquired generalized lipodystrophy, CGL = congenital generalized lipodystrophy, CHF = congestive heart failure.

\* It is probable that these papers are reporting the same patients.

† These patients were evaluated also at the NIH.