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Case report

A Case of Diabetes Mellitus Type MODY5 as a feature of 17q12 Deletion Syndrome

Yaşar Köstek et al. MODY5 and 17q12 Deletion Syndrome

Hümeyra Yaşar Köstek[1], Fatma Özgüç Çömlek[1], Hakan Gürkan[2], Emine Neşe Özkayın[3], Filiz Tütüncüler Kökenli[1]
1Trakya University, Department of Pediatric Endocrinology
2Trakya University, Department of Medical Genetics
3Trakya University, Department of Pediatric Nephrology

What is already known on this topic?
HNF1B has a substantial role in the regulation of tissue-specific gene expression. Mutations in *HNF1B may* lead to organ abnormalities. The HNF1B mutation is difficult to diagnose and has a large phenotypic variation. 17q12 microdeletion syndrome, also known as 17q12 deletion syndrome, is a rare chromosomal anomaly caused by the deletion of a small amount of material from a region in the long arm of chromosome 17. It is typified by deletion of the more than 15 genes including HNF1B resulting in organ abnormalities and neurodevelopmental disorders.

What does this study add?
The HNF1B mutation is difficult to diagnose and has a large phenotypic variation . In case of clinical suspicion,further genetic examination (MLPA, array CGH) may be required since deletions and duplications can not be detected even if mutations in the HNF1B gene are not detected with NGS.

Abstract
Maturity onset diabetes of the young (MODY) is characterized by noninsulin-dependent diabetes diagnosed at a young age (<25 years) with an autosomal dominant inheritance. Rare mutations in the hepatocyte nuclear factor-1-beta (*HNF1B*) gene produce a syndrome that resemble MODY and about half of patients diagnosed with MODY5 (HNF1B mutation) have a a whole gene deletion, called as 17q12 deletion syndrome, is a rare chromosomal anomaly and is typified by deletion of the more than 15 genes including HNF1B resulting in kidney abnormalities and renal cysts and diabetes syndrome and neurodevelepmental or neuropsychiatric disorders. A 12-year-old girl was referred to our clinic, after high blood sugar was detected in the hospital where she suffered with the complaints of poliuria and polydipsia for the last 1 month. Her serum magnessium level was low (1.5 mg/dl) (normal value 1.6–2.6) and HbA1c level was 14% (normal value 3.6–5.8) and c-peptide level was 1.54 ng/ml (normal value 0.8–4). MODY5 was suspected and followed NGS gene panel (ABCC8, BLK, CEL, GCK, HNF1A, HNF1B, HNF4A, INS, KCNJ11, KLF11, NEUROD1, PAX4, PDX1, RFX6, ZFP57, GLIS3, FOXP3, NEUROG3, G6PC2) analysis revealed that there was no any mutation. On follow-up period, her serum magnessium level was low (1.2 mg/dl) and her urinary magnessium excretion was high at 172.5 mg/day. HNF1B gene mutation was considered in the patient with chronic hypomagnesemia with increased basal C peptide level. Abdominal CT and MR imagings revealed that there was a 43 mm diameter cystic lesion in the head of the pancreas, and agenesis of the pancreatic neck, trunk and tail as well. Because of there is no mutation in HBF1B gene in NGS panel, microarray analysis was performed, heterozygous deletion at 17q12 including HNF1B was detected. The HNF1B mutation is difficult to diagnose and has a large phenotypic variation . In case of clinical suspicion,further genetic examination (MLPA, array CGH) may be required since deletions and duplications can not be detected even if mutations in the HNF1B gene are not detected with NGS.
Keywords: MODY5, 17q12 Deletion, diabetes mellitus, hypomagnesemia

Corresponding Author: Hümeyra Yaşar Köstek, MD, Trakya University, School of Medicine, Department of Pediatric Endocrinology
+90 505 926 25 93
yasarrhumeyra@hotmail.com
0000-0003-4268-3535
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Introduction
Maturity onset diabetes of the young (MODY) is a clinically heterogeneous disorder characterized by noninsulin-dependent diabetes diagnosed at a young age (<25 years) with an autosomal dominant inheritance that results from heterozygous mutations in various transcription factors acting in the development and function of pancreatic beta cells(1). Mutations in hepatocyte nuclear factor-1-alpha (HNF1A) and the glucokinase (GCK) gene are most commonly identified (2) and rare mutations in the hepatocyte nuclear factor-1-beta (HNF1B) gene produce a syndrome that resembles MODY and formerly called as MODY5 (3).
HNF1B has a substantial role in the regulation of tissue-specific gene expression. Mutations in HNF1B may lead to organ abnormality in pancreas and kidney. Affected patients can develop a variety of manifestations in addition to early-onset diabetes. These include pancreatic atrophy (on computed tomography [CT] scan), abnormal renal development (renal dysplasia that can be detected on ultrasonography in the fetus, single or multiple renal cysts, glomerulocystic disease, oligomeganephronia [a form of renal hypoplasia]), slowly progressive renal insufficiency, hypomagnesemia, elevated serum aminotransferases, and genital abnormalities (epididymal cysts, atresia of vas deferens, and bicornuate uterus) (4). Almost half of patients diagnosed with MODY5 (HNF1B mutation) have a mutation in the form of a whole gene deletion(5).In addition, 17q12 microdeletion syndrome, also known as 17q12 deletion syndrome, is a rare chromosomal anomaly caused by the deletion of a small amount of material from a region in the long arm of chromosome 17. It is typified by deletion of the more than 15 genes including HNF1B resulting in kidney abnormalities and renal cysts and diabetes syndrome and neurodevelopmental or neuropsychiatric disorders (6).
Here, we report a patient presenting with MODY5 diabetes who diagnosed as 17q12 deletion syndrome revealed by microarray analysis

Case Report
A 12-year-old girl was referred to our clinic, after high blood sugar was detected in the hospital where she applied with complaints of polyuria and polydipsia for the last 1 month. She was born 2250 g (-2.5 SD) at term with normal spontaneous vaginal delivery. There was no family history of DM.Physical examination revealed that her body weight was 45 kg (0.29 SDS), height was 149 cm (-0.81 SDS), body mass index was 20.0 kg/m2 (0.18 SDS), and vital signs were stable. There was no acanthosis nigrigans. On admission, random blood glucose level

was 429 mg/dl, blood ketone was 2.2 mmol/L with normal blood PH, and serum magnesium level was low (1.5 mg/dl) (normal value 1.6–2.6). Her HbA1c level was 14% (normal value 3.6–5.8) and c-peptide level was 1.54 ng/ml (normal value 0.8–4). She was initially treated with basal-bolus insulin regimen and oral magnesium treatment. Control magnesium level increased to 1.9 mg/dl. Type 2 DM was not considered because the patient did not have obesity and signs of insulin resistance (etc, acanthosis nigricans, hypertension, hirsutism). Early-onset type DM or MODY was considered in the differential diagnosis. Anti-GAD antibody was negative .Although there was no history of diabetes in 3 generations ,based on the other finding,MODY5 was suspected and followed NGS gene panel (ABCC8, BLK, CEL, GCK, HNF1A, HNF1B, HNF4A, INS, KCNJ11, KLF11, NEUROD1, PAX4, PDX1, RFX6, ZFP57, GLIS3, FOXP3, NEUROG3, G6PC2) analysis revealed that there was no any mutation. The patient was follow up with 1 U/kg/day basal bolus insulin therapy. When she was 16 years old, she developed morbid obesity (BM: 39.1 kg/m^2).Physical examination revealed clinical sign of insuline resistance(acanthosis nigricans and hypertension.).C peptide level was 3.04 ng/ml when postprandial blood sugar level was 391 mg/dl .His mother had been diagnosed with type 2 diabetes mellitus 1 year ago. Metformin was started (500 mg/day) considering type 2 DM, but she could not tolerate the treatment due to abdominal cramp. When she was 17 years old, the patient complained of numbness in the hands and feet. Her serum magnesium level was low (1.2 mg/dl) and her urinary magnesium excretion was high at 172.5 mg/day. HNF1B gene mutation was considered in the patient with chronic hypomagnesemia with increased basal C peptide level. For the targeted diagnostic work up by abdominal CT and MR imagings revealed that there was a 43 mm diameter cystic lesion in the head of the pancreas, and agenesis of the pancreatic neck, trunk and tail as well (Figure 1). There was no renal or urinary anomaly and liver function tests were normal. Despite fecal elastase level could not be measured, there were no symptoms of malabsorption.Because of there is no mutation in HBF1B gene in NGS panel , Microarray analysis was performed, heterozygous deletion of 1.63 –Mb-spanning DNA sequence at chromosomal localization 17q12 including HNF1B was detected (Figure 2). No mutation was detected in her parents. In terms of accompanying anomalies, an arcuate uterus anomaly was found in the pelvic MRI imaging. When she was evaluated in terms of neuropsychiatric disorders that may accompany the 17q12 deletion, she was followed in the pediatric psychiatry clinic with the diagnoses of anxiety disorder and obsessive compulsive disorder. The informed consent form was taken by parents of the patient.

Discussion

We presented a patient with 17q12 microdeletion harbouring more than 15 genes and one of these is HNF1B gene. 17q12 deletion syndrome consists of MODY5 type DM, renal malformation, impaired renal funcitons, pancreatic malformations and neurodevelopmental/neuropsychiatric disorders. The HNF1B gene located in this region plays important role in the development of kidney, liver, pancreas and urogenital tract during embriyonic period (7).

Renal dysfunction and anatomic malformations is frequently seen as a result of HNF1B gene mutation (8). Multicystic dysplastic kidney is the most common renal cystic disease. Apart from cystic renal disease, other renal problems such as solitary kidney, renal hypoplasia, and horse-shoe kidney can be seen (9). There was no structural renal anomaly in our patient.Serum electrolyte imbalances, including hypokalemia, hyperuricemia, and hypomagnesemia are also common in patients with *HNF1B* mutations. *HNF1B* is esencial for expression of *FXYD2*, which subunit of Na^+/K^+-ATPase and is involved in the reabsorption of magnesium in the distal convoluted tubule (10). These electrolyte imbalances developes with age and became apparent in late childhood.Our patient had hypomagnesemia ,hyperuricemia (uric acid 7,9) (normal value 2,6-6,0) and normal serum potassium level .The low magnesium level became obvious in the late adolescence period. HNF1B mutation-related MODY5 DM was detected in about 63% of patients with 17q12 deletion syndrome(9). Since, HNF1b gene is related to pancreatic organogenesis, its mutation is also associated with pancreatic malformations(11). Diabetes mellitus is caused by insulin deficiency due to pancreatic hypoplasia(12). However, hepatic insulin resistance also plays a role in the pathogenesis. Patients are diagnosed in adolescence and early adulthood. In the UK study, it was reported that about 24% of patients with HNF1B gene mutations developed diabetes mellitus at average age of 12 years (10-14 range)(13).Our patient was diagnosed with diabetes at the age of 12,5 years old. In a study, it was reported that patients with 17q12 deletion syndrome had lower BMI and a higher need for insulin therapy at time of diagnosis compared to patients with intragenic HNF1B mutation(14). Our patient's BMI was at normal range at the time diagnosis and at the follow-up, morbid obesity developed despite without receiving high-dose insulin treatment(1 U/kg/day basal-bolus insulin at the time of diagnosis). Although radiological imagings demonstrated pancreatic neck, trunk and tail agenesis, there was no clinical sign and symptoms of exocrine pancreas disorder, but not confimed by fecal elastase level as well.

Liver function test abnormality (elevation of AST, ALT) and mild hyperbilirubinemia may be seen in patients with HNF1B gene mutation and 17q12 deletion syndrome(15).The reason is not completely clear. Liver biopsy histology reported increased steatosis, periportal fibrosis and decreased bile duct(16).In our patient, there was no remarkable liver function test abnormality.

Autism, cognitive disorders, neuropsychiatric and neurodevelopmental disorders have been reported in patients with 17q12 deletion syndrome, unlike patients with HNF1B intragenic mutations(17). Clissod et al. detected neurodevelopmental disorders in patients with 17q12 deletion/without HNF 1B mutation (17).On the other hand, Seon hee et al. reported that 3 (21%) patients had neurologic findings in 14 patients with isolated HNF1B mutations. (1 of them whole gene deletion, 2 of them is a missense mutation)(7). Also, 17q12 deletion includes the LHX1 and ACACA genes. LHX1 is expressed in the brain in early development and therefore represent a candidate gene for neurocognitive phenotype is associated with epilepsy ,autism,mental retardation (18)On the other hand ,Loirat et al. reported that 3 patients with 17q12 deletion in a large cohort of 86 patients with HNF1B gene mutations had developed autism, growth reterdation and social interaction impairment over time(19). These patients had negative genetics test for autism. In these 3 patients and 32 control patients with autism, no mutation was found in the LHX1 gene and it was considered that autism might be an additional finding to the HNF1B deletion (19). Our patient had a mutation in the LHX1 gene and was being followed up by a child psychiatrist with diagnosis of anxiety disorder and obsessive-compulsive disorder.Although it has been reported that facial dysmorphism can be detected in some patients with 17q12 deletion (9). In our patient, there was no any facial dysmorphism.17q12 deletion can be inherited as autosomal dominant or de novo, and 70% develops as a result of de novo mutation.The absence of diabetes and other clinical features in the family does not exclude 17q12 deletion syndrome. In our patient, because there was no history of diabetes in 3 generations and no mutation was found in the genetic analysis of the parents, the mutation developed as de novo.

The HNF1B mutation is difficult to diagnose and has a large phenotypic variation, most of its mutation occurs as de novo. Faguer et al developed a HNF1B scoring system to select patients for HNF1B gene analysis baased on clinical,imaging and biological variabilitiys n(20). This scoring system consists of 17 parameters and a total score of > 8 increases the probability of HNF1B and genetic analys is recommended for these patients(20). Our patient had 6 points from this scoring system. As mentioned in other studies, when evaluated together with our case, it shows that the specificity of the scoring system is low(21). In patients with 17q12 deletion syndrome, genital malformations due to unsuccessful fusion of the mullerian ducts can be seen. It has been reported to be a risk factor for Mayer Rokitansky-Küster Hauser syndrome(22). Although this situation is thought to be related to LHX1 mutation (23). Bernardini et al. did not detect a mutation in the LHX1 gene in the 17th chromosome array CGH analysis of 20 patients with Mayer Rokitansky-Küster Hauser syndrome (22). It was reported that genital anomalies might be seen in patients with only HNF1B point mutation (with intact LHX1 gene). Interestingly, despite our patient had no HNF1B point mutation,she had arcuate uterus anomaly and also LHX1 gene mutation.

On the other hand, it was reported that HNF1B is required in the expression of parathormone and that HNF1B mutation can be reason for hyperparathyroidism without renal failure(24). There were no hyperparathyroidism findings in our patient.

In conclusion, findings accompanying diabetes in children and should be carefully evaluated. Since 17q12 deletion may be de novo, monogenic diabetes should be considered in the presence of clinical findings, even if there is no family history of diabetes.In case of clinical

suspicion,further genetic examination (MLPA, array CGH) may be required since deletions and duplications can not be detected even if mutations in the HNF1B gene are not detected with NGS.Additionally patients diagnosed with MODY5 should be screened for 17q12 deletion sydrome in the presence of neurological developmental delay and psychiatric disorder.

References

1. Fu J, Wang T, Zhai X, Xiao X. Primary hepatocellular adenoma due to biallelic HNF1A mutations and its co-occurrence with MODY 3: case-report and review of the literature. Endocrine 2020;67:544-551. Epub 20191121
2. Fajans SS, Bell GI, Polonsky KS. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. N Engl J Med 2001;345:971-980.
3. Horikawa Y, Iwasaki N, Hara M, Furuta H, Hinokio Y, Cockburn BN, Lindner T, Yamagata K, Ogata M, Tomonaga O, Kuroki H, Kasahara T, Iwamoto Y, Bell GI. Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. Nat Genet 1997;17:384-385.
4. Bellanné-Chantelot C, Chauveau D, Gautier JF, Dubois-Laforgue D, Clauin S, Beaufils S, Wilhelm JM, Boitard C, Noël LH, Velho G, Timsit J. Clinical spectrum associated with hepatocyte nuclear factor-1beta mutations. Ann Intern Med 2004;140:510-517.
5. Laffargue F, Bourthoumieu S, Llanas B, Baudouin V, Lahoche A, Morin D, Bessenay L, De Parscau L, Cloarec S, Delrue MA, Taupiac E, Dizier E, Laroche C, Bahans C, Yardin C, Lacombe D, Guigonis V. Towards a new point of view on the phenotype of patients with a 17q12 microdeletion syndrome. Arch Dis Child 2015;100:259-264. Epub 20141016
6. Nakamura M, Kanda S, Kajiho Y, Morisada N, Iijima K, Harita Y. A case of 17q12 deletion syndrome that presented antenatally with markedly enlarged kidneys and clinically mimicked autosomal recessive polycystic kidney disease. CEN Case Rep 2021;10:543-548. Epub 20210503
7. Lim SH, Kim JH, Han KH, Ahn YH, Kang HG, Ha IS, Cheong HI. Genotype and Phenotype Analyses in Pediatric Patients with HNF1B Mutations. J Clin Med 2020;9. Epub 20200721
8. Faguer S, Decramer S, Chassaing N, Bellanné-Chantelot C, Calvas P, Beaufils S, Bessenay L, Lengelé JP, Dahan K, Ronco P, Devuyst O, Chauveau D. Diagnosis, management, and prognosis of HNF1B nephropathy in adulthood. Kidney Int 2011;80:768-776. Epub 20110720
9. Roehlen N, Hilger H, Stock F, Gläser B, Guhl J, Schmitt-Graeff A, Seufert J, Laubner K. 17q12 Deletion Syndrome as a Rare Cause for Diabetes Mellitus Type MODY5. J Clin Endocrinol Metab 2018;103:3601-3610.
10. Ferrè S, Veenstra GJ, Bouwmeester R, Hoenderop JG, Bindels RJ. HNF-1B specifically regulates the transcription of the γa-subunit of the Na+/K+-ATPase. Biochem Biophys Res Commun 2011;404:284-290. Epub 20101202
11. Haldorsen IS, Vesterhus M, Raeder H, Jensen DK, Søvik O, Molven A, Njølstad PR. Lack of pancreatic body and tail in HNF1B mutation carriers. Diabet Med 2008;25:782-787.
12. Chen YZ, Gao Q, Zhao XZ, Chen YZ, Bennett CL, Xiong XS, Mei CL, Shi YQ, Chen XM. Systematic review of TCF2 anomalies in renal cysts and diabetes syndrome/maturity onset diabetes of the young type 5. Chin Med J (Engl) 2010;123:3326-3333.
13. Adalat S, Woolf AS, Johnstone KA, Wirsing A, Harries LW, Long DA, Hennekam RC, Ledermann SE, Rees L, van't Hoff W, Marks SD, Trompeter RS, Tullus K, Winyard PJ, Cansick J, Mushtaq I, Dhillon HK, Bingham C, Edghill EL, Shroff R, Stanescu H, Ryffel GU, Ellard S, Bockenhauer D. HNF1B mutations associate with hypomagnesemia and renal magnesium wasting. J Am Soc Nephrol 2009;20:1123-1131. Epub 20090423
14. Dubois-Laforgue D, Cornu E, Saint-Martin C, Coste J, Bellanné-Chantelot C, Timsit J. Diabetes, Associated Clinical Spectrum, Long-term Prognosis, and Genotype/Phenotype Correlations in 201 Adult Patients With Hepatocyte Nuclear Factor 1B (HNF1B) Molecular Defects. Diabetes Care 2017;40:1436-1443. Epub 20170418
15. Kotalova R, Dusatkova P, Cinek O, Dusatkova L, Dedic T, Seeman T, Lebl J, Pruhova S. Hepatic phenotypes of HNF1B gene mutations: a case of neonatal cholestasis requiring portoenterostomy and literature review. World J Gastroenterol 2015;21:2550-2557.
16. Adalat S, Hayes WN, Bryant WA, Booth J, Woolf AS, Kleta R, Subtil S, Clissold R, Colclough K, Ellard S, Bockenhauer D. HNF1B Mutations Are Associated With a Gitelman-like Tubulopathy That Develops During Childhood. Kidney Int Rep 2019;4:1304-1311. Epub 20190529
17. Clissold RL, Shaw-Smith C, Turnpenny P, Bunce B, Bockenhauer D, Kerecuk L, Waller S, Bowman P, Ford T, Ellard S, Hattersley AT, Bingham C. Chromosome 17q12 microdeletions but not intragenic HNF1B mutations link developmental kidney disease and psychiatric disorder. Kidney Int 2016;90:203-211. Epub 20160524
18. Bedont JL, LeGates TA, Slat EA, Byerly MS, Wang H, Hu J, Rupp AC, Qian J, Wong GW, Herzog ED, Hattar S, Blackshaw S. Lhx1 controls terminal differentiation and circadian function of the suprachiasmatic nucleus. Cell Rep 2014;7:609-622. Epub 20140424
19. Loirat C, Bellanné-Chantelot C, Husson I, Deschênes G, Guigonis V, Chabane N. Autism in three patients with cystic or hyperechogenic kidneys and chromosome 17q12 deletion. Nephrol Dial Transplant 2010;25:3430-3433. Epub 20100628
20. Faguer S, Chassaing N, Bandin F, Prouheze C, Garnier A, Casemayou A, Huart A, Schanstra JP, Calvas P, Decramer S, Chauveau D. The HNF1B score is a simple tool to select patients for HNF1B gene analysis. Kidney Int 2014;86:1007-1015. Epub 20140604
21. Nagano C, Morisada N, Nozu K, Kamei K, Tanaka R, Kanda S, Shiona S, Araki Y, Ohara S, Matsumura C, Kasahara K, Mori Y, Seo A, Miura K, Washiyama M, Sugimoto K, Harada R, Tazoe S, Kourakata H, Enseki M, Aotani D, Yamada T, Sakakibara N, Yamamura T, Minamikawa S, Ishikura K, Ito S, Hattori M, Iijima K. Clinical characteristics of HNF1B-related disorders in a Japanese population. Clin Exp Nephrol 2019;23:1119-1129. Epub 20190527
22. Bernardini L, Gimelli S, Gervasini C, Carella M, Baban A, Frontino G, Barbano G, Divizia MT, Fedele L, Novelli A, Béna F, Lalatta F, Miozzo M, Dallapiccola B. Recurrent microdeletion at 17q12 as a cause of Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome: two case reports. Orphanet J Rare Dis 2009;4:25. Epub 20091104
23. Cheroki C, Krepischi-Santos AC, Szuhai K, Brenner V, Kim CA, Otto PA, Rosenberg C. Genomic imbalances associated with mullerian aplasia. J Med Genet 2008;45:228-232. Epub 20071126
24. Ferrè S, Bongers EM, Sonneveld R, Cornelissen EA, van der Vlag J, van Boekel GA, Wetzels JF, Hoenderop JG, Bindels RJ, Nijenhuis T. Early development of hyperparathyroidism due to loss of PTH transcriptional repression in patients with HNF1β mutations? J Clin Endocrinol Metab 2013;98:4089-4096. Epub 20130826

Figure 1. Abdominal CT and MR imagings demonstrated a cystic lesion in the head of the pancreas, and agenesis of the pancreatic neck, trunk and tail

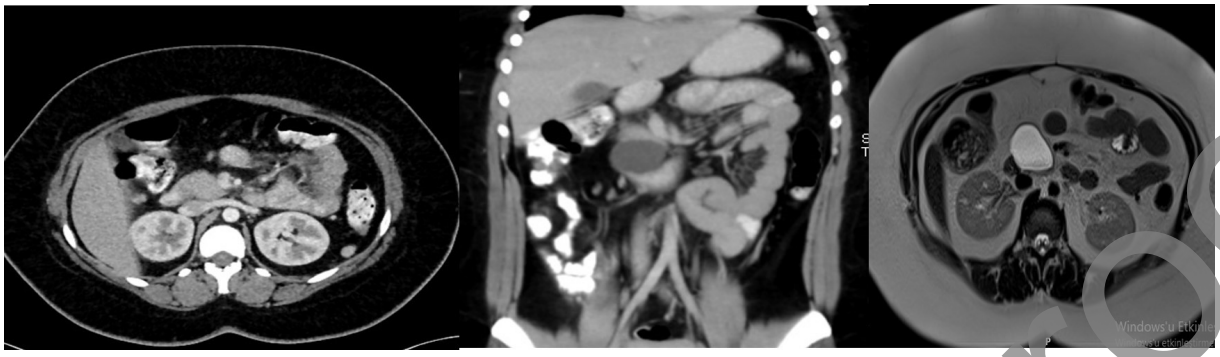

Figure 2. Microarray analysis demonstrated a prominent heterozygous deletion of 1.63 –Mb-spanning DNA sequence at chromosomal localization 17q12 including HNF1B