CASE REPORT

DOI: 10.5336/caserep.2020-75862

The First Turkish Family with Skeletal Abnormality and Novel *NPR2* Gene Mutation

Nadide Cemre RANDA[a]

[a]Department of Medical Genetics, University of Health Sciences Antalya Training and Research Hospital, Antalya, TURKEY

ABSTRACT The skeletal dysplasias are rare and extremely heterogeneous group of developmental abnormalities. The genetic etiology of approximately 500 skeletal diseases has been identified, and molecular mechanism of all the remaining dysplasias is unclear. Recently, identification of numerous genes implicated in genetic disorders helped in the understanding of the pathophysiology of various conditions. Skeletal dysplasias are considered as good models to illustrate these scientific advances. Further advances had allowed new therapeutic approaches for several conditions, whether they are targeted to specific genes,gene products, or pathways and processes that are altered by the gene mutations. Here we report the first turkish family with lower limb anomalies and NPR2 gene mutations.

Keywords: Bone development; bone diseases, developmental; atrial natriuretic factor receptor B

Presently, there are more than 450 characterized skeletal dysplasias that are frequently recognizing in neonatal or prenatal period with short stature, disproportion and ultrasonographic or radiographic abnormalities.[1] These displasias result from mutations in several genes which have various function in many processes such as regulation of transcription, inta/extracellular signalling, transporting, and a number of gene products of currently unknown function.[2] Known skeletal dysplasias could be inherited in both Mendelian and non-Mendelian manner. Determination of inheritance mode is crucial for recurrence risk calculation and genetic counseling. Besides since the genes that cause skeletal dysplasias have a wide range of functions in troughout the body, they could also be targets for the treatment of any other diseases.[1,2]

Here, by reporting the Atrial Natriuretic Factor Receptor B (*NPR2*) gene mutation that we detected in a family with developmental anomalies in the lower limbs, we wanted to point out the importance of elucidating the genetic etiology of developmental anomalies for new treatment options.

CASE REPORT

A 3 year-old male patient was referred to our outpatient clinic from orthopaedics department. The disproportion of right femur was recognized in the newborn period, and prosthetic surgery was planned.

The patient had any dysmorphic features and developmental delay. The patient's head circumference, height and weight were 42 cm (10-25p), 97 cm (3-10p) and 1500 gr (25p), respectively. The left and right femoral length, and lower legs' measures follow approximately 220, 50, 192 and 192 mm. After physical examination, complete anterior/posterior and lateral radiographs of the spine, pelvis and lower extremities were obtained (the informed consent from signed by mother, and she permitted to share radiographic images of the patient but did not allow to publish the photos that taken during physical examination) (Figure 1). Any organ abnormalities beyond the skeleton was not found.

Correspondence: Nadide Cemre RANDA
Department of Medical Genetics, University of Health Sciences Antalya Training and Research Hospital, Antalya, TURKEY
E-mail: dr.nadidecemreranda@gmail.com

Peer review under responsibility of Turkiye Klinikleri Journal of Case Reports.

Received: 06 May 2020 ***Accepted:*** 25 May 2020 ***Available online:*** 11 May 2020

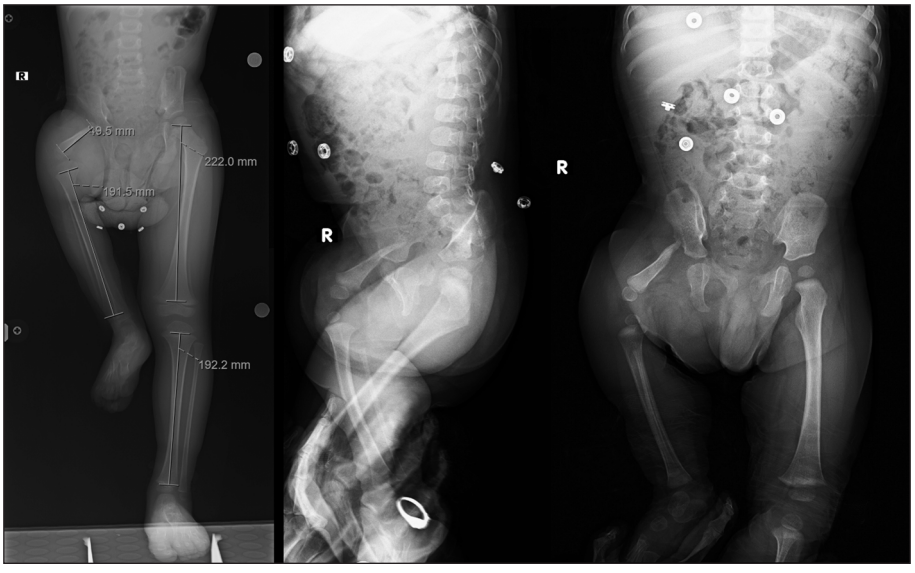

FIGURE 1: The X-ray images of the patient.

The patient's mother also had disproportion of the left lower extremity without any health issues. In her physical examination, left leg was 3 cm shorter, and approximately 10 cm thinner than the right leg. Her height was 150 cm and no one in her family as short as her.

In order to determine whether the patient and his mother have any gene mutations, we performed whole exome sequencing (WES), and analysed possible causative genes that only exists both in patient and mother (Table 1). Our WES analysis revealed that a novel c.494G>A mutation in *NPR2* gene which leads to disruption of bone development in embryologic period.

WES ANALYSIS

All variants that were obtained from the patient and mother were filtered according to zygosity status. Genes that were heterozygous in both patient and mother were selected. The variants of these selected genes were eliminated which are with a population frequency above %5, not defined in OMIM and not associated with any skeletal diseases. After this step, there were only the *NPR2* c.494G>A and LTBP3 c.-26C>T variants left, and evaluated according to the American College of Medical Genetics (ACMG) criteria.[3] The variant was considered as likely pathogenic due to its missense nature (PP2), absence

TABLE 1: The variant list that both found in the patient and the mother.

Shared variants	Zygosity	Population frequency	Variant location/nature	Associated diseases	Segregation analysis	ACMG criterias*	Conclusion
NPR2 c.494G>A	Heterozygous	NA	Exon 1/missense	Acromesomelic dysplasia, Maroteaux type, AR Epiphyseal chondrodysplasia, Miura type, AD Short stature with nonspecific skeletal abnormalities, AD	P+ M+ F-	PP1_mod,PP2, PP4_mod,PM2	Likely pathogenic
LTBP3 c.-26C>T	Heterozygous	0.02%	5' UTR/NA	Dental anomalies and short stature, AR Geleophysic dysplasia 3,AD	P+ M+ F-	BP7,PM2	Not causative

ACMG criterias were well defined in reference 3.
NA: Not applicable; UTR: Untranslated region; AR: Autosomal recessive; AD: Autosomal dominant; P+ M+ F-: Found in patient and mother, not found in healthy father.

in population databases (PM2), family segregation (PP1_mod), and compatible clinical findings with the *NPR2* gene (PP4_mod).

DISCUSSION

Heritable skeletal dysplasias are highly heterogeneous disorders group and divided into 42 subgroups. Over time, after developments in molecular genetics era, radiographic, clinical and molecular overlapping had been recognized, and it became difficult to distinguish these disorders.[1,2]

Medical care of children with skeletal disorders should be managed with a multidisciplinary approach and should be tailored to the patient's problems. Genetically approved diagnosis improves the medical care given to patients, helps in giving familial recurrence risk, and preventing morbidity and mortality. The principles of long-term follow-up are based on determining of the associated conditions with skeletal dysplasias.[2,4]

Life expectancy in children with non-lethal skeletal dysplasia is normal, and they do not need any medical treatment other than protheses and/or orthopedic surgery.[4] However, if there are any other allelic disorders caused by the identified gene, molecular diagnosis can be life-saving for these diseases. Finding the genetic causes of skeletal dysplasias, whether the patient needs medication or not, may give a chance to develop drugs for other diseases in which the same gene has a role.

In this report, we identified a novel *NPR2* gene mutation in a family with varying severity of lower limb developmental abnormality. To our knowledge, there is not a case report presenting severe unilateral limb hypoplasia with *NPR2* gene mutations in the literature. Unsignificance skeletal findings have been described in the phenotypic spectrum of individuals with *NPR2* mutations, but the frequency or details of these abnormalities have not been reported.[5-7] Variable responses to rhGH treatment have been reported in 8 patients with *NPR2* heterozygosity, with the change in height SDS ranging from -0.3 to + 1.8.[4]

NPR2, also known as guanylyl cyclase B, is one of the regulatory pathways which control division and differentiation of chondrocytes and cartilage growing. Inactivating mutations in *NPR2*, which reduce cGMP, result in severe shortening of bones in mice and humans beings.[8,9]

Additionally, Geister et al. identified that defective *NPR2* gene reduces bone growth and suggested that inhibition of the MEK/ERK MAPK pathway could restore negative affects of *NPR2* gene mutation.[7,9,10] In the future, new treatment options may be developed by well-documented patient dataset and clarifying the unknown mechanisms with advancing molecular tests.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

REFERENCES

1. Mortier GR, Cohn DH, Cormier-Daire V, Hall C, Krakow D, Munglos S, et al. Nosology and classification of genetic skeletal disorders: 2019 revision. Am J Med Genet A. 2019;179(12):2393-419. [Crossref] [PubMed]
2. Marzin P, Cormier-Daire V. New perspectives on the treatment of skeletal dysplasia. Ther Adv Endocrinol Metab. 2020;11: 2042018820904016. [PubMed]
3. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-24. [PubMed]
4. Vasques GA, Hisado-Oliva A, Funari MFA, Lerario AM, Quedas EPS, Solberg P, et al. Long-term response to growth hormone therapy in a patient with short stature caused by a novel heterozygous mutation in NPR2. J Pediatr Endocrinol Metab. 2017;30(1):111-6. [Crossref] [PubMed]
5. Jacob M, Menon S, Botti C, Marshall I. Heterozygous NPR2 mutation in two family members with short stature and skeletal dysplasia. Case Rep Endocrinol. 2018;2018:7658496. [Crossref] [PubMed] [PMC]
6. Wang W, Song MH, Miura K, Fujiwara M, Nawa N, Ohata Y, et al. Acromesomelic dysplasia, type maroteaux caused by novel loss-of-function mutations of the NPR2 gene: three case reports. Am J Med Genet A. 2016;170A(2):426-34. [Crossref] [PubMed]
7. Geister KA, Brinkmeier ML, Hsieh M, Faust SM, Karolyi IJ, Perosky JE, et al. A novel loss-of-function mutation in NPR2 clarifies primary role in female reproduction and reveals a potential therapy for acromesomelic dysplasia, Maroteaux type. Hum Mol Genet. 2013;22(2):345-57. [PubMed]
8. Miura K, Namba N, Fujiwara M, Ohata Y, Ishida H, Kitaoka T, et al. An overgrowth disorder associated with excessive production of cGMP due to a gain-of-function mutation of the natriuretic peptide receptor 2 gene. PLoS One. 2012;7(8):e42180. [Crossref] [PubMed] [PMC]
9. Peake NJ, Hobbs AJ, Pingguan-Murphy B, Salter DM, Berenbaum F, Chowdhury TT. Role of C-type natriuretic peptide signalling in maintaining cartilage and bone function. Osteoarthritis Cartilage. 2014;22(11):1800-7. [PubMed]
10. Sogawa C, Tsuji T, Shinkai Y, Katayama K, Kunieda T. Short-limbed dwarfism: slw is a new allele of NPR2 causing chondrodysplasia. J Hered. 2007;98(6):575-80. [Crossref] [PubMed]