Skeletal Dysplasia with short stature and a Larsen-like Phenotype due to a homozygous mutation in B3GAT3

Elisabeth Steichen-Gersdorf, Department of Pediatrics 1, Medical University of Innsbruck
Franco Laccone, Institute of Medical Genetics, Vienna, Austria

E-mail: Elisabeth.steichen@i-med.ac.at

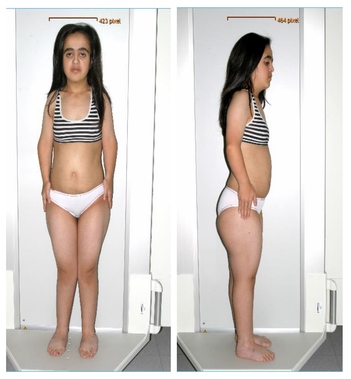
Introduction

Proteoglycans are important components of cell plasma membranes and extracellular matrices of connective tissues.
The basic structure of each proteoglyan consists of a gylcosaminoglycan side chain attached to a core protein via a tetrasaccharide linker region . The first sugar is a Xylose unit enzymatically added onto the serine residue of the core protein. Subsequent addition of two galactose and one glucuronic acid completes the process. The specific enzymes that catalyze each of the steps have well been characterized and defects have been asigned to a pleiotropic spectrum of connective tissue disorders (Fig2). Most of them with short stature, dislocation of large joints, joint laxity and/or skoliosis.
B3GAT3 mutations are rare and have been reported previously in two Arabian families with short stature and joint laxity. The female patient with a novel homozygous mutation expands the spectrum of the impaired proteoglycan synthesis.

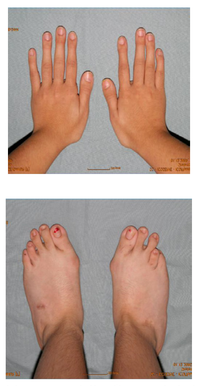
Patient Report

We report on a girl with disproportionate short stature and joint laxity with pes planus and radial head dislocation. The girl is the 1st child of a consanguinous turkish mating, born at 37 weeks, BW 2140g, L 43cm (<P3rd), mildly delayed motor devellopement and normal intelligence. She was previously assigned to Spondylo-epimetaphyseal dysplasia with joint laxity type 1 (SEMDJL1), a similar phenotype with progressive severe kyphoscoliosis, thoracic asymmetry, and respiratory compromise resulting in early death. A novel homozygous mutation in B3GAT3 was detected by whole-exome-sequencing causing a Larsen-like phenotype with skeletal involvement including elbow deformities with radial head dislocation, genu valgum, hypermobile joints, flat feet, and tapered fingers with spatulate distal phalanges. The girl had a round face, bifid uvula, high arched palate, flat midface, prominent eyes with blue sclerae, and a long philtrum. Bone density (BMD) at the age of 18 years was low with L1-4 ,Z score-1,8. Final height was 129,5 cm (-5,3 SDS),weight 37kg (<3rd centile)

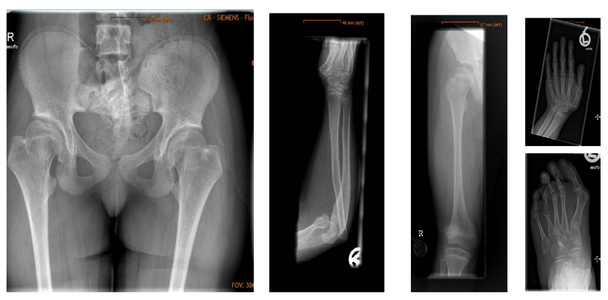
Clinical features



Patient at 13 years, dysproportionate short stature, round flat face, prominent eyes, radial head dyslocation, genu valgum



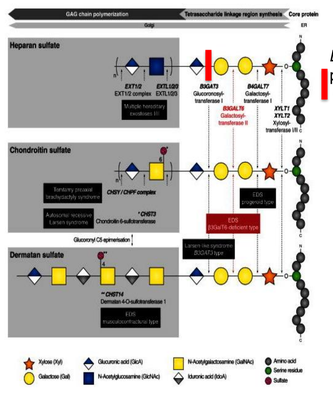
Hypermobile finger joints, spatulate distal phalages, pes planus, halux valgus



Short femoral neck, radial head dyslocation, subluxation of knee joint, irregular carpal bones, halux valgus

Fig.1

Glycosaminoglycan Synthesis



B3GAT3- c.416C>T, p.Thr139Met
Glucoronyltransferase 1 deficiency

Schematic Illustration of Glycosaminoglycan Synthesis Malfait et al Am J Hum Genet 2013

Fig. 2

Whole Exome Sequencing

Whole Exome Sequencing by SOLID 5500 (ThermoFIsher) revealed a homozygous missense mutation in B3GAT3-gene coding for Glucoronyl-transferase I (enzymatic step in the Golgi apparatus for a linkage region synthesis of proteoglycans i.e heparan sulfate) c.416C>T, p.Thr139Met. (Fig2): This residue is highly conserved and predicted as pathogenic by Polyphen-2 and MutationTaster.

Discussion

We add an additional case with a spondyloepimetaphyseal dysplasia to a group of patients with features of Ehlers-Danlos or Larsen-like phenotype with a unique combination of multiple dyslocations and joint laxity, caused by mutations in the linker region of glycosaminoglycans (GAG). This includes syndromes with mutations of enzymes in the GAG side chain polymerization such as B3GAT3, B3GALT6 (Ehlers-Danlos- like), B4GALT6 (Ehlers-Danlos-like syndrome with kyphoskoliosis), B4GALT7 (Larsen of Reunion Island Syndrome) and XYLT1 (Desbuquois Dysplasia Type 2).
Glucoronosyl-transferase deficiency 1, encoded by *B3GAT3* is supposed to result in defects in collagen supramolecular organisation, which is responsible for several of the observed clinical features. Bone mineral density was in the lower range, however compared to Galactosyl-transferase II (*B3GALT6*) mutations, early onset fractures did not occur in this patient.

References:

1. Von Oettingen J, Tan WH, Dauber A. 2014: Am.J. Med. Genet 164A,1580-6
2. Baasanjav S, Al-Gazali L, Hashiguchi T et al. , Am J Hum Genet 89:15-27
3. Malfait F, Kariminejad A, Van Damme T et al 2013, Am J Hum Genet 92,935-45

The authors declare no conflict of interests

ESPE 2015 452-P2
Growth
Elisabeth Steichen-Gersdorf
DOI: 10.3252/pso.eu.54espe.2015
Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology
PosterSessionOnline.com