Egyptian Journal of Medical Human Genetics

CASE REPORT Open Access

Case report: a de-novo 7p12.3 microduplication detected in an infant with perineal hamartoma and imperforate anus

Ayca Kocaaga[1*], Sevgi Yimenicioglu[2] and Cigdem Arslan Alıcı[3]

Abstract

Background: Anorectal malformations (ARM) represent a wide spectrum of defects. Caudal and genitourinary malformations can associate with anorectal malformations. Genetic factors may play role in the development of anorectal malformations. Perineal masses like sacrococcygeal teratoma, rectal prolapse, or duplication cysts were reported before, but their association with perineal hamartoma and anal atresia is extremely rare.

Case presentation: Here, we report an 11-month-old female infant. She had 551 kb duplication at 7p12.3 with perineal hamartoma and anal atresia consisting a cystic lesion with a diameter of 4 mm at the filum terminale (L2 vertebra) on lumbar magnetic resonance imaging (MRI) in neonatal period. She presented with hypotonia. She had anorectal anomaly and external perineal mass bulging from left major labium extending across anal region with imperforate anus. There was 1 × 1 cm polyp-like protrusion on it. She was operated in neonatal period. Genetic laboratory investigations showed karyotype 46, XX. The microduplication of the chromosome 7p12.3 was detected by microarray analysis. There were not any significant homozygous or heterozygous variants determined by whole-exome sequencing.

Conclusions: To the best of our knowledge, this is the first report of a patient with a microduplication of the chromosome 7p12.3, and second case with perineal hamartoma and imperforate anus. Clinicians should pay attention to microdeletions and microduplications while giving genetic counseling to patients with urogenital and anorectal abnormalities.

Keywords: 7p12.3 microduplication, Anorectal malformations, Hamartoma, Microarray analysis

Background

Anorectal malformations (ARM) represent a wide spectrum defects and present in 2–5 per 10,000 live births. These malformations include a variety of caudal and genitourinary malformations, e.g. sacral masses, gynecologic, sacral anomalies, esophageal, duodenal, and anal atresia [1]. Perineal masses are sacrococcygeal teratoma, rectal prolapse, or duplication cysts. Its association with perineal hamartoma and anal atresia is extremely rare [2]. Chromosomal microdeletions and microduplications are present the main genetic etiologies for children who have dysmorphic features and congenital abnormalities [3]. The association between 7p12.3 microduplication and ARM has not been fully understood. Here, we report a female infant with 551 kb duplication at 7p12.3 with perineal hamartoma and anal atresia.

Case presentation

An 11-month-old girl admitted the genetic outpatient clinic due to congenital hypotonia with genetic test results. She was the first child from a non-consanguineous marriage. There was not any significant family history. She was born with C/S delivery at a gestational age

*Correspondence: dr.aycacelikmakas@hotmail.com
[1] Department of Medical Genetics, Eskişehir Şehir Hastanesi, 71 Evler Mahallesi, Çavdarlar Sokak, 26080 Odunpazarı, Eskişehir, Turkey
Full list of author information is available at the end of the article

of 40 weeks and her birth weight was 3400 g. She was hospitalized in the neonatal intensive care unit because of anal atresia, and a mass in the genital area. The mass was 4 × 5 cm size, soft in nature bulging from left major labium extending across anal region with imperforate anus. There was 1 × 1 cm polyp-like protrusion on it. Meconium passage was open (Fig. 1A, 1B). She was operated when she was on neonatal period. The perineal poly-like lesion was excised. A colostomy was opened due to anal atresia. Colostomy was closed one month later. The histopathological examination of perineal poly-like lesion revealed a hamartoma containing adipose tissue, which was separated with fibroid tissue. In physical examination, there was not edema, joint laxity or tenderness, leg length asymmetry, other cutaneous lesions. She had a length of 74 cm (25th to 50th percentile), a weight of 8.430 kg (10th to 25th percentile) and a head circumference of 44.5 cm (25th percentile). She had long philtrum, thin upper lip, big round eyes, and wide forehead. Her visual and hearing examinations were normal. She could not sit without support. Deep tendon reflexes were normal. The Babinski sign was flexor and there was not a clonus sign. She slipped her head back with traction. Denver 2 development test revealed; personal-social task: one delay (self-eating biscuit), fine motor function: one warning (do not hit cubes together), language: compatible with age, great motor function: one warning (standing by holding). The brain magnetic resonance imaging (MRI) was normal. Lumbar MRI revealed a cystic lesion with a diameter of 4 mm at the filum terminal (L2 vertebra) (Fig. 1C, 1D). Diagnostic studies to localize other abnormalities

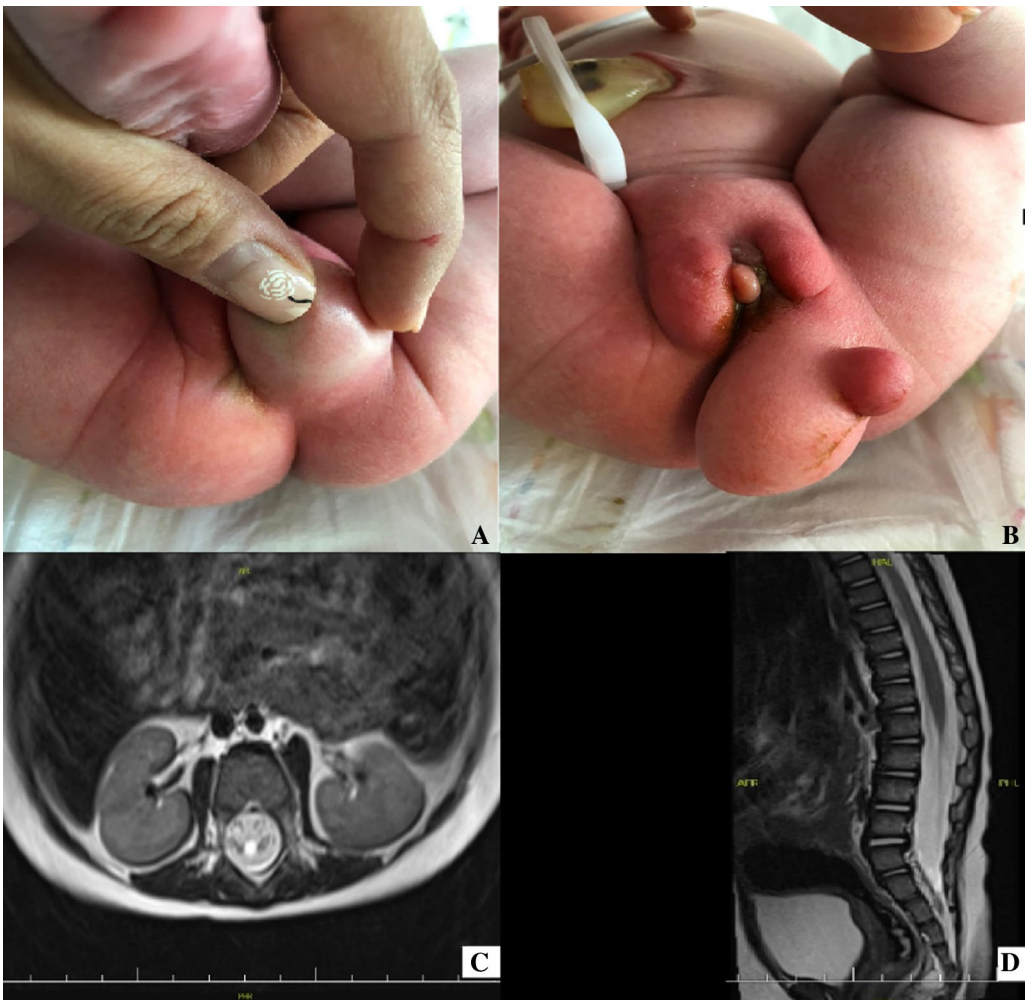

Fig. 1 Mass on anorectal region and filum terminale cyst. **1A** Mass with 4 × 5 cm, **1B** 1 × 1 cm polyp-like skin protrusion, **1C**, **1D**: cystic lesion at filum terminale

in the urinary tract and cardiovascular system were normal. Laboratory findings were as follows: Creatinine kinase = 114 (N: 26–192 U/L), methyl malonic acid = 24.4 (N: 1.9–17 Umol/L, homocysteine = 10.24 (N: 4.4–13.5 Umol/L) in the blood. Urine organic acid analysis and tandem mass were normal. Chromosome analysis of patient was showed 46 XX female karyotype (Fig. 2). DNA sample obtained from peripheral blood was studied by using Agilent Oligonucleotide microarray to investigate for copy number variants was done using the 8X60K probe. The results were analyzed in Agilent Cytogenomic 5.0.0.38/GRCh37/hg19 analysis program. Microarray analysis was revealed 551 kb region on 7p12.3 duplication (position: 7:47,596,152–48,148,091; Fig. 3). This interval includes four genes (*TNS3, PKDILI, HUSI, UPP1*) associated with OMIM genes. Karyotype analysis of maternal was 46, XX and paternal was 46, XY. The microarray analysis of both parents were showed normal copy number and hybridization signals. We suggested that the microduplication of 7p12.3 was de-novo. Whole-genome sequencing of a DNA sample from our patient was performed by MGI (DNBSEQ-G400). The exome sequencing was negative for pathogenic variants or uncertain significance

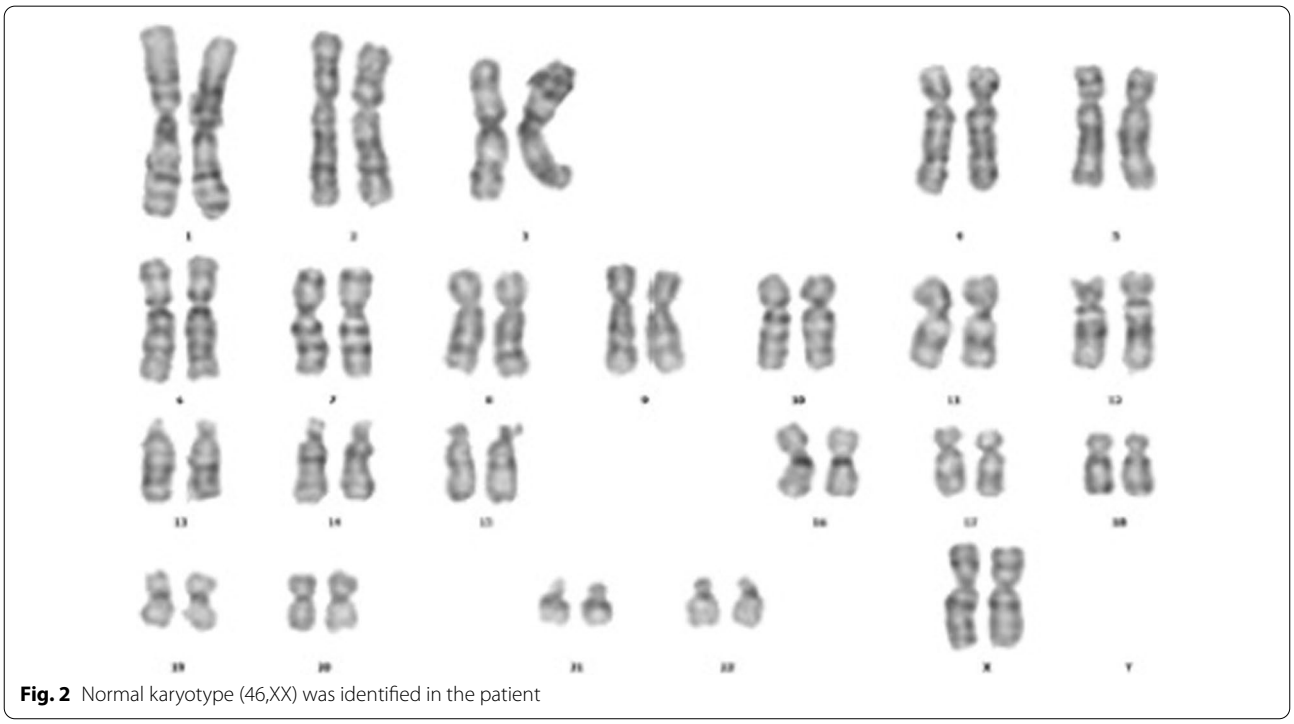

Fig. 2 Normal karyotype (46,XX) was identified in the patient

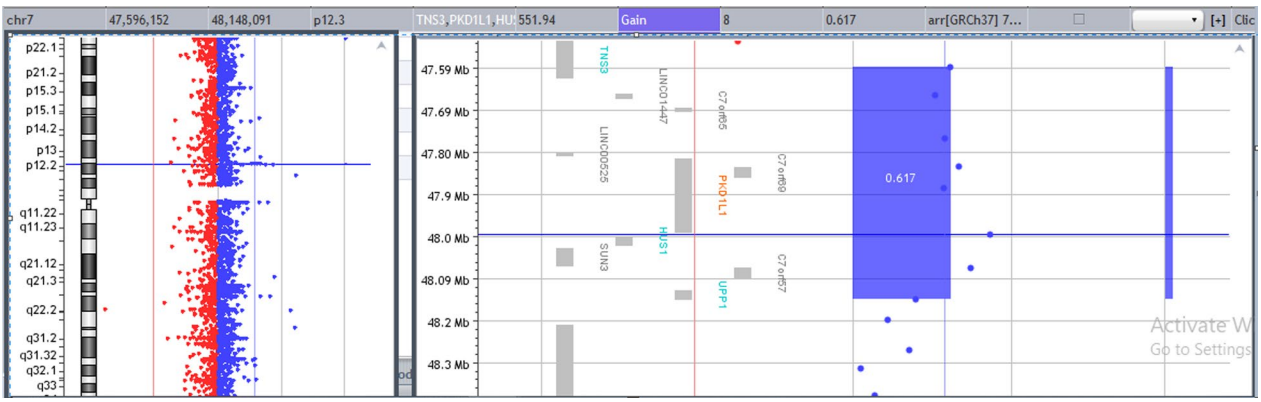

Fig. 3 Array-CGH results showing a 7p12.3 microduplication (47,596,152–48,148,091)

Table 1 Gene and gene functions in the region of 7p12.3 (position 47,596,152–48,148,091)

Gene	Description	Function of gene product
TNS3	Tensin 3	Role in actin remodeling. Involved in the dissociation of the integrin-tensin-actin complex. EGF activates TNS4 and down-regulates TNS3, which results in capping the tail of ITGB1.
PKD1L1	Polycystin 1-Like 1	Component of a ciliary calcium channel that controls calcium concentration within primary cilia without affecting cytoplasmic calcium concentration.
HUSI	Human Seminal Plasma İnhibitor-I	The antileukoprotease from human seminal plasma HUSI-I (human seminal plasma inhibitor-I) and the inhibitor found in mucous secretions from the cervix, although isolated from different tissues, seem to be identical proteins. Involved in the regulation of serine protease-dependent germ cell apoptosis. It also inhibits trypsin.
UPP1	Uridine phosphorylase 1	Catalyzes the reversible phosphorylytic cleavage of uridine and deoxyuridine to uracil and ribose- or deoxyribose-1-phosphate. The produced molecules are then utilized as carbon and energy sources or in the rescue of pyrimidine bases for nucleotide synthesis.

variants in genes possibly associated with this phenotype (Table 1).

Discussion

Anal atresia is a congenital anorectal malformation. The anus is not perforated and the distal enteric component ends blindly. Hamartoma is defined as a benign tumor-like nodule composed of an overgrowth. The etiology of such malformations remain unclear and it is multifactorial [4]. Perineal masses are divided into three categories: lipomas, vascular anomalies, and hamartomas. Association of a perineal hamartoma with anorectal anomaly is extremely rare. In a review with 2000 cases of anorectal malformations there were presented only eight cases with hamartoma. The all patients were female [5]. The coexistence of perineal hamartoma and anal atresia was documented in the literature in only one child. Yamaçake et al., reported the association of perineal hamartoma with anorectal malformations in a neonate male. The karyotype of their case was 46, XY. They did not perform any molecular genetic test [2]. The karyotype of our proband was 46,XX. We also studied molecular genetic tests (microarray and whole exome sequencing) in our patient.

Array comparative genomic hybridization or comparative genomic hybridization, is a high-resolution genome-wide screening testing to detect a majority of chromosomal imbalance and microdeletion and microduplication [6]. Our patient had anorectal malformations due to 7p12.3 duplication of 551 kb, this duplication involves the four OMIM genes *TNS3, PKD1L1, HUSI, UPP1*. The whole exome sequencing did not reveal pathogenic or VUS (variant of uncertain significance) variants in genes possibly associated with this clinical picture. There are only a few patients with "pure" 7p12 microduplication at public databases (DECIPHER). One male case was described before. He had 23.19 kb deletion at 7p12.3 chromosome (position 47,829,924–47,853,114/GRCh38). His clinical features showed intestinal malrotation, polydactyly, and renal abnormalities. This overlapped region included the *PKD1L1* gene like our patient's. The other case reported in the literature was female. She had disproportionate short stature, hypoglycemia and microcephaly. Her cytogenetic duplication was at 7p12.3 chromosome (568.84 kb) including *PKDILI, HUSI, UPP1, ABCA13* and *SUN3* genes. The duplicated coordinate was between 48,106,082–48,595,326 regions. To our knowledge the duplication at 7p12.3 chromosome is seen very rare. Therefore, its clinical impact remains uncertain and the associated phenotypes poorly characterized.

Polycysiin 1-Like 1 (PKD1L1) is a gene associates with ciliary calcium signaling and embryonic laterality determination in humans and mice. Heterozygous *PKD1L1* variants were found in patients with biliary atresia [7]. Rodriguez et al. described a patient with a homozygous *PKD1L1* mutation with situs inversus, atrial septal defect, pulmonary artery stenosis and bicytopenia [8]. In 2019, Le Fevre et al. reported bi-allelic variants in the *PKD1L1* gene associated with heterotaxy (abnormal organ arrangement) and congenital heart defects in four individuals from three unrelated families [9]. Heterotaxy of splenic, hepatic anomalies and bilobed lungs were described in the literature [10].

Human seminal inhibitor I (*HUSI*) gene encodes an inhibitor, which protects epithelial tissues from serine proteases. This gene is associated with renal osteodystrophy [11]. *UPP1* (*Uridine phosphorylase 1*) gene encodes a uridine phosphorylase that functions in the degradation and salvage of pyrimidine ribonucleotides. Gene ontology analysis shows immune and inflammatory response [12]. *Tensin 3* (*TNS3*) gene is encoding an intracellular protein. TNS3 may play an important role in actin remodeling and the dissociation of the integrin-tensin-actin complex. Downregulation of this gene contributes to metastasis in renal cell carcinoma [13]. In a study rs3750163 polymorphism of *TNS3* gene was not associated with

Immunoglobulin A nephropathy susceptibility in a Chinese Han population [14]. Duplication of chromosome 7p12.3 (including OMİM genes: *TNS3, PKD1L1, HUSI, UPP1*) can cause a spectrum of phenotypic features as seen in our patient with minor dysmorphic findings and anorectal malformations. The microduplication of our patient was not clearly associated with the clinical traits reported before. According to our knowledge, the duplication at 7p12.3 chromosome are rarely seen to date. It is expected that our case will contribute to the literature. Different phenotypic features may accompany the 7p12.3 microduplications. More detailed genetic and/or functional studies, or patients with point mutations/CNVs (copy number variants) affecting only one or a few of these genes, are needed to elucidate this possibility.

To date, this present case is the second case concerning the special coexisting of hamartoma, imperforate anus, and cystic lesion with a diameter of 4 mm at the filum terminale (L2 vertebra) on lumbar magnetic resonance imaging. Characteristics and pathogenesis of such patients have yet to be discussed and revealed. Genome-wide CNV analysis of our patient with perineal hamartoma and anal atresia was identified microduplication at 7p12.3. This case showed that association of duplication of 7p12.3 chromosome with the rare clinical entity with hypotonia, cystic lesion observed at the level of the filum terminale. Our case may help identify more cases with duplications in this region. Further studies are needed to describe anorectal malformations.

Conclusion

This case report shows the importance of molecular genotype and correlation of clinical phenotype. Although 7p12.3 duplication has not been reported before, this clinical features were suggestive it to be associated with anorectal malformations. Therefore, it is important to using the microarray analysis to identify microdeletion/microduplication with accompanied congenital malformations.

Abbreviations

ARM: Anorectal malformations; *ABCA13*: ATP-bindıng cassette, subfamily a, member 13; C/S: Caesarean delivery; ChAS: Chromosome Analysis Suite; CNV: Copy number variant; GRCh38: Genome Reference Consortium Human Build 38; *HUSI*: Human Seminal Proteinase Inhibitor; kb: Kilobase; MRI: Magnetic resonance imaging; OMİM: Online Mendelian Inheritance in Man; *TNS3*: Tensin 3; *PKD1L1*: Polycystin 1-like 1; *SUN3*: SUN domain-containing protein; *UPP1*: Uridine Phosphorylase 1; VUS: Variant of uncertain significance.

Acknowledgements

We are grateful to the participating family.

Authors' contributions

AK, SY, CAA made substantial contribution to the conception of the patient's diagnostic process, conducted the diagnostic procedures, and collected and interpreted clinical data concerning the patient. AK and SY were major contributors in drafting the initial version of the manuscript. AK reviewed and revised the manuscript. All authors read and approved the final manuscript.

Funding

Not available.

Availability of data and materials

The datas can be found in the archives of the Department of Medical Genetics, Eskişehir City Hospital.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from patient's parents for publication of this case report and accompanying images.

Competing interests

The authors declare no conflicts of interest.

Author details

[1]Department of Medical Genetics, Eskişehir Şehir Hastanesi, 71 Evler Mahallesi, Çavdarlar Sokak, 26080 Odunpazarı, Eskişehir, Turkey. [2]Department of Pediatric Neurology, Eskişehir Şehir Hastanesi, 71 Evler Mahallesi, Çavdarlar Sokak, 26080 Odunpazarı, Eskişehir, Turkey. [3]Department of Pediatric Surgery, Eskişehir Şehir Hastanesi, 71 Evler Mahallesi, Çavdarlar Sokak, 26080 Odunpazarı, Eskişehir, Turkey.

Received: 4 May 2021 Accepted: 2 September 2021
Published online: 31 October 2021

References

1. Falcone RA Jr, Levitt MA, Peña A, Bates M (2007) Increased heritability of certain types of anorectal malformations. J Pediatr Surg 42(1):124–128
2. Yamaçake KGR et al (2014) A rare case of perineal hamartoma associated with cryptorchidism and imperforate anus: case report. Einstein (São Paulo) 12(2):234–236
3. Watson CT, Marques-Bonet T, Sharp AJ, Mefford HC (2014) The genetics of microdeletion and microduplication syndromes: an update. Annu Rev Genom Hum Genet 15:215–244
4. Alamo L, Meyrat BJ, Meuwly JY, Meuli RA, Gudinchet F (2013) Anorectal malformations: finding the pathway out of the Labyrinth. Radiographics 33(2):491–512
5. Shaul DB et al (2005) Surgical management of perineal masses in patients with anorectal malformations. J Pediatr Surg 40(1):188–191
6. Belfield EJ, Brown C, Gan X et al (2014) Microarray-based optimization to detect genomic deletion mutations. Genom Data 2:53–54
7. Berauer J-P et al (2019) Identification of polycystic kidney disease 1 like 1 gene variants in children with biliary atresia splenic malformation syndrome. Hepatology 70(3):899–910
8. Rodriguez S, Chaturvedi R, Blanchette V et al (2019) PKD1L1-related situs inversus associated with sideroblastic anemia. Clin Genet 95(5):629–630
9. Le Fevre A, Baptista J, Ellard S et al (2020) Compound heterozygous Pkd1l1 variants in a family with two fetuses affected by heterotaxy and complex Chd. Eur J Med Genet 63(2):103657
10. Lin AE, Krikov S, Riehle-Colarusso T et al (2014) Laterality defects in the national birth defects prevention study (1998–2007): birth prevalence and descriptive epidemiology. Am J Med Genet A 164A(10):2581–2591

11. Averdunk L, Fitzner C, Levkovich T, Leaf DE, Sobotta M, Vieten J, Ochi A, Moeckel G, Marx G, Stoppe C (2019) Secretory Leukocyte Protease Inhibitor (SLPI)—a novel predictive biomarker of acute kidney injury after cardiac surgery: a prospective observational study. J Clin Med 8(11):1931
12. Wang J et al (2020) Uridine phosphorylase 1 is a novel immune-related target and predicts worse survival in brain glioma. Cancer Med 9(16):5940–5947
13. Carter JA et al (2013) CpG dinucleotide-specific hypermethylation of the TNS3 gene promoter in human renal cell carcinoma. Epigenetics 8(7):739–747
14. Feng Y, Su Y, Ma C et al (2019) 3'UTR variants of TNS3, PHLDB1, NTN4, and GNG2 genes are associated with IgA nephropathy risk in Chinese Han population. Int Immunopharmacol 71:295–300

Publisher's Note