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# Cytogenomic Aberrations in Isolated Multicystic Dysplastic Kidney in Children

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## Abstract

**Background:** Multicystic dysplastic kidney (MCDK) is a common form of congenital kidney anomaly. The cause of MCDK is unknown. We investigated whether MCDK in children is linked to cytogenomic aberrations.

**Methods:** We conducted Array Comparative Genomic Hybridization (aCGH) in 10 unrelated children with MCDK. The pattern of inheritance was determined by real-time PCR in patients and their biological parents.

**Results:** Pathogenic aberrations were detected in three patients: a deletion at 7p14.3 with a size of 2.07 Mb housing 12 genes, including *BBS9* and *BMPER*; a duplication at 16p13.11p12.3 with a size of 3.28 Mb that included more than 20 genes; and monosomy X for a female patient. The deletion at 7p14.3 was inherited from patient's father, while the duplication at 16p13.11p12.3 was derived from patient's mother.

**Conclusions:** Up to 30% of patients with MCDK possess cytogenomic aberrations. *BBS9* and *BMPER* variants have been reported to result in cystic kidney dysplasia, suggesting possible pathogenic function for the deletion at 7p14.3 in children with MCDK. The duplication at 16p13.11p12.3 was not reported previously to associate with MCDK. Both variations were inherited from parents, indicating hereditary contributions in MCDK. Thus, aCGH is an informative tool to unravel pathogenic mechanisms of MCDK.



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Author Contributions

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**Category of study:** Clinical research.

**Patient consent**: Informed consent was obtained from the parents of children and, when appropriate, assent was acquired from children themselves.

## Introduction

Multicystic dysplastic kidney (MCDK) is a form of congenital anomaly of the kidney and urinary tract (CAKUT). CAKUT are a major cause of kidney failure in children, accounting for 30 to 50% of cases of end-stage kidney disease (ESKD) [1]. Multiple lines of evidence, including discovery of causative genes and intrafamilial CAKUT segregation, support the contribution of genetic factors to CAKUT in humans. A recent large-scale study by Verbitsky et al. reported presence of a large size (≥100 kb) copy number variations (CNVs) in 4.1% of patients with diverse forms of CAKUT recruited in the United States, Europe and Brazil, demonstrating that genomic disorders represent a common etiology of CAKUT [2]. However, the gene variants causing a discrete form of CAKUT such as MCDK remain incompletely defined. MCDK consists of macroscopic cysts with absent working kidney tissue and arises in 1 in 1000 to 1 in 4300 live births [3, 4]. MCDK is unilateral in most cases, but may affect both kidneys. Bilateral MCDK causes Potter syndrome (hypoplastic lungs, deformed limbs, widely separated eyes, broad nasal bridge, low set ears). Histological examination of MCDK tissue demonstrates presence of connective tissue and immature epithelium [3, 4]. MCDK is believed to result from either abnormal inductive interactions between the ureteric bud and the metanephric mesenchyme during embryonic kidney development or from intrauterine fetal urinary tract obstruction [5, 6]. Variants in genes critical for normal kidney development (so called renal developmental genes), including *HNF1B*, *ACE, PAX2, REN, ROBO2, AGTR1, SALL1, AGT* genes, have been linked to pediatric MCDK [7–10]. These observations indicate that genetic alterations may play a causative role in MCDK.

In addition to single variants of discrete genes, large cytogenetic defects, including the number of copies of a particular gene, insertions, deletions, and duplications of large DNA segments, are associated with CAKUT [11]. CNVs are defined as any gain or loss of germline DNA. The characterization of DNA CNVs by Array Comparative Genomic Hybridization (aCGH) analysis has demonstrated to be highly valuable in revealing pathogenic mechanisms of CAKUT (2, 11). However, the pathogenic roles of cytogenomic aberrations in children with MCDK were not investigated well. Here, we report the results of a study using aCGH in ten pediatric patients with isolated MCDK.

## Materials and Methods

### Patients

The study was approved by the Tulane University School of Medicine IRB#:150438–4. Informed consent was obtained from the parents of children and, where appropriate, assent was acquired from children themselves. 10 unrelated patients with MCDK (mean age 8.5±1.1 years) were enrolled in the study after clinical diagnosis of MCDK was established by renal ultrasonography (US). Blood was obtained from MCDK patients and 20 pooled age-, race- and sex-matched controls (6 black and 5 white males, 5 black and 4 white females). Buccal cells were obtained from patients' biological parents. Children in control group had US performed for kidney diseases different from CAKUT (e.g., minimal proteinuria and microscopic hematuria,). Six MCDK patients were females and four- males.

Kidney function was estimated from plasma creatinine with Schwartz equation (height in cm x 0.413/plasma creatinine in mg/dL) [12].

### DNA isolation

DNA was obtained from blood or from patients' biological parents' buccal cells as previously described [10].

### Array Comparative Genomic Hybridization (aCGH) analysis

DNA was isolated and labelled using Agilent-recommended protocol. CGH was performed on an Agilent Microarray platform with 105k probes (Agilent Inc., Santa Clara, CA). Array image was acquired with an Agilent Array Scanner. Microarray data was analyzed using the Cytogenomics software package from Agilent Inc. Interpretation of detected CNVs was conducted according to the ACMG standards and guidelines revision 2013 [13], and technical standards recommendation by ACMG and ClinGen [14]. Information for clinical significance on reported cases was extracted from Databases of Genomic Variants (ClinVar) at www.ncbi.nim.nih.gov/clinvar, and DECIPHER at www.decipher.sanger.ac.uk. Association analysis of gene function and clinical features is based on the information from Online Mendelian Inheritance in Man (OMIM at www.omim.org).

### Real-time quantitative polymerase chase reaction (qPCR)

Primers for qPCR were designed to detect the relative copy number of targeted genes within the aberrations and to avoid any potential common genomic variants encountered in the general population reported in the Database of Genomic Variants. The SYBR green assay (Thermo Fisher Scientific) was performed on *BMPER* (BMP Binding Endothelial Regulator) in the deleted region and XYLT1 (Xylosyltransferase 1) in the duplicated region, using *RPPH1* (Ribonuclease P RNA Component H1) and *TERT* (Telomerase Reverse Transcriptase) genes as references. The relative copy number was calculated using the $\Delta\Delta C_t$ method compared to an unaffected human DNA sample. Primers used for qPCR were as follows: *BMPER*-forward: ctgtggtttgcaagaggaag, *BMPER*-reverse: atgtcttctgggggcactc, *XYLT1*-forward: caacgagtccagccatcc, *XYLT1*-reverse: cagagcttccagagcctaaac, *TERT-E3*-forward: tcccacgacgtagtccat, *TERT-E3*- reverse: cagaggtca-ggcagcatc, *RNaseP*-forward: ggagagtagtctgaattgggttatg, and *RNaseP*-reverse: ggagcttggaaca-gactcac.

## Results

### Clinical findings

Mean age of MCDK patients was 8.5±1.1 years and of children in the control group-9.7±0.9 years (Tables 1 and 2). Four MCDK patients were males and six- females. Eight children were African-American and two- Caucasian. All children manifested normal blood pressure and renal function. In all children, family history was negative for MCDK or other anomalies of the kidney and urinary tract. MCDK was isolated in nine of ten cases and was associated with Turner's syndrome in one of patient. MCDK was unilateral in all children with ratio of right vs. left MCDK 1:1 (Table 1). Contralateral kidney underwent proper compensatory hypertrophy in all instances. Mild hydronephrosis was identified in the contralateral kidney of one patient. US did not reveal any renal malformations in children

from the control group. All biological parents had apparently normal phenotype and reported absence of known kidney disease or abnormalities of the urinary system.

### aCGH results

Three diverse pathogenic aberrations (a deletion, a duplication, and a numerical abnormality) were detected in 3 of 10 patients (in 2 of 9 patients with isolated MCDK and in a single patient with known Turner syndrome). The results are summarized in Table 3. No pathogenic aberrations were detected from the other seven patients using the laboratory standard cutoff at the resolution of 300 kb. The deletion detected from subject 3 was located at 7p14.3 with a size of 2.07 Mb. This alteration results in deletion of 7 protein coding genes, including *BBS9* (Bardet-Biedl Syndrome 9), *BMPER,* and *RP9 (*Retinitis Pigmentosa 9), (Figure 1 and 2A), as well as a pseudogene, *RP9P* (Retinitis Pigmentosa 9 Pseudogene), and three copies of non-coding gene of *NPSR* (Neuropeptide S Receptor)-*AS1* (antisense RNA 1). The duplication detected from subject 41was located at 16p13.11p12.3 with a size of 3.28 Mb. There are more than 30 genes in this duplicated region, including 16 protein coding genes, 18 microRNA (miRNA) genes in three clusters, and two pseudogenes. (Figure 1 and 2B). The third aberration was monosomy X (Figure 1) from a female patient (subject 22). The data of the laboratory analysis are shown in Table 3.

### qPCR results

The results from qPCR assay confirmed the findings from aCGH of the deletion and duplication. qPCR studies of the two families showed the deletion at 7p14.3 was inherited from patient's father (Fig 3A), while the duplication at 16p13.11p12.3 was derived from patient's mother (Fig 3B). The monosomy X is a known product of meiotic nondisjunction and no further confirmation study was carried.

## Discussion

The current study identified novel cytogenomic aberrations in children with isolated MCDK. The overall prevalence of cytogenomic aberrations was about 33% (3 of 10 patients). The prevalence of cytogenomic aberrations in patients with isolated MCDK in this study was about 22% (2 of 9). These findings are in line with other reports showing that molecular diagnosis due to a copy-number disorder can be established in 4.1% to 14.5% of children with diverse forms of CAKUT [2, 11]. Relative enrichment for CNVs in our analysis (22%) could be due to study of a single discrete form of CAKUT such as MCDK rather than diverse forms of CAKUT. Our present findings support the role of genetic factors in the pathogenesis of MCDK. Understanding the genetic architecture of MCDK as a discrete form of CAKUT has important implications for the development of preventive and therapeutic interventions that aim to mitigate the associated cardiovascular comorbidities and curtail progression of kidney disease. In addition, identification of CNVs helps to identify novel intracellular pathways that are implicated in the pathogenesis of MCDK and to provide molecular diagnosis, thus establishing the etiology of MCDK.

The deletion at 7p14.3 results in the deletion of *BBS9* and *BMPER* genes. Mutations in *BBS9* cause Bardet-Biedl Syndrome (BBS, OMIM 209900), a rare autosomal-recessive

ciliopathy distinguished by mental retardation, polydactyly, obesity, retinitis pigmentosa and CAKUT [15, 16]. Renal manifestations of BBS include collecting duct microcysts rather than macrocysts observed in MCDK [15, 16]. In the Databases of Decipher and ClinVar, 10 patients with 7p14.3 deletion were reported with deletions in size from 200Kb to 2100kb, and all these deletions have *BBS9* and *BMPER* involved. Six of these patients showed clinical features of intellectual disability, autistic behavior and developmental delay. One patient also manifested unilateral renal hypoplasia. Our patient with the 7p14.3 deletion (subject 3 in Table 1 and 3) has clinical features of MCDK and autistic feature, similar to this case. It is worth to notice that the clinical features of these patients are different from that of BBS patients, suggesting that phenotype of 7p14.3 deletion may be due to more complex mechanism of multiple gene deletions rather than to loss of function of a single *BBS9* gene.

Animal studies demonstrate that mice deficient in a related gene, *BBS4*, (*Bbs4*$^{-/-}$) exhibit renal glomerular macrocysts [17]. These findings underscore the importance of *BBS* spectrum genes in cystogenesis in mammals. Mutations in *BMPER*, which encodes the bone morphogenetic protein (BMP)-binding endothelial cell precursor-derived regulator, cause diaphanospondylodysostosis (DSD, OMIM 608022), a rare autosomal-recessive disease characterized by aberrant vertebral segmentation and a small chest. Renal findings in DSD include nephroblastomatosis with cystic kidneys [18, 19]. Bmp4 is a member of the transforming growth factor $\beta$ (TGF-$\beta$) family and is essential for normal kidney organogenesis. It inhibits ectopic outgrowth of the ureteric bud and promotes elongation of UB-derived ureter in mice [20]. In addition, recombinant BMP4 induces cell apoptosis during early stages of kidney formation [21]. Inhibition of the BMP signaling is critical for survival and proliferation of the nephron progenitor cells in the metanephric mesenchyme. Of interest, kidneys of newborn *Bmp4*+/− mice contain multicystic dysplastic areas [22]. In humans, *BMP4* variants are associated with renal hypodysplasia (RHD), defined as reduced renal size and/or abnormal formation of the kidney tissue during renal organogenesis [23]. Collectively, disruption of *BMPER/BMP* signaling is linked to variable types of cystogenesis in both mice and humans.

The duplication at 16p13.11p12.3 spans over the region for 16p13.11 recurrent microduplication locus and extends to its downstream region. More than 20 genes are located within the duplicated region, including 10 miRNA genes, and disease associated genes such as *NDE1*, *MYH11*, *ABCC6*, and *XYLT1*. Two pseudo genes, *PKD1P1* and *ABCC6P1*, are located within the duplication. *PKD1P1* is a pseudogene for *PKD1* (Polycystic Kidney Disease 1). *PKD1* mutations result in an autosomal-dominant polycystic kidney disease in humans. The *PKD1P1* shares a 97.7% sequence identity with the genuine *PKD1. PKD1P1* is expressed during the early stages of embryogenesis [24]. However, its function has not been determined yet. Recent reports indicate that pseudogenes might affect the expression of their parental genes by diverting miRNAs away from corresponding parental mRNA [25]. If this is the case for *PDK1P1*, an extra copy of *PDK1P1* might have impacts on the expression of *PKD1*. *ABCC6P1* is a pseudogene for *ABCC6* (ATP Binding Cassette Subfamily C Member 6). Mutation of *ABCC6* results in pseudoxanthoma elasticum, an inherited disease characterized by calcification of arteries and kidney tissue. Both genes are located in the duplicated region. ABCC6 is expressed in the kidney,

suggesting its possible role in kidney development or function [24, 26]. The duplication will add extra one copy of *ABCC6P1* and possibly alter the expression level of this gene in the fetal kidney. In addition, there are about 18 copies of miRNA genes within the duplicated region. Increasing copy number of miRNA genes may have an impact on the regulation of gene expression as well. Therefore, the pathogenic role of *ABCC6P1* duplication in MCDK cannot be excluded. Both the deletion at 7p14.3 and the duplication at 16p13.11p12.3 were inherited from each patient's phenotypically normal corresponding parents. These two cytogenomic aberrations have not been reported previously as CNVs from general population, suggesting that they may be specific to MCDK.

Identification of CNVs in the minority of children with MCDK in this study is consistent with such general characteristics of CAKUT as incomplete penetrance and variable expressivity of disease. Additional mechanism explaining lack of identifiable CNVs in children with MCDK include epigenetic imprinting and unmarked single nucleotide variants (SNVs) in the aberration regions. Detailed analysis of genes located within identified aberrations will allow to better elucidate genetic mechanisms of MCDK. In this regard, next generation sequencing (NGS), including whole exome sequencing (WES), should improve discovery of novel causative genes in patients with MCDK and their families.

In summary, current study describes two novel candidates of cytogenomic alterations as MCDK susceptibility loci. Unilateral renal defect was shown in 2 of 7 patients with 7p14.3 deletion (including one case described in this study), suggesting that it is a common clinical feature of 7p14.3 deletion. We report the novel finding of MCDK association with the 16p13.11 duplication. We explored the mechanisms for several genes located within the identified cytogenomic alterations as possible genetic drivers for MCDK in children. Therefore, these results provide significant insight into the genomic landscape of MCDK in humans.

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**Impact statement:**

Cytogenomic aberrations are common in children with MCDK.

Cytogenomic aberrations are inherited from parents, indicating hereditary contributions in MCDK.

aCGH is a valuable tool to reveal pathogenic mechanisms of MCDK.

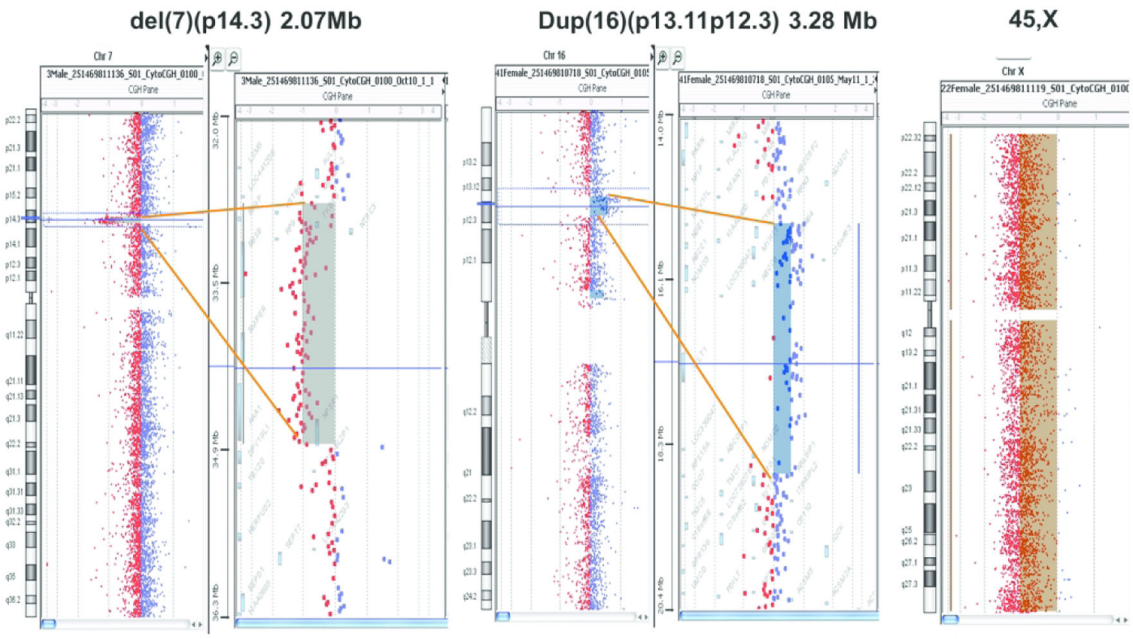


**Figure 1.**

Pathogenic alterations detected by arrayCGH. A: Deletion at 7p14.3 with size of 2.07 Mb; B: Duplication at 16p13.11p12.3 with size of 3.28 Mb; C: monosomy X

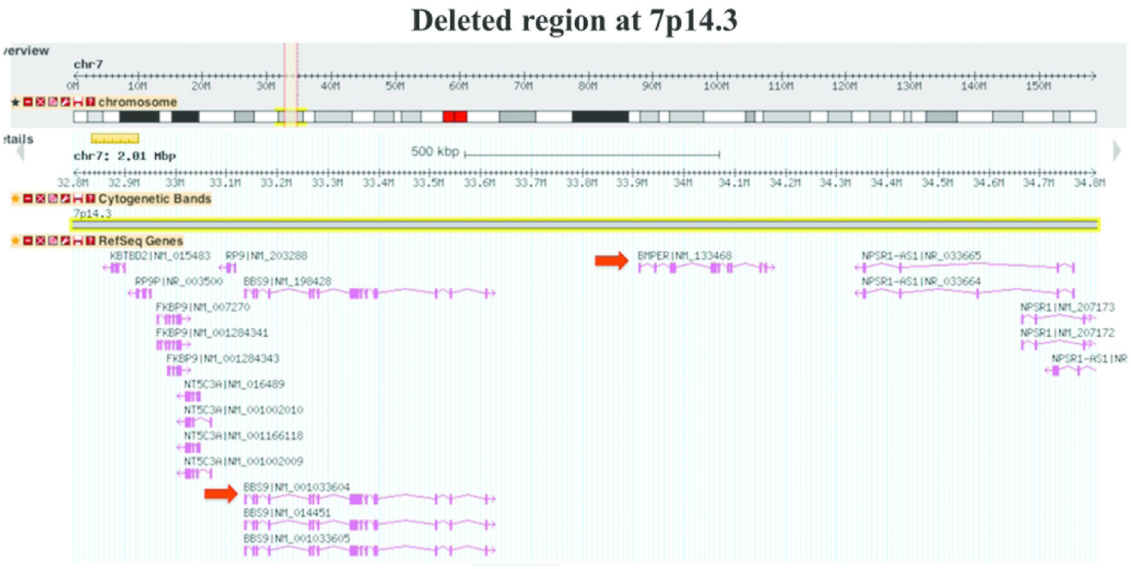


**Figure 2A.**

Alteration regions and their genetic contents. Deletion at 7p14.3 from subject 3. Red arrows: genes in the detected regions with function possibly contributing to clinical phenotype (please see discussion for details) or disease causing.

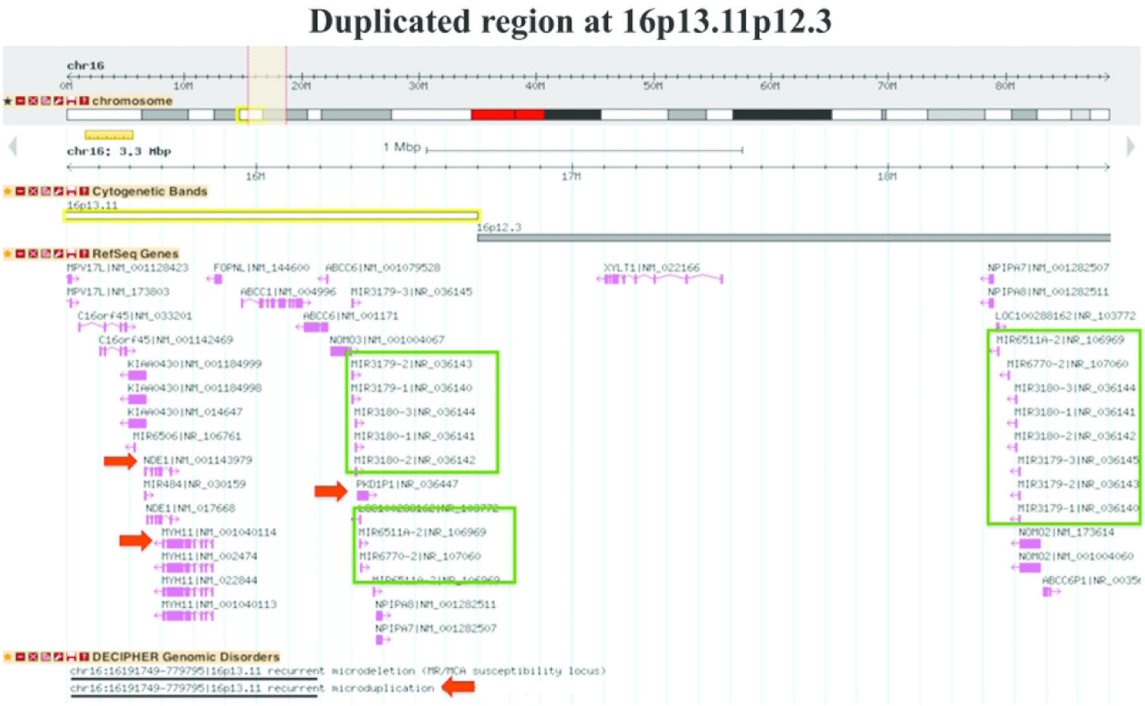


**Figure 2B.**

Duplication at 16p13.11p12.3 from subject 41. Red arrows: genes in the detected regions with function possibly contributing to clinical phenotype (please see discussion for details) or disease causing. Rectangles: clusters of microRNA genes which may play roles in the regulation of gene expression.

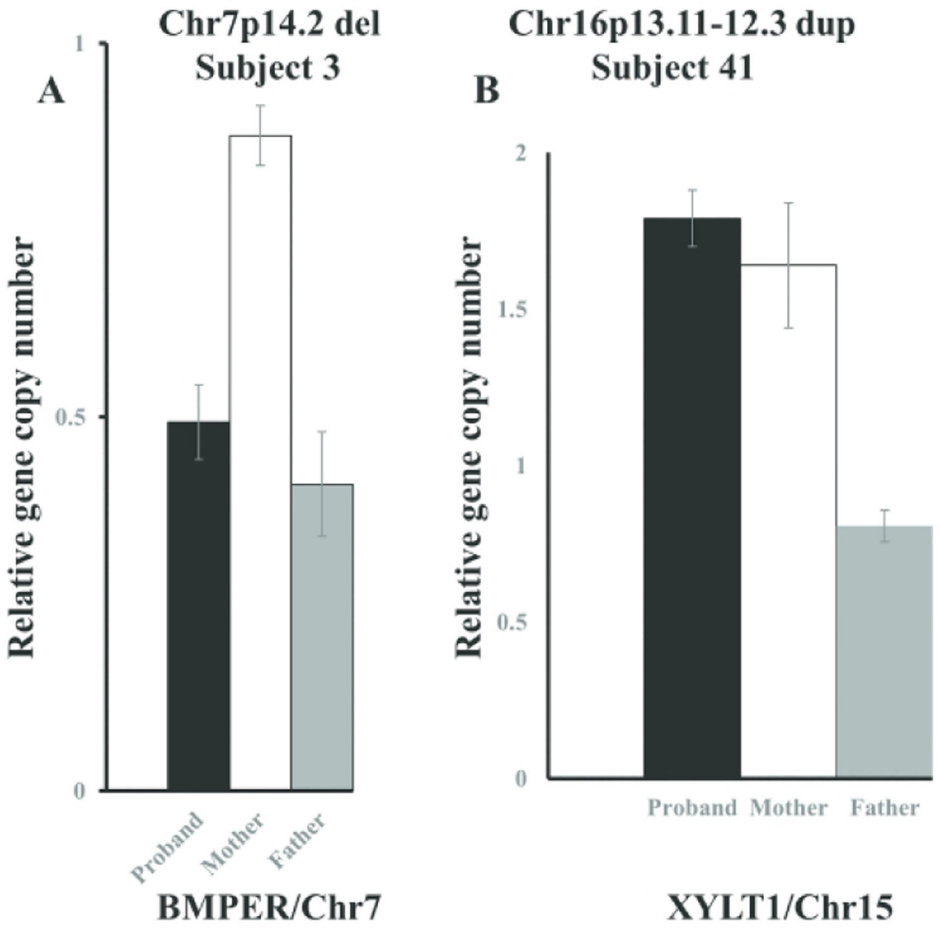


**Figure 3.**

Results from qPCR assay confirmed the aCGH findings on 7p14.3 and 16p13.11p12.3. qPCR results also revealed that the 7p14.3 deletion was paternally inherited (A), and the 16p13.11–12.3 duplication was maternally inherited (B).

**Table 1.**

Clinical characteristics of children with MCDK.

| Subject | Sex | Age (year) | Race | Height (cm) | Weight (Kg) | Patient phenotype |
|---|---|---|---|---|---|---|
| 3 | Male | 10 | White | 140 | 32 | Left MCDK<br>Aspergers |
| 14 | Female | 9 | White | 139 | 31 | Left MCDK |
| 16 | Female | 9 | Black | 124 | 21 | Right MCDK |
| 22 | Female | 20 | Black | 148 | 41 | Right MCDK<br>Turner syndrome |
| 26 | Male | 11 | Black | 140 | 35 | Left MCDK |
| 36 | Female | 12 | Black | 136 | 33 | Right MCDK<br>Left hydronephrosis |
| 39 | Male | 7 | Black | 117 | 20 | Right MCDK |
| 41 | Female | 5 | Black | 115 | 21 | Left MCDK |
| 42 | Male | 4 | Black | 107 | 21 | Right MCDK |
| 43 | Male | 8 | Black | 121 | 22 | Left MCDK |

**Table 2.**

Clinical characteristics of children in control group.

| Subject | Sex | Age (year) | Race | Height (cm) | Weight (Kg) | Patient phenotype |
|---|---|---|---|---|---|---|
| 1 | Female | 12 | White | 142 | 34 | Mild proteinuria |
| 2 | Female | 4 | Black | 115 | 20 | Microscopic hematuria |
| 4 | Male | 13 | Black | 156 | 42 | Mild proteinuria |
| 5 | Male | 9 | Black | 136 | 30 | Microscopic hematuria |
| 6 | Male | 7 | Black | 125 | 25 | Microscopic hematuria |
| 8 | Male | 12 | White | 150 | 48 | Microscopic hematuria |
| 10 | Male | 4 | White | 110 | 32 | Microscopic hematuria |
| 11 | Female | 15 | Black | 162 | 60 | Mild proteinuria |
| 13 | Male | 6 | White | 120 | 20 | Mild proteinuria |
| 28 | Female | 14 | Black | 161 | 64 | Microscopic hematuria |
| 29 | Female | 11 | White | 142 | 36 | Microscopic hematuria |
| 30 | Male | 7 | Black | 128 | 26 | Mild proteinuria |
| 31 | Male | 16 | Black | 175 | 68 | Mild proteinuria |
| 32 | Male | 9 | Black | 138 | 35 | Microscopic hematuria |
| 33 | Male | 12 | White | 151 | 55 | Microscopic hematuria |
| 34 | Male | 11 | White | 146 | 38 | Microscopic hematuria |
| 35 | Female | 7 | White | 128 | 25 | Microscopic hematuria |
| 40 | Female | 8 | Black | 131 | 27 | Microscopic hematuria |
| 45 | Female | 5 | White | 112 | 20 | Mild proteinuria |
| 46 | Female | 10 | Black | 143 | 37 | Microscopic hematuria |

**Table 3.**

Pathogenic aberrations detected in patients with MCDK.

| Subject | Location | Dup/del | Size (Mb) | Genes Related with MCKD | # of genes | Inherited (confirmed by qPCR) |
|---|---|---|---|---|---|---|
| 3 | 7p14.3 | Deletion | 2.07 | BBS9, BMPER | 11 | Father |
| 41 | 16p13.11p12.3 | Duplication | 3.28 | ABCC6<br>PDK1P1<br>ABCC6P1 | ~30 | Mother |
| 22 | Chromosome X | Monosomy X | 157 | Unknown | ~2000 | - |