Next Generation Sequencing Approach for Molecular Genetic Diagnosis of Familial Partial Lipodystrophy

Nihal Thomas , H.S.Asha, Aaron Chapla, Manika. V, Shrinath Shetty

Department of Endocrinology, Diabetes and Metabolism, Christian Medical College, Vellore, India.

BACKGROUND

- Lipodystrophies are a heterogeneous group of diseases characterized by abnormal fat distribution.
- Familial partial lipodystrophy 2 (FPLD2) is autosomal dominant condition due to mutations in the LMNA gene.
- It is characterized by selective loss of subcutaneous adipose tissue from the limbs and trunk, and accumulation of fat in the neck and face.
- Usually associated with a variety of metabolic disorders including insulin resistance, diabetes mellitus, dyslipidemia, hepatic steatosis and high blood pressure.

OBJECTIVES

To study the clinical and molecular features of 2 subjects with FPLD.

SUBJECTS AND METHODS

Utilizing Next Generation Sequencing (NGS) we carried out mutational analysis of LMNA gene in a woman and her daughter with FPLD phenotype

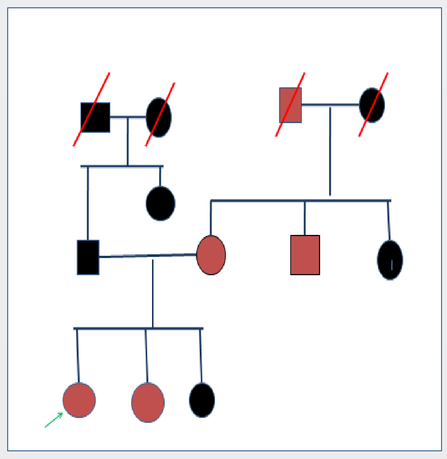
CLINICAL PRESENTATION

MOTHER AND DAUGHTER

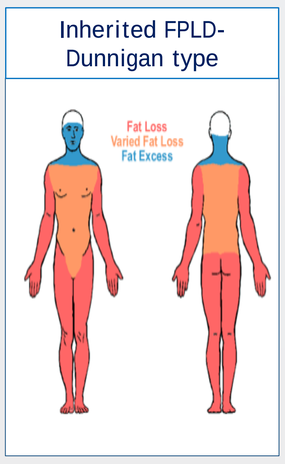
- Diabetes detected less than 30 years of age.
- On insulin from the time of diagnosis
- No history of Diabetic ketoacidosis
- Hypertriglyceridemia

Family history :

Maternal uncle and younger sister with similar fat distribution



Inherited FPLD-Dunnigan type



Examination: In both mother and daughter

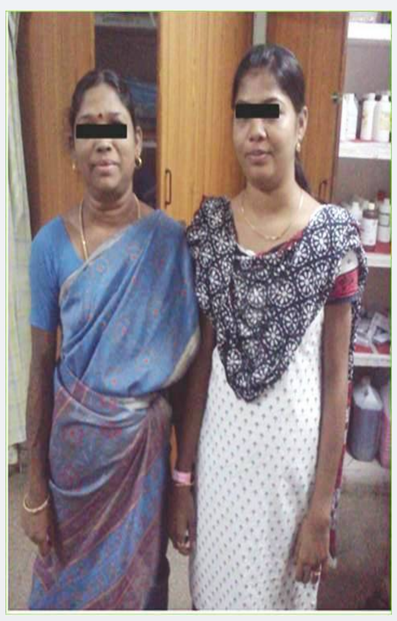
- Cushingoid facies
- Acanthosis nigricans
- Prominent veins – UL>LL
- Calf muscles and deltoid appear prominent
- Vulval fat appears hypertrophic
- Hepatomegaly

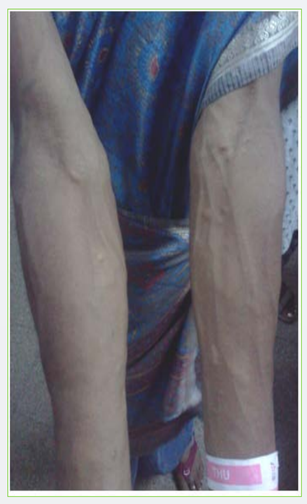
BODY COMPOSITION

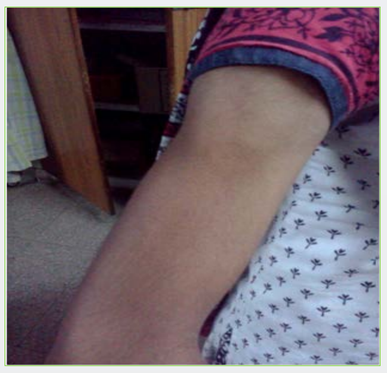
Body composition was assessed by DXA scan

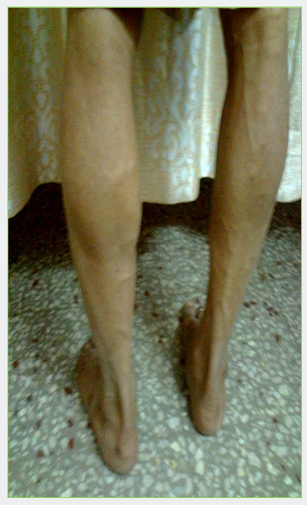
REGION	FAT (gm)	% FAT
Lt Arm	249.6	13.7
Rt Arm	295	15
Trunk	3361.2	14.2
Lt Leg	837.7	12.0
Rt Leg	1053	14.3
Head	**833**	**20.3**
Total	6629.7	14.4

Limbs and trunk had very less fat with increased fat in the head









INVESTIGATIONS

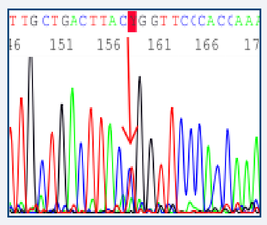
Parameters	Mother	Daughter
C-peptide (ng/ml) Fasting 2h Post-meal	3.2 3.6	1.43 3.67
Fasting insulin (µIU/ml)	52.5	6.99
HOMA-IR	23.33	3.11
Triglycerides (mg/dl)	118 (on treatment)	1070

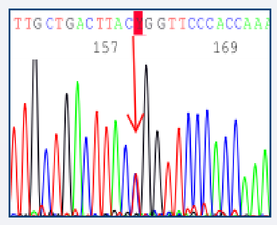
HOMA-IR- Homeostatic model assessment of Insulin resistance

RESULTS OF GENETIC TESTS

The NGS of LMNA gene showed that mother and daughter were both heterozygous for a reported c.1444C > T missense mutation which causes the substitution of the Arginine at residue 482 by a Tryptophan. This identified mutation was confirmed by Sanger sequencing.

LMNA Mutation in the mother and daughter





DISCUSSION

- The subject and her mother were diagnosed to have diabetes mellitus at young age, never had keto-acidosis, had cushingoid appearance of face, features of insulin resistance, fat atrophy in the limbs with prominent muscle contours, and hepatomegaly consistent with familial partial lipodystrophy.
- Both subjects also had elevated C-peptide levels and HOMA-IR suggestive of insulin resistance, and Dual energy X-ray absorptiometry showed increased fat in the face with decreased limb fat confirming fat redistribution. Further, genetic testing helped in confirming the diagnosis.
- With this diagnosis, Metformin was added and better glycaemic control was achieved.

CONCLUSIONS

Our subjects had a clinical form of FPLD2 due to a mutation affecting LMNA gene. A high index of clinical suspicion based on the phenotype, followed by appropriate biochemical and genetic testing led to the diagnosis in this family. A clear understanding of the disease process is very important to choose the right treatment modalities, predict the natural history of the disease and to determine the prognosis.

REFERENCES

1. C. Vantyghem, et al, Patients with Familial Partial Lipodystrophy of the Dunnigan Type Due to LMNA R482W Mutation Show Muscular and Cardiac Abnormalities. Journal of Clinical Endocrinology and Metabolism; November 2004, 89(11):5337-346

2. Nicholas Cholas Tritos et al ,Syndromes of Severe Insulin Resistance, Journal of Clinical Endocrinology and Metabolism; 1998: Vol 83 :3025-3030

3. Nabrdalik et.al., Endokrynol Pol. 2013;64(4):306-11.

E-mail- nihal_thomas@yahoo.com