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Case Report

Maternal Transmission of 17q12 Microdeletion: Intrafamilial Phenotypic Variability and Diagnostic Hurdles

Susanna Negrisolo [1,2], Gianluca Caridi [3], Benedetta Antoniello [1,2] and Elisa Benetti [1,2,4,*]

[1] Laboratory of Immunopathology and Molecular Biology of the Kidney, Department of Women's and Children's Health, Padua University Hospital, Corso Stati Uniti, 4, 35127 Padua, Italy
[2] Pediatric Research Institute "IRP Città della Speranza", Corso Stati Uniti, 4, 35127 Padua, Italy
[3] Nephrology and Renal Transplantation, Laboratory of Molecular Nephrology, Istituto Giannina Gaslini IRCCS, Via Gaslini, 5, 16147 Genoa, Italy
[4] Pediatric Nephrology, Department of Women's and Children's Health, Padua University Hospital, Via Giustiniani, 3, 35128 Padua, Italy
* Correspondence: elisa.benetti@aopd.veneto.it

Abstract: The relatively rare proximal 17q12 microdeletion, including the deletion of the HNF1B gene, is associated with renal cysts and diabetes syndrome (RCAD). This genomic rearrangement results in a wide range of phenotypes, including renal cysts and diabetes, which are consistent with maturity-onset diabetes of the young type 5 (MODY5), Mullerian aplasia/dysgenesis, autism spectrum disorder and schizophrenia, speech delay, learning difficulties, transient neonatal hypercalcemia, and neonatal cholestasis. We describe a girl with a 17q12 microdeletion identified using CGH array analysis (about 1.4 Mb, including HNF1B and LHX1 genes). The same deletion was identified in her mother. The proband had shown cystic and hypodysplastic bilateral kidneys since birth and hypertension, while her mother had bilateral renal cysts and diabetes. Despite suggestive findings in the girl and in the mother, no clinical suspicion arose, and genetic testing was carried out only after referral to a pediatric nephrologist. In children, the identification of 17q12 microdeletion may have a significant impact on the diagnosis, prognosis, and management of renal disease and early-onset type II diabetes. This family with a 17q12 microdeletion confirms intrafamilial phenotypic variability and highlights the importance of including it early on in the analysis of the diagnostic workup of children with renal cystic diseases.

Keywords: chromosome 17; genetics; microdeletion; renal cysts; familial transmission; pediatric nephrology

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1. Introduction

The relatively rare 17q12 microdeletion (including the deletion of HNFB gene) is a recurrent genomic disorder with breakpoints in flanking segmental duplications, and it is known to be associated with renal cysts and diabetes syndrome (RCAD). RCAD (also referred to as MODY5) is an autosomal dominant disorder that includes renal disease resulting from abnormal renal development and diabetes. MODY5 syndrome encompasses a wide clinical spectrum, including diabetes, pancreas atrophy with subclinical exocrine deficiency, progressive non-diabetic nephropathy, kidney and genital malformations, and liver test abnormalities [1]. HNF1B is part of the homeodomain-containing superfamily of transcription factors. It plays an important role in the tissue-specific regulation of gene expression in various organs, such as the liver, kidneys, intestine, and pancreatic islets [2]. It is also involved in the embryonic development of these organs and its haploinsufficiency is proven to cause RCAD. The 17q12 microdeletion is also a candidate locus for a subset of Mayer–Rokitanski–Küster–Hauser (MRKH) syndrome in individuals with or without renal defects [3]. Subjects with a deletion of 17q12 involving HNF1B may suffer from cognitive impairment, seizures, and brain structural abnormalities, in addition to cystic

renal disease and diabetes [4]. Moreno-De-Luca et al. described the association between a recurrent deletion in 17q12 harbouring HNF1B and both autism and schizophrenia [5]. A candidate gene that may be involved in the neurological phenotype is LIM homeobox 1 (LHX1) [6], which encodes a member of a large protein family containing the LIM domain. The LHX1 protein is expressed in the brain and involved in Purkinje cell development in the cerebellum as well as in the migration of motor axons to the limbs [7]. Moreover, LHX1 is a major and dose-dependent regulator of various steps of renal and urogenital development [8]. HNF1β and LHX1 gene products are involved in a signalling pathway in which HNF1β directly activates the promoter of LHX1 [9]. To our knowledge, few cases of familial 17q12 microdeletion are still reported. We describe a family and segregate the 17q12 microdeletion that highlights the variable expressivity of multiple features of this condition and the importance of including its analysis in the diagnostic workup of children with renal diseases.

2. Materials and Methods

2.1. Clinical Case

The proband was born at 30 gestational weeks with delivery by Caesarean section due to pre-eclampsia and diabetes. No ultrasound anomalies were detected during pregnancy. At birth, the female child weighed 0.920 kg (3rd–10th percentile), measured 37 cm (10th percentile) in length and her head circumference was 26.5 cm (25th percentile). An abdominal ultrasound performed soon after birth because neonatal screening showed hyperechoic kidneys of reduced size with poor cortico-medullary differentiation and cortical small cysts but no urinary tract dilatation. Renal function was normal. Psychomotor development was delayed in the first years of life, but progressive improvement was observed over the following years. She started to walk at 18 months and had normal language development. The girl was followed up with annual evaluations by her pediatrician. At the age of 8 years, the girl developed hypertension (atenolol therapy was started), and hyperuricemia (0.45 mmol/L) was found during follow up blood examination, so she was referred to pediatric nephrology. At the first nephrological evaluation, the girl had normal physical examination and auxological parameters (weight 28.5 kg and height 127.5 cm, both corresponding to the 50th percentile for sex and age). Blood pressure was normal (103/60 mmHg, 75th percentile for sex, age and height) with atenolol therapy. Renal function was normal (estimated glomerular filtration Rate (eGFR) according to the modified Schwartz formula: 100 mL/min/1.73 mq), but no improvement of hyperuricemia despite low-uric acid diet was observed, so allopurinol therapy was started [10]. Fasting hyperglycaemia was detected (serum glucose 108 mg/dL). Urinalysis was negative. Renal ultrasound showed kidneys of reduced size: left kidney length (68 mm) and right kidney length (71 mm), both corresponding to the 5th percentile for height, with small cortical cysts (maximum diameter 10 mm) but no urinary tract dilatation. She showed mild learning difficulties (she was in a mainstream school but with little learning support). Family history was positive for non-insulin-dependent diabetes mellitus (NIDDM) in the grandmother, unilateral renal agenesis in a maternal uncle and NIDDM in the mother, arising as gestational diabetes during pregnancy. The mother was suggested to undergo renal ultrasound and blood analyses at the age of 36 years: kidneys were both of normal size and shape but showed diffuse cortical cysts (maximum diameter 18 mm). Renal function was normal, as well as uric acid. The mother had always been healthy, but she had attended mainstream school with additional support due to learning difficulties too.

At the last follow-up at 16 years of age, the girl had 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), normal electrolyte balance, and normal uric acid levels (allopurinol therapy was still ongoing). Her impaired fasting glucose was managed with diet and urinalysis was normal [11]. Renal ultrasound showed small hyperechoic kidneys—left kidney length (70 mm) and right kidney length (72 mm), both corresponding to the 5th percentile for height, with bilateral cortical cysts (maximum diameter 12 mm).

Blood pressure was still normal, even though atenolol had been withdrawn by the patient. The girl attended a vocational school and played volleyball on the school team.

2.2. Molecular Analysis

Based on renal findings, impaired fasting glucose and family history, the girl underwent mutational analysis of the HNF1β gene using Sanger direct sequencing. Oligonucleotide array–CGH analysis was also performed using 180 K SurePrint G3 Human Kit (Agilent Technologies), according to the manufacturer's protocol, on 800 ng of patient's and sex-matched reference DNA. Changes in DNA copy number were observed as the deviation of the log2ratio value from 0 (minimum 3 probes), using Agilent Cytogenomics Software (algorithm: ADM-2, threshold: 5), referring to Human Genome Assembly February 2009 (GRCh37/hg19). Benign CNVs of the Database of Genomic Variants (http://projects.tcag.ca/variation/ accessed on 20 May 2013) were excluded. The analysis was extended to the proband's mother. Before proceeding, all the analyses had been authorized by the proband's parents.

3. Results

No HNF1B mutation was detected in the proband by direct sequencing, but the presence of a large number of SNPs in a homozygous state indicated the possibility of a total HNF1B heterozygous gene deletion. CGH array analysis showed a proximal microdeletion of about 1.4 Mb in 17q12 (ISCN 2013) arr17q12 (34,817,481 × 2, 34,832,402, 36,243,028 × 1, 36,407,774 × 2) inherited from her mother (Figure 1). In its full extension, the deletion proved to have 19 precisely located genes, including HNF1B and LHX1 genes.

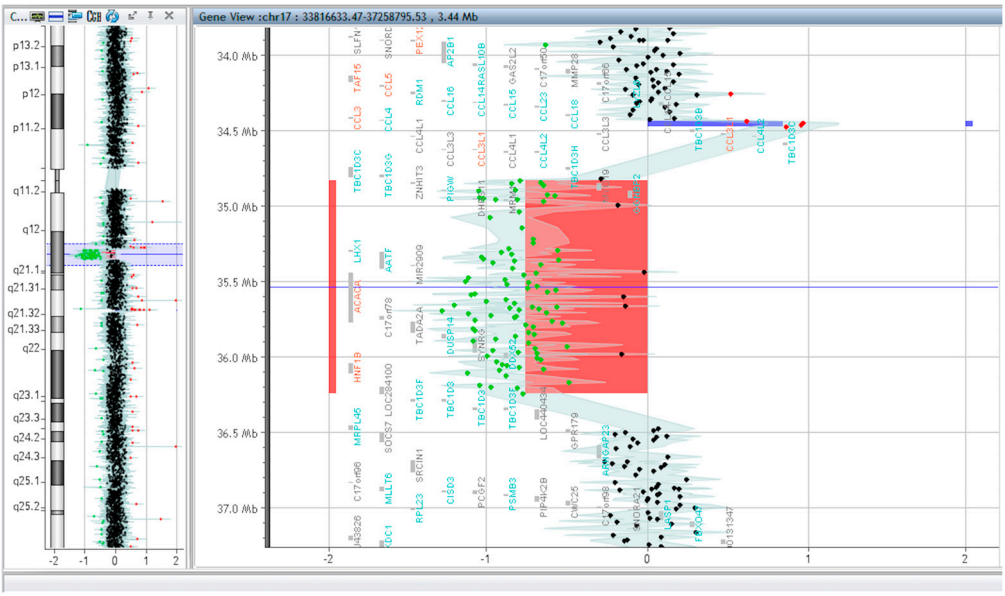

Figure 1. Array CGH graphical overview (proband).

4. Discussion

The 17q12 deletion results in a wide range of phenotypes with considerable interindividual variation in terms of expressivity. Individuals with nearly identical deletions may have variable renal manifestations, MODY5, pancreatic atrophy, Mullerian aplasia, variable neurocognitive involvement, autism, and schizophrenia [4,5,9,12–15]. However, some patients do not show the typical clinical features of this deletion. The case reported by Roberts et al. showed autism spectrum disorder, behavioural difficulties, cognitive impairment and joint laxity with a remarkable Marfanoid body habitus, a clinical feature that had never been previously described in 17q12 microdeletion [16]. Palumbo et al. reported a case with dysmorphic features, serious speech delay, intellectual disability, stereotyped behaviours and unusual obesity [17]. All these cases had no renal abnormalities despite the HNF1B

gene deletion. HNF1B is the main gene expressed in renal metanephros at preglomerular stages during meta nephrogenesis [18]. Urinary and genital systems are embryologically correlated, both originating from a common mesodermal ridge. Haploinsufficiency of the hepatocyte nuclear factor 1B has been shown to be causative of RCAD syndrome. The deletion of the entire gene, deletion of one exon, and small mutations of HNF1B are all associated with the RCAD phenotype [19]. Given the master role of HNF1B in normal renal development, it is very difficult to justify the absence of renal disease in cases with complete haploinsufficiency. LHX1 also plays a role in renal development and is comprised in the 17q12 region. It is a candidate gene for MRKH syndrome, which may include (MRKH type II) anomalies of renal number or position [20]. A deeper understanding of the involvement of HNF1B and LHX1 genes in embryogenesis, assuming that regulatory mechanisms for their haploinsufficiency must act differently, could help in interpreting the variable clinical features observed in patients.

Few cases of the familial transmission of 17q12 microdeletion are still reported. All familial 17q12 microdeletion cases except for the one reported by Moreno-de-Luca et al. are associated with a wide phenotypic spectrum, as shown in Table 1 [5]. We also observed a variable renal phenotype in our patients: while the proband had bilateral cystic hypodysplasia, her mother had well-differentiated and normal-sized kidneys with cysts. Furthermore, the child, but not her mother, had hypertension and hyperuricemia. Both the girl and the mother had mild learning difficulties without overt intellectual disability (Table 2).

Table 1. Phenotypic spectrum reported in the literature. Case report comparison.

Ref. #	Case Report	Variability in Expressivity	Renal Abnormalities	Diabetes	Hyperuricemia	Cognitive Impairment	Motor Delay
[5]	Mother Child	no	yes yes	-	-	-	-
[12]	Mother Child Sibling	yes	no no cysts	-	-	no yes mild	-
[13]	Mother Child	yes	multicystic * cysts	-	-	-	-
[21]	Mother Fetus	yes	no CAKUT	-	-	-	-
[22]	FatherChild	yes	CAKUT multicystic *	-	-	yes	no yes
[23]	Mother Daughter	yes	CAKUT no	yes yes	-	-	-
[24]	Mother Son M. Grandfather	yes	No cysts/CAKUT cysts	yes severe yes	no yes no	mild mild mild	-

* monolateral.

Table 2. Phenotypic features of the reported family case.

Subject	Kidney Function	Cortical Cysts	Kidney Size	Kidney Dysplasia	Hypertension	Hyperuricemia	Learning Difficulties
Mother	normal	diffuse (Ø 18 mm)	normal	no	no	no	yes
Daughter (16Y)	CKD stage 2	yes (Ø 12 mm)	Bilateral hypoplasia	bilateral	yes	yes	yes

Dixit et al. reported a case of a child with bilateral renal cysts identified by an antenatal ultrasound scan [13]. His mother had the same deletion and a multicystic dysplastic right kidney that was initially identified by an antenatal ultrasound scan. Her left kidney was normal, and she had no other health problems. George et al. described a family segregating the 17q12 microdeletion, which was associated with renal disease and intellectual

impairment, but with variability in expressivity [12]. The proband was a 7-year-old female with attention deficit, hyperactivity, disruptive behaviour, and learning difficulties, but no renal abnormalities. Her sibling carried the same deletion and showed mild developmental delay and bilateral renal cystic disease, whereas her mother carrier had a normal renal ultrasound. Chen et al. reported a case of 17q12 microdeletion in a fetus with a prenatal ultrasound diagnosis of hydronephrosis, hydroureter, and multicystic kidneys. The mother, who carried the same deletion, was normal and healthy [21]. A patient with duodenal atresia, multicystic and dysplastic left kidney, dysmorphic features and motor delay was also reported. The patient's father had undergone a right nephrectomy two weeks after birth for a congenital kidney abnormality. He had cognitive impairment but no intestinal tract malformations [22]. A 25-year-old woman, with serous ovarian carcinoma and diabetes but no renal abnormalities, and her mother, affected with diabetes, partially septated uterus, and a solitary kidney, have recently been described [23]. In another recent report, a case of familial recurrent 17q12 microdeletion syndrome was described: the 16-year-old proband presented obesity, mild facial dysmorphism, severe diabetic ketoacidosis, multicystic renal disease, hydronephrosis, hepatosteatosis, hypomagnesemia and hyperuricemia, mild intellectual disability with mild diffuse cerebral and cerebellar atrophy and a partially empty sella in magnetic resonance imaging. Her mother had diabetes, hypomagnesemia, and mild intellectual disability; her maternal grandfather and uncle had diabetes; and her grandfather had renal cystic disease [24]. Since the deletion is found in subjects at both ends of the phenotypic spectrum, it has been suggested that individuals with earlier-onset disease or different features are more likely to have a larger genomic deletion. Individuals that carry the same 17q12 deletion in terms of Mb, may have very different phenotypes. However, this does not explain completely the observed variation within families in which the number of deleted genes is the same. The phenotypic expression variability observed within families carrying the 17q12 microdeletion may be due to the influence of different genetic backgrounds between children and parents with the same genomic rearrangement.

Many familial cases are detected by prenatal diagnosis performed because of ultrasound abnormalities and a large number of deletions are de novo. Reported prenatal cases of the 17q12 microdeletion are increasing, and its clinical description is frequently being updated. Two recent papers carried out a comprehensive review of all the prenatal diagnoses described thus far [25,26]. Prenatal renal phenotypes cover a large spectrum of ultrasound abnormalities, from none or mild hydronephrosis to hyperechogenic, dysplastic or enlarged kidneys, and renal unilateral agenesis. However, renal cysts or multicystic kidneys are the most common renal findings. Urinary tract anomalies, such as lower urinary tract obstruction, megabladder, and hydroureter have also been described [27]. These alterations are often detected along with other findings (such as persistent left superior vena cava or other cardiovascular anomalies, amniotic fluid alterations, diaphragmatic hernia, lung or digestive tract malformations), but isolated urinary tract abnormalities with normal fetal development have also been reported, including ultrasound markers (such as prenatal bright kidney or hydronephrosis), which resolve after birth and do not represent an indication for genetic testing [28]. For this reason, prenatal testing has been suggested in cases of fetal hyperechogenic kidneys or renal cysts [29]. However, prenatal or early diagnosis may allow multidisciplinary team care, improving the patient's outcome. In our patient, the diagnosis was delayed until she was referred to a pediatric nephologist at the age of 8 years, despite suggestive renal findings since birth. The mother was not diagnosed either, despite diabetes and a positive family history. Both our proband and the mother had mild learning difficulties but not a clear intellectual impairment. Beyond renal abnormalities, postnatal testing is mostly performed for psychomotor deficits or behaviour anomalies, but very mild intellectual impairment is rarely investigated and may be simply attributed to family socio-economic or cultural status. As shown by our cases, the diagnosis of 17q12 microdeletion remains challenging due to the wide clinical spectrum and the high variability of manifestations (even within the same family) and can be often delayed or remain undetected. Due to the lack of specific clinical diagnostic markers, genetic testing

remains the gold standard for definitive diagnosis. However, bilateral renal abnormality, renal cysts, simultaneous concomitant renal abnormalities and hypomagnesaemia have been identified to be predictive for HNF1B mutations and included in a scoring system to select patients for HNF1B gene analysis [30]. Extra-renal manifestations, particularly neurobehavioral ones, should be regarded as suspected for 17q12 microdeletion. These features can guide the clinician in the differential diagnosis between RCAD (HNF1B gene-associated) and chromosome 17q12 deletion syndrome. However, as single or mild clinical manifestations may be present, a key clinical issue remains a high index of suspicion for clinicians. Bilateral anatomic findings may be a good clue for performing genetic investigations, as bilateral, rather than unilateral, abnormalities are more commonly reported.

5. Conclusions

We describe one of few reported families segregating the 17q12 microdeletion, a relatively rare genomic disorder characterized by a wide phenotypic variability, even among members of the same family. Despite suggestive findings, our patient and her mother presented mild clinical manifestations, and the syndrome remained undetected until referral to a pediatric nephrologist. Despite improvements in knowledge and in diagnostics, our case underlies how the diagnosis of 17q12 microdeletion is still challenging and possible hurdles still exist. Facing a child with renal cystic disease, particularly if extra-renal manifestations are also present, the clinical suspicion could be the clue to include this microdeletion in the diagnostic workup, providing an early genetic diagnosis and ultimately improving the patient's outcome.

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