P-110

Inherited COL6A3 gene mutations in a patient with gross motor delay; a case report

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INTRODUCTION

The **COL6A3 gene** encodes the main chain of **collagen VI** which is one of key component of extracellular matrix comprising the musculoskeletal system. The gene is responsible for dystrophy of skeletal muscles, thereby leading to **congenital muscular disorders** such as **Ullrich congenital muscular dystrophy (UCMD)** or **Bethlem myopathy (BM).** Clinical symptoms include **general muscular weakness** and **decreased muscle tone** with **distal joint looseness**. Previous studies revealed that the various mutation of the genes can cause phenotypes of varying degrees, even within the same disease. Here we present the inherited mutation of COL6A3 gene presenting gross motor delay and hypotonia beyond the normal range, but not as severe as diagnosed with 'myopathy'.

CASE REPORT

A 13-months-old girl was referred for delayed gross motor development
In the initial physical exam, there was mild hypotonia of trunk and limb muscles.

Birth history

- Full term – 2.78Kg – Vaginal delivery

Developmental evaluation

Bayley-III Scales were administered at 13, 19 and 24 months of age and results are displayed in the table below (Table 1). Overall balance was evaluated by using **Berg Balance Scale for Pediatrics (PBS)**, scoring **36** out of 56, which falls behind peers around the same age

Genetic evaluation

In targeted next generation sequencing (NGS), **COL6A3 gene (c.539C>T, heterozygous)** was detected. Subsequent segregation study of her family was done and **the same mutation was found in her father**. He was later found to have the history of delayed milestone in motor area.
Eventually he grew up normally and has no problem with walking and carrying out activities of daily living in present, which may imply favorable prognosis of the patient.

Developmental evaluation (The Bayley III)	12 months		19 months		24 months	
	DAE (months)	Composite Score	DAE (months)	Composite Score	DAE (months)	Composite Score
Cognitive	14	100	19	100	27	110
Receptive communication	16	112	23	112	29	97
Expressive communication	17		19		19	
Fine motor	15	79	22	88	29	107
Gross motor	9		11		21	
Social-emotional	-	100	-	105	-	100
Adaptive behavior	-	111	-	104	-	108

DAE; Developmental age equivalent

Table 1. Developmental evaluation of the patient using the Bayley III scales of Infant Development.

Speech evaluation (25 months)	**SELSI**		**PRES**	
	DAE	Quotient	DAE	Percentile
Receptive communication	27 months	108	22 months	90%
Expressive communication	19 months	76	19 months	<1%

DAE; Developmental age equivalent

Table 2. Speech evaluation by using Sequenced language scale for infants (SELSI) and Preschool Receptive-Expressive language Scale (PRES)

DISCUSSION

We report the **inherited mutation of COL6A3 gene (c.539C>T)** presenting **hypotonia** and **gross motor delay**. The gene is well known to be related with myopathies of various degrees of severity, such as BM or *UCMD* and may explain the gross motor delay of the patient. As the father of the patient only showed mild transient delay in motor development during infancy, we may expect good prognosis of the patient and further follow up would be necessary. As the found mutation is variant of unknown significance (VUS), additional research will also be needed.

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