SÃO PAULO MEDICAL JOURNAL

CASE REPORT

*Estela Maria Novak, Carlos Alberto Longui, Sergio Paulo Bydlowski*

# Uncommon allele in APO AI-CIII-AIV gene cluster in a family with congenital generalized lipodystrophy

*Research and Molecular Biology Division, Pró-Sangue Hemocentro de São Paulo Foundation, Department of Pediatrics, Faculdade de Ciências Médicas da Santa Casa de São Paulo, Department of Hematology, Faculdade de Medicina - USP - São Paulo, Brazil*

Congenital generalized lipodystrophy is a rare inherited disease. One of its features is a disturbance in lipid metabolism characterized by hypercholesterolemia and hypertriglyceridemia. A brother and a sister with congenital generalized lipodystrophy, an 8-year old male and a 12-year old female were studied. The mother and a 6-year old brother were healthy. The genetic analysis of SstI RFLP of the apo AI-CIII-AIV gene cluster showed the presence of the rare SstI allele ($S_2$) in the patients but not in the healthy mother and brother. As this uncommon allele has been reported to be related to high plasma triglyceride levels, this association could be relevant in explaining in part the hypertriglyceridemia observed in these patients.

**UNITERMS:** Apolipoproteins. Congenital generalized lipodystrophy. Apo AI-CIII-AIV gene.

Congenital generalized lipodystrophy (Seip - Berardinelli syndrome) is a rare hereditary disease inherited as an autosomic recessive trait. Its most striking features are extreme paucity of fat in adipose tissue, increased growth rate, muscular/pseudohypertrophy, and disturbances of carbohydrate and lipid metabolism characterized by insulin resistance and hyperlipidemia. The mechanism behind these alterations is unclear.

The genes coding for apolipoproteins (apo) A-I, C-III, and A-IV are clustered within a 15-Kb DNA segment on the long arm of human chromossome 11. Several DNA polymorphisms have been identified in this gene cluster. Digesting genomic DNA with restriction endonuclease SstI yields two fragments after hybridization with apoAI probe: 5.7-Kb and 4.2-Kb in length ($S_1$ allele). In mutated alleles, a 3.2-Kb fragment ($S_2$, rare allele) is observed instead of the 4.2-Kb fragment. It has previously been demonstrated that the rare allele ($S_2$) could be associated with certain types of hyperlipoproteinemia in which hypertriglyceridemia is a feature[1]. We describe here the SstI polymorphism of the apoAI-CIII-AIV gene cluster in a family with congenital generalized lipodystrophy.

A brother and a sister with congenital generalized lipodystrophy, an 8-year old male (F.F.) and a 12-year old female (A.F.), were studied. The mother and another brother (6-year old, R.F.) were healthy, as shown by clinical and laboratory evaluation. The father had died of unknown causes and it was not possible to know whether he had suffered from any disease. The clinical diagnosis of congenital generalized lipodystrophy was made when the children were babies. The patients (F.F.and A.F.) had a complete absence of adipose tissue. They showed acromegaloid aspect with muscular hypertrophy and phlebomegaly, abdominal protrusion with hepatomegaly, and acanthosis nigricans. Among the laboratory findings, the patients showed normal fasting blood glucose, impaired glucose tolerance and insulin resistance. Other striking features were hypertriglyceridemia and hypercholesterolemia with increased LDL-cholesterol levels.

***Address for correspondence:***
*Sergio Paulo Bydlowski,*
*Av. Dr. Enéias de Carvalho Aguiar, 155 - 1st floor*
*São Paulo/SP - Brasil - CEP 05403-000*

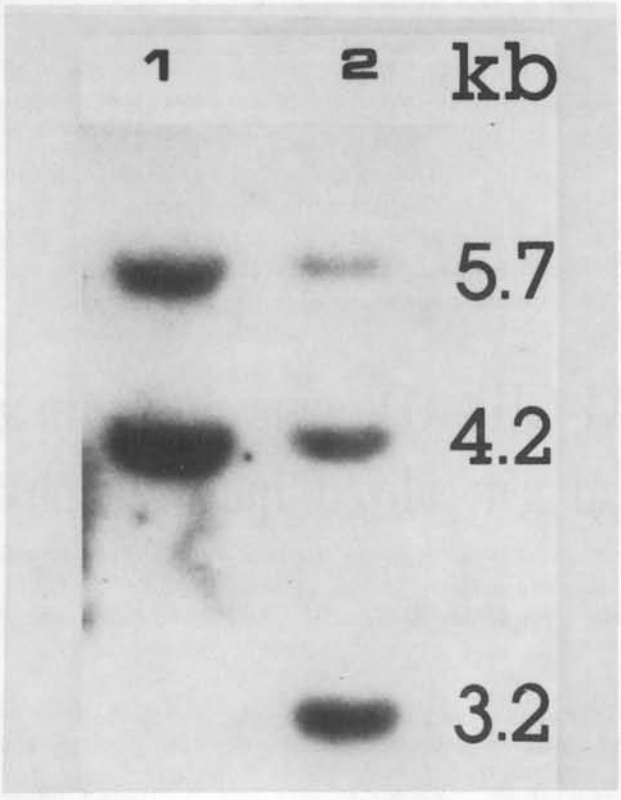


**Figure 1 -** Molecular analysis of SstI RFLP of the apoAI-CIII-AIV gene cluster. 1 : mother; 2: patient (A.F.)

DNA was isolated from the nuclear fraction of 5 ml of venous blood, and used for genomic blotting analysis. Restriction fragment length polymorphism (RFLP) studies with restriction endonuclease SstI were performed as described[2].

Molecular analysis of SstI RFLP of the apoAI-CIII-AIV gene complex showed in the mother and young brother the 5.7- and 4.2-Kb long fragments (genotype $S_1S_1$), while in the patients, 5.7, 4.2 and 3.2- Kb long fragments were yielded (genotype $S_1S_2$) (Figure 1).

Several genetic mutations have been linked to alterations in plasma lipoproteins. It has been suggested that variant alleles of the non-coding region of the apoAI-CIII-AIV gene cluster constitute a genetic marker for hypertriglyceridemia, although the mechanism of this association remains an enigma. Aalto-Setälä et al[3] have found the $S_2$ allele in 16% of healthy controls, 23% of patients with CHD and 62% of unrelated subjects with hypertriglyceridemia. These data are in accord with Rees et al[4] who did not find any normolipemic individual carrying the $S_2$ allele, but reported the presence of this allele in 26 out of 74 hypertriglyceridemic subjects. We have found the $S_2$ allele in only 2% of a normolipemic Brazilian population[2]. Other investigators have also indicated that there could be a significant relationship between lipid metabolism disorders and the SstI polymorphism of the apoAI-CIII-AIV gene complex in patients with hypertriglyceridemia or even hypercholesterolemia.

In the present study the $S_2$ allele was present in the patients with congenital generalized lipodystrophy and absent in the healthy mother and brother.

In conclusion, we have described the presence of the uncommon allele $S_2$ in the apoAI-CIII-AIV gene cluster in a family with congenital generalized lipodystrophy, which could contribute to the high levels of plasma triglycerides observed in the patients. Moreover, although one cannot make any inferences about allelic association from only two cases in one family, the present study has provided additional evidence that genetic variation at this site could be involved in hypertriglyceridemia.

## ACKNOWLEDGMENTS

This work was supported by a grant (10/6186-7) from Fundação Banco do Brasil (SPB).

The authors wish to thank to Dr. J. Ordovas (Human Nutrition Research Center, Tufts University, Boston, MA) his help in providing the probes used in this study. We thank Mrs. A. Nakayama for her assistance in preparing the manuscript.

## RESUMO

A lipodistrofia congênita é uma rara doença hereditária. Uma de suas características é o distúrbio no metabolismo lipídico caracterizado por hiper-colesterolemia e hipertrigliceridemia. Foram estudados um irmão (8 anos de idade) e uma irmã (12 anos) que apresentavam esta patologia. A mãe e um irmão de 6 anos eram sadios. A análise genética do RFLP SstI dos genes do complexo apo AI-CIII-AIV mostrou a presença do alelo SstI raro (S2) nos pacientes, mas não na mãe e no irmão saudável. Desde que este alelo incomum tem sido associado a altos níveis plasmáticos de triglicérides, esta associação poderia ser relevante para explicar em parte a hipertrigliceridemia observada nestes pacientes.

## REFERENCES


1. Tibjaerg-Hansen A, Nordestgaard BG, Gerdes LU, Faergeman O, Humphries SE. Genetic markers in the apo AI-CIII-AIV gene cluster for combined hyperlipidemia, hypertriglyceridemia, and predisposition to atherosclerosis. Atherosclerosis 1993; 100: 157-69.
2. Bydlowski SP, Novak EM, Issa JS, Forti N, Giannini SD, Diament J. DNA polymorphisms of apolipoproteins B and AI-CIII-AIV genes in a Brazilian population: a preliminary report. Braz J Med Biol Res 1996; 29: 1269-74.
3. Aalto-Setälä, Kontula K, Sane T, Nieminen M, Nikkillä E. DNA polymorphisms of apolipoprotein A-I/C-III and insulin genes in familial hypertriglyceridemia and coronary heart disease. Atherosclerosis 1987; 66: 145-52.
4. Rees A, Stocks, J, Sharpe CR, et al. Deoxyribonucleic acid polymorphism in the apolipoprotein AI-CIII gene cluster. Association with hypertriglyceridemia. J Clin Invest 1985; 76: 1090-5.