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Case Report

An Example Of Intrafamilial Phenotypic Variability And Diagnostic Challenges In The Transmission Of 17q12 Microdeletion From Mother To Child.

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Abstract

Renal cysts and diabetes syndrome are linked to the very uncommon proximal 17q12 microdeletion, which includes the deletion of the HNF1B gene (RCAD). Numerous phenotypes, including as diabetes and renal cysts, are brought on by this chromosomal rearrangement and are consistent with Mullerian aplasia/dysgenesis, autism spectrum disorder and schizophrenia, learning disabilities, speech delay, transient newborn hypercalcemia, neonatal cholestasis, and maturity-onset diabetes of the young type 5 (MODY5). Using CGH array analysis, we describe a girl who has a 17q12 microdeletion (about 1.4 Mb, including the HNF1B and LHX1 genes). Her mother had the identical deletion found in her. Her mother had diabetes and bilateral renal cysts, whereas the proband had been born with hypertension and bilateral kidneys that were hypodysplastic and cystic.Genetic testing was only done following a referral to a pediatric nephrologist, and no clinical concern was raised despite suggestive signs in the mother and girl. The discovery of a 17q12 microdeletion in youngsters may have A major influence on early-onset type II diabetes diagnosis, prognosis, and treatment of renal impairment. This 17q12 microdeletion family demonstrates the significance of incorporating it early in the examination of the diagnostic workup of children with renal cystic disorders and validates intrafamilial clinical diversity.

Keywords : *Genetics, microdeletion, renal cysts, familial transmission, chromosome 17, and pediatric nephrology.*

INTRODUCTION

Renal cysts and diabetes syndrome (RCAD) are known to be linked to the extremely uncommon 17q12 microdeletion, which includes the deletion of the HNFB gene. This recurrent genetic abnormality has breakpoints in neighboring segmental duplications. Additionally, RCAD known as MODY5) is an autosomal dominant condition that encompasses diabetes and renal illness brought on by aberrant renal development. Diabetes, pancreatic atrophy with subclinical exocrine deficit, progressive non-diabetic nephropathy, renal and genital deformities, and abnormal liver tests are all part of the broad clinical spectrum that is MODY5 syndrome [1]. HNF1B belongs to the transcription factor superfamily that contains homeodomains.

In a number of organs, including the liver, kidneys, gut, and pancreatic islets, it is crucial for the tissue-specific control of gene expression [2]. RCAD is proved to be caused by its haploinsufficiency, and it also plays a role in the embryonic development of these organs. In those with or without renal abnormalities, the 17q12 microdeletion is potentially a potential site for a subset of Mayer-Rokitanski-Küster-Hauser (MRKH) syndrome [3]. Along with diabetes and cystic renal disease, subjects with a 17q12 deletion involving HNF1B may also experience cognitive impairment, seizures, and abnormalities in the structure of their brains [4]. According to Moreno-De-Luca et al., autism and schizophrenia are linked to a recurrent deletion in 17q12 that harbors HNF1B [5]. A member of a large protein family that contains the LIM domain is encoded by LIM homeobox 1 (LHX1) [6], a candidate gene that may be involved in the neurological phenotype. The brain expresses the LHX1 protein, which plays a role in the migration of motor axons to the limbs and the formation of Purkinje cells in the cerebellum [7]. Furthermore, a number

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of renal and urogenital development phases are significantly and dose-dependently regulated by LHX1 [8]. In a signaling network including HNF1β and LHX1 gene products, HNF1β directly activates the LHX1 promoter [9]. There aren't many instances of familialA member of a large protein family that contains the LIM domain is encoded by LIM homeobox 1 (LHX1) [6], a candidate gene that may be involved in the neurological phenotype. The brain expresses the LHX1 protein, which plays a role in the migration of motor axons to the limbs and the formation of Purkinje cells in the cerebellum [7]. Furthermore, a number of renal and urogenital development phases are significantly and dose-dependently regulated by LHX1 [8].

SUPPLIES AND PROCEDURES

Clinical Situation

Due to pre-eclampsia and diabetes, the proband was delivered via Caesarean section at 30 weeks gestation. During pregnancy, no abnormalities on ultrasonography were found. The female child's birth weight was 0.920 kg (3rd–10th percentile), head circumference was 26.5 cm (25th percentile), and her length was 37 cm (10th percentile). Since neonatal screening revealed hyperechoic kidneys of reduced size with poor cortico-medullary differentiation and cortical small cysts but no urinary tract dilatation, an abdomen ultrasound was conducted shortly after birth. The kidneys were functioning normally. Although psychomotor development was delayed in the first few years of life, it gradually improved in the years that followed.

She developed her language normally and began to walk at the age of 18 months. The girl's pediatrician followed up with yearly assessments. The kid was sent to pediatric nephrology at the age of 8 due to hypertension (atenolol medication was initiated) and hyperuricemia (0.45 mmol/L) discovered during a follow-up blood test. The girl's physical examination and auxological parameters were normal at the initial nephrological evaluation (weight 28.5 kg, height 127.5 cm, all of which were within the 50th percentile for age and sex). With atenolol treatment, blood pressure was within the 75th percentile for height, age, and sex (103/60 mmHg). According to the modified Schwartz method, the estimated glomerular filtration rate (eGFR) was 100 mL/min/1.73 mq, indicating normal renal function; however, there was no improvement inThe girl's pediatrician followed up with yearly assessments. The kid was sent to pediatric nephrology at the age of 8 due to hypertension (atenolol medication was initiated) and hyperuricemia (0.45 mmol/L) discovered during a follow-up blood test. The girl's physical examination and auxological parameters were normal at the initial nephrological evaluation (weight 28.5 kg, height 127.5 cm, all of which were within the 50th percentile for age and sex).

During the last follow-up at age 16, the girl had normal electrolyte balance, normal uric acid levels, and mild chronic kidney disease (CKD) (eGFR according to the modified Schwartz formula: 70 mL/min/1.73 mq; CKD stage 2 according to KDOQI classification). Allopurinol therapy was still being administered. Her urinalysis was normal, and her impaired fasting glucose was controlled with diet [11]. The renal ultrasonography revealed bilateral cortical cysts with a maximal diameter of 12 mm and small hyperechoic kidneys, with the left kidney measuring 70 mm and the right kidney measuring 72 mm. Both kidneys were in the 5th percentile for height.Even after the patient stopped taking atenolol, their blood pressure remained normal. The girl played volleyball for the school team while attending a trade school.

Analysis of Molecular Structure

The girl underwent Sanger direct sequencing for mutational investigation of the HNF1β gene based on kidney symptoms, impaired fasting glucose, and family history. Following the manufacturer's instructions, oligonucleotide array–CGH analysis was also carried out on 800 ng of patient and sex-matched reference DNA using the 180 K SurePrint G3 Human Kit (Agilent Technologies). Using Agilent Cytogenomics Software (algorithm: ADM-2, threshold: 5), changes in DNA copy number were measured as the deviation of the log2ratio value from 0 (minimum 3 probes), with reference to the Human Genome Assembly February 2009 (GRCh37/hg19). We did not include benign CNVs from the Database of Genomic Variants (http://projects.tcag.ca/variation/, accessed May 20, 2013). The mother of the proband was also included in the analysis. Prior to moving on, every analysis has beenThe girl underwent Sanger direct sequencing for mutational investigation of the HNF1β gene based on kidney symptoms, impaired fasting glucose, and family history. Following the manufacturer's instructions, oligonucleotide array–CGH analysis was also carried out on 800 ng of patient and sex-matched reference DNA using the 180 K SurePrint G3 Human Kit (Agilent Technologies).

FINDINGS

Direct sequencing revealed no HNF1B mutation in the proband; nevertheless, the presence of several homozygous SNPs suggested the potential of a complete heterozygous deletion of the HNF1B gene. According to ISCN (2013), CGH array analysis revealed a proximal microdeletion of roughly 1.4 Mb in 17q12 (34,817, 481 × 2, 34,832,402, 36,243,028 × 1, 36,407,774 × 2).inherited (Figure 1) from her mother. When the deletion was fully extended, 19 precisely placed genes, including the LHX1 and HNF1B genes, were found.

DISCUSSION

Numerous phenotypes with significant interindividual heterogeneity in expressivity are produced by the ablation of 17q12. varying renal symptoms, MODY5, pancreatic atrophy, Mullerian aplasia, varying neurocognitive involvement, autism, and schizophrenia can all be present in people with essentially identical deletions [4,5,9,12–15]. Some patients, meanwhile, do not exhibit the usual clinical signs of this loss. A case with autism spectrum disorder, behavioral issues, cognitive impairment, and joint laxity with a striking Marfanoid body habitus—a clinical characteristic never before documented in 17q12 microdeletion—was reported by Roberts et al. [16]. A patient with dysmorphic traits, severe speech delay, intellectual incapacity, stereotyped behaviors, and atypical obesity was reported by Palumbo et al. [17].

The primary gene expressed in renal metanephros during preglomerular phases of metanephrogenesis is HNF1B [18]. The genital and urinary systems have a shared mesodermal ridge and are therefore embryologically connected. RCAD syndrome has been demonstrated to be caused by haploinsufficiency of the hepatocyte nuclear factor 1B. The RCAD phenotype is linked to minor mutations of HNF1B, loss of one exon, and deletion of the complete gene [19]. It is quite difficult to defend the lack of renal illness in cases of total haploinsufficiency given the key role of HNF1B in normal renal development. LHX1, which is located in the 17q12 area, is likewise involved in renal development. It is a potential gene for MRKH syndrome, which might result in abnormalities of MRKH type II.The genital and urinary systems have a shared mesodermal ridge and are therefore embryologically connected. RCAD syndrome has been demonstrated to be caused by haploinsufficiency of the hepatocyte nuclear factor 1B. The RCAD phenotype is linked to minor mutations of HNF1B, loss of one exon, and deletion of the complete gene [19].

There are currently few documented occurrences of 17q12 microdeletion transmission through family. According to Table 1 [5], every incidence of familial 17q12 microdeletion, with the exception of the one documented by Moreno-de-Luca et al., is linked to a broad range of phenotypes. Additionally, we observed a varied renal phenotype in our patients: her mother had well-differentiated, normal-sized kidneys with cysts, but the proband had bilateral cystic hypodysplasia. In addition, the child had hypertension and hyperuricemia, but not her mother. Without an obvious intellectual handicap, the mother and daughter both had modest learning disabilities.

An prenatal ultrasound examination revealed bilateral kidney cysts in a child, as described by Dixit et al. [13]. An prenatal ultrasound scan first revealed that his mother had a multicystic dysplastic right kidney along with the same deletion. She had no additional health issues, and her left kidney was normal. According to George et al., a family segmentation of the 17q12 microdeletion was linked to intellectual disability and renal illness, but expressivity varied [12]. The 7-year-old girl who was the proband had learning disabilities, hyperactivity, disruptive behavior, and attention deficit disorder, but no kidney abnormalities. While her mother carrier had a normal renal ultrasonography, her sibling, who also had the same deletion, displayed bilateral renal cystic disease and slight developmental delay. Chen andAn prenatal ultrasound scan first revealed that his mother had a multicystic dysplastic right kidney along with the same deletion. She had no additional health issues, and her left kidney was normal. According to George et al., a family segmentation of the 17q12 microdeletion was linked to intellectual disability and renal illness, but expressivity varied [12].

who was healthy and normal and had the same deletion [21]. There was also a patient with dysmorphic features, a left kidney that was multicystic and dysplastic, duodenal atresia, and motor delay. Two weeks after birth, the patient's father had a right nephrectomy due to a congenital kidney defect. He did not have any intestinal tract abnormalities, but he did have cognitive impairment [22]. Recently, a mother with diabetes, a partly septated uterus, and a single kidney was documented, along with a 25-year-old lady who had serous ovarian cancer, diabetes, and no renal abnormalities [23]. A case of familial recurrent 17q12 microdeletion syndrome was reported in another recent report. The 16-year-old proband had multiple cystic renal disease, hydronephrosis, hepatosteatosis, hypomagnesemia and hyperuricemia, mild intellectual disability, obesity, and mild facial dysmorphism. There was also a patient with dysmorphic features, a left kidney that was multicystic and dysplastic, duodenal atresia, and motor delay. Two weeks after birth, the patient's father had a right nephrectomy due to a congenital kidney defect. He did not have any intestinal tract abnormalities, but he did have cognitive impairment [22]. Recently, a mother with diabetes, a partly septated uterus, and a single kidney was documented, along with a 25-year-old lady who had serous ovarian cancer, diabetes, and no renal abnormalities [23].

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CONCLUSIONS

We present one of the few families that have been shown to segregate the 17q12 microdeletion, a rather uncommon genetic condition that exhibits significant clinical diversity, even within the same family. Our child and her mother had moderate clinical symptoms despite suggestive results, and the syndrome was not identified until a pediatric nephrologist was consulted. Our example illustrates how the diagnosis of 17q12 microdeletion remains difficult and potential obstacles persist despite advancements in understanding and technologies. The clinical suspicion may be the hint to include this microdeletion in the diagnostic workup when dealing with a child who has renal cystic disease, especially if extra-renal symptoms are also present. This would provide an early genetic diagnosis and eventually improve the patient's outcome.

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