Gene 642 (2018) 398–407

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Research paper

# Mucolipidosis type III gamma: Three novel mutation and genotype-phenotype study in eleven patients

Beyhan Tüysüz[a,*], Özgür Kasapçopur[b], Dilek Uludağ Alkaya[a], Sezgin Şahin[b], Betül Sözeri[c], Gözde Yeşil[d]

[a] Department of Pediatric Genetics, Cerrahpasa Medical School, Istanbul University, Istanbul, Turkey
[b] Department of Pediatric Rheumatology, Cerrahpasa Medical School, Istanbul University, Istanbul, Turkey
[c] Department of Pediatric Rheumatology, Ege University Medical School, Izmir, Turkey
[d] Department of Medical Genetics, BezmialemVakif University, Istanbul, Turkey

ARTICLE INFO

*Keywords:*
Mucolipidosis III gamma
*GNPTG*
Genotype
Phenotype

ABSTRACT

Mucolipidosis type III gamma (MLIII gamma) is a lysosomal storage disease characterized by joint stiffness, mild coarse face and corneal clouding, which becomes recognizable usually in childhood. Biallelic mutations in the *GNPTG* gene, which encode the γ subunit of the *N*-acetylglucosamine-1-phosphotransferase enzyme, are the underlying cause of MLIII gamma. The aim of this study is to evaluate the longitudinal findings and genotype of eleven patients from eight families with MLIII gamma and to establish a genotype-phenotype correlation. The most frequently observed initial finding was stiffness of finger joints, which detected in patients between 18 month-olds and five year-olds. However, in four patients presented here, initial finding was knee pain or waddling gait, which started between six-16 years of age. All patients also had variable degrees of stiffness on large joints. The longest follow up period was 16 years while the shortest was three years and six months. We observed that the patients who had an early onset disease and severe joint stiffness had also rapidly progressive joint involvement mostly localized in hands, shoulders, and hip. However; the patients with late onset and/or mild joint stiffness experienced slowly progressive symptoms. Most patients dropped in their growth curve in time and the ones who were severely affected reached the final height below the third centile. Seven disease-causing mutations, three of them novel, were detected in *GNPTG* gene. According to our clinical observations c.493_494insC and c.283_284insC mutations lead to a severe phenotype and c.196C > T, c.347_349del, c.652_655delTACT and c.445delG/c.367A > G mutations seemed to generate a milder phenotype.

## 1. Introduction

Mucolipidosis II (MLII) (OMIM#252500) and III (OMIM#252600 and 252605) are rare autosomal recessive lysosomal storage disorders. The fundamental defect is related with *N*-acetylglucosamine-1-phosphotransferase enzyme, which has an essential role in the trafficking of almost all lysosomal hydrolases by controlling mannose-6-phosphate activity. This enzyme is composed of three subunits. Alpha and beta subunits are encoded as a single αβ polypeptide by *GNPTAB* gene and the gamma subunit is encoded by *GNPTG* gene (Braulke et al., 2008; Qian et al., 2010). Mutations in the *GNPTAB* gene have been associated with MLII and MLIIIalpha/beta phenotypes, whereas *GNPTG* mutations have only been found in MLIIIgamma patients.

While patients with MLII have complete deficiency of this enzyme, MLIII alpha/beta patients show varying amounts of residual enzyme activity (Cathey et al., 2010). MLII is characterized by prenatal onset coarse face and severe skeletal abnormalities and visceral involvement leading to death during the first year of life. However, MLIII is a slowly progressing disorder that generally becomes recognizable between the ages of three to six; the clinical features are characterized by stiffness of finger and large joints, mild short stature and scoliosis (Tiede et al., 2005; Bargal et al., 2006). MLIII gamma is a milder form of MLIII and differs from MLIII alpha/beta with the absence of intellectual disability (Raas-Rothschild et al., 2000, 2004, Raas-Rothschild and Spiegel, 2010;

*Abbreviations:* α, alpha; bp, base pair(s); β, beta; cDNA, DNA complementary to RNA; dNTP, deoxyribonucleoside triphosphate; γ, gamma; GERP, Genomic Evolutionary Rate Profiling; GNPTAB, gene encoding the alpha/beta subunit of the *N*-acetylglucosamine-1-phosphotransferase; GNPTG, gene encoding the gamma subunit of the *N*-acetylglucosamine-1-phosphotransferase; kb, kilobase; JIA, Juvenile idiopathic arthritis; MLII, mucolipidosis type II; MLIII, mucolipidosis type III; mRNA, messenger RNA; OMIM, Online mendelian inherited men; PCR, polymerase chain reaction; PhyloP, Phylogenetic *P*-values; PolyPhen, polymorphism phenotyping; PVS, very strong pathogenity; RNA, ribonucleic acid; SIFT, sorting intolerant from tolerant

* Corresponding author at: Department of Pediatric Genetics, Cerrahpasa Medical School, Istanbul University, Istanbul, Turkey.
*E-mail address:* beyhan@istanbul.edu.tr (B. Tüysüz).

https://doi.org/10.1016/j.gene.2017.11.052
Received 30 July 2017; Received in revised form 7 November 2017; Accepted 17 November 2017
Available online 21 November 2017
0378-1119/ 

**Table 1**
Initial and Follow-up Clinical Manifestation of eleven patients with MLIII gamma.

| Families | | 1 | | 2 | | 3 | | 4 | | 5 | | 6 | | 7 | | 8 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patient numbers | | 1 | | 2 | 3 | 4 | | 5 | 6 | 7 | 8 | 9 | | 10 | | 11 | |
| Sex | | F | | M | F | M | | M | M | M | M | M | | M | | M | |
| Onset of initial findings (years) | | 4 | | 12 | 16 | 6 | | 5 | 4.5 | 6 | 7 | 3.5 | | 1.5 | | 1.5 | |
| Initial findings | | Stiffness of finger joints | | Knee pain | Knee pain | Walking gait | | Stiffness of fingerjoints | Stiffness of finger joints | Knee pain | Stiffness of finger joints | Stiffness of finger joints | | Stiffness of finger joints | | Stiffness of finger joints | |
| Initial diagnosis | | JIA | | Arthritis | − | − | | − | − | JIA | JIA | − | | JIA | | − | |
| Age at diagnosis (years) | | 6.5 | | 21 | 19 | 7 | | 7.5 | 5 | 19.5 | 14.5 | 8.5 | | 12.5 | | 4.5 | |
| Age at most recent examination (years) | | 22.5 | | 28 | 26 | 14.5 | | 13.5 | 11 | 23.5 | 18.5 | 20.5 | | 16 | | 8.5 | |
| Duration of follow-up (years) | | 16 | | 7 | 7 | 7.5 | | 6 | 6 | 4 | 4 | 12 | | 3.5 | | 4 | |
| Short neck | | + | | + | + | − | | − | − | − | − | + | | + | | − | |
| Scoliosis | | − | | ++ | ++ | − | | + | − | + | + | − | | − | | − | |
| Hyperlordosis | | + | | − | − | + | | − | − | ++ | ++ | + | | + | | ++ | |
| IQ | | 107 | | 100 | 95 | 103 | | 100 | 100 | 106 | 95 | 90 | | 60 | | 90 | |
| Joint stiffness | | * | ** | * ** | * ** | * ** | | * ** | ** ** | * ** | * ** | * ** | | * ** | | * ** | |
| Fingers | | ++ | ++ | + + | + + | + + | | + + | + + | + ++ | + + | ++ | +++ | +++ | +++ | ++ | ++ + |
| Shoulders | | + | + | − − | − − | − − | | + + | + + | + + | + + | ++ | +++ | ++ | +++ | ++ | ++ + |
| Elbow | | + | + | − − | − − | − − | | + + | − + | + + | + + | + | + | + | ++ | + | + + |
| Wrist | | + | + | − − | − − | − − | | − + | − + | + + | + + | + | + | + | + | + | + + |
| Hip | | + | + | + + | + + | + + | | + + | + + | + + | + + | + | ++ | ++ | +++ | + | ++ |
| Knees | | + | + | − − | − + | − − | | − − | − − | + + | + + | + | + | + | ++ | − | + |
| Ankles | | − | − | − − | − − | − − | | − − | − − | − + | + + | + | + | − | + | − | − |
| Coarse face | | Mild | | − | − | − | | Mild | Mild | − | − | Mild | | − | | Mild | |
| Corneal clouding | | + | | − | − | − | | + | + | − | − | − | | − | | − | |
| Hepatosplenomegaly | | − | | − | − | − | | − | − | − | − | − | | − | | − | |
| Echocardiography | * | N | | MVI, AVT | MVI, AVT | N | | MVI | N | AVI MVI | MVP | ST | | N | | N | |
| | ** | N | | No change | No change | N | | No change | N | No change | No change | No change | | N | | N | |
| Height (cm/SDS) | * | 116/− 0.5 | | 162/− 2 | 150/− 2 | 129/+2.4 | | 120/− 1.1 | 107/− 0.1 | 173/− 0.5 | 151/− 0.3 | 123/− 1.6 | | 126/− 3.7 | | 100/− 2 | |
| | ** | 150/− 2 | | 162/− 2 | 150/− 2 | 168/+0.7 | | 144/− 1.7 | 132/− 1.4 | 173/− 0.4 | 170/− 0.6 | 150/− 4 | | 148/− 4 | | 120/− 2 | |
| Bone mineral densitometry (DEXA) | * | − 2.7 | | − 1.3 | − 1.5 | − 0.1 | | − 1.0 | − 1.2 | − 2.9 | − 0.93 | − 2.5 | | − 1.8 | | − 1.3 | |
| | ** | + 1 | | − 1.0 | − 1.0 | + 0.3 | | − 0.5 | − 1.0 | − 1.2 | − 1.3 | − 1.28 | | − 2.1 | | − 1.6 | |
| Surgical interventions | | − | | Carpal tunnel | − | Coxa valga | | − | − | Carpal tunnel | Carpal tunnel | Atlantoaxial instability | | − | | − | |

F: Female, M: Male, JIA: Juvenile idiopathic arthritis; *: first examination, **: Most recent examination; +: mild; ++: moderate; +++: severe; IQ: intelligence quotient, MVI: Mitral valve insufficiency; AVT: aortic valve thickening; AVI: aortic valve insufficiency; MVP: Mitral valve prolapse; ST: Septal thickening; N: Normal; SDS: Standard deviation score.