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Mapping of a new locus for congenital anomalies of the kidney and urinary tract on chromosome 8q24

Shazia Ashraf¹, Bethan E. Hoskins¹, Hassan Chaib¹, Julia Hoefele², Andreas Pasch³, Pawaree Saisawat¹, Friedrich Trefz⁴, Hans W. Hacker⁵, Gudrun Nuernberg⁶, Peter Nuernberg⁶, Edgar A. Otto¹ and Friedhelm Hildebrandt^{1,7}

¹Department of Pediatrics and of Human Genetics, University of Michigan, Ann Arbor, USA, ²Center of Human Genetics and Laboratory Medicine, Martinsried, Germany, ³Department of Nephrology and Hypertension, Inselspital, University of Bern, Bern, Switzerland, ⁴Children's Hospital of Reutlingen, Reutlingen, Germany, ⁵Department of Pediatric Surgery, University of Tübingen, Tübingen, Germany, ⁶Cologne Center for Genomics, University of Cologne, Germany and ⁷Howard Hughes Medical Institute

Correspondence and offprint requests to: Friedhelm Hildebrandt; E-mail: fhilde@umich.edu

Abstract

Background. Congenital anomalies of the kidney and urinary tract (CAKUT) account for the majority of end-stage renal disease in children (50%). Previous studies have mapped autosomal dominant loci for CAKUT. We here report a genome-wide search for linkage in a large pedigree of Somalian descent containing eight affected individuals with a non-syndromic form of CAKUT.

Methods. Clinical data and blood samples were obtained from a Somalian family with eight individuals with CAKUT including high-grade vesicoureteral reflux and unilateral renal agenesis. Total genome search for linkage was performed using a 50K SNP Affymetric DNA microarray. As neither parent is affected, the results of the SNP array were analysed under recessive models of inheritance, with and without the assumption of consanguinity.

Results. Using the non-consanguineous recessive model, a new gene locus (CAKUT1) for CAKUT was mapped to chromosome 8q24 with a significant maximum parametric Logarithm of the ODDs (LOD) score (LOD_{max}) of 4.2. Recombinations were observed in two patients defining a critical genetic interval of 2.5 Mb physical distance flanked by markers *SNP_A-1740062* and *SNP_A-1653225*.

Conclusion. We have thus identified a new non-syndromic recessive gene locus for CAKUT (CAKUT1) on chromosome 8q24. The identification of the disease-causing gene will provide further insights into the pathogenesis of urinary tract malformations and mechanisms of renal development.

Keywords: congenital anomalies of the kidney and urinary tract (CAKUT); kidney development; total genome search for linkage; ureteropelvic junction obstruction; vesicoureteral reflux

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) occur in as many as 0.5% of all pregnancies and cover a wide range of structural and functional malformations that result from a defect in the development of the kidney and urinary tract [1,2]. CAKUT phenotypes include renal agenesis, ureteropelvic junction obstruction, prevesical stenosis, megaureter [3] and vesicoureteral reflux (VUR). They represent the most common cause for end-stage kidney disease (ESKD) in infants and children and account for ~50% of cases [4,5]. Urinary tract abnormalities occur in about three to six per 1000 live births. CAKUT can be inherited in an autosomal dominant, autosomal recessive or X-linked manner. In the dominant forms of CAKUT, there may be incomplete penetrance (skipping of a generation) or variable expressivity (varying severity and extent of abnormalities) [4]. As demonstrated in animal models, this phenotype variability, which ranges from VUR to renal agenesis, occurs on the basis of stochastic spatiotemporal differences during embryogenesis, when the ureteric bud grows out to meet and induce the metamorphogenic mesenchyme [6]. Dominant CAKUT may occur with isolated genitourinary involvement (non-syndromic CAKUT) or as part of over 200 multiorgan malformation syndromes that affect the central nervous, cardiovascular and skeletal systems (syndromic CAKUT). The overall incidence of CAKUT is difficult to estimate, because many cases are not diagnosed as they may appear non- or oligosymptomatic.

Mutations in renal developmental genes have been demonstrated in patients with various forms of CAKUT such as *TCF2* (also called *HNF1 β*) mutations in renal cysts and diabetes syndrome (RCAD) associated with maturity-onset diabetes of the young type 5 [7–9], *EYAI*, *SIX1* and *SIX5* mutations in branchio-oto-renal (BOR) syndrome [10–13], *PAX2* mutations in renal-coloboma syndrome [14,15], *KALI* mutations in Kallmann syndrome [16,17] and mutations in *SALL1* in patients with Townes–Brocks syndrome (TBS) [18,19]. Recently, *TCF2* mutations were identified in 25 of 80 children with renal hypodysplasia typically with cortical microcysts [20].

Previous studies have also suggested autosomal dominant loci for urinary tract malformation on chromosomes 1p13 [21], 6p21 [22–24], 19q13 [25], 10q26 [26] and 13q33–34 [27]. Mutations in angiotensin I-converting enzyme (ACE), angiotensin type-2 receptor (AT2R) [28] and *FOXC1* [29] genes have been associated with an increased incidence of CAKUT. Also, mutations in *Uroplakin IIIa* (*UPIII*) are now known to be a rare cause of renal hypodysplasia (RHD) in humans [30]. In 2007, Lu *et al.*, [31] illustrated that mutations in the *ROBO2* gene can contribute to the pathogenesis of VUR/CAKUT in a small proportion of families. Furthermore, dominant mutations with incomplete penetrance have been demonstrated in *BMP4* and *SIX2* in patients with RHD. The roles of *SIX2* and *BMP4* have been implicated in the development of renal cysts, and defects in these proteins are shown to affect kidney development at multiple stages, leading to CAKUT [32]. Reduced *BMP4* abundance in *Gata2* hypomorphic mutant mice has also been shown to result in uropathies resembling human CAKUT [33].

Recently, Weber *et al.* performed a very interesting study in which they screened 99 unrelated patients with non-syndromic RHD for mutations in *TCF2*, *PAX2*, *EYAI*, *SIX1* and *SALL1* genes (European multicenter Effect of Strict Blood Pressure Control and ACE Inhibition on CRF Progression in Pediatric Patients/ESCAPE study) [34]. In the study, mutations or variants in these genes were detected in 17 (17%) of the patients. Fifteen percent of patients with RHD had mutations in *TCF2* or *PAX2*, whereas abnormalities in *EYAI*, *SALL1* and *SIX1* were rare. This demonstrated that mutations in *TCF2* or *PAX2* are more frequently observed than mutations in other genes. Interestingly, they identified a *SIX1* sequence variant in two siblings with renal-coloboma syndrome as a result of *PAX2* mutation, which suggested an oligogenic inheritance in these cases with CAKUT. The variability in the severity of CAKUT between individuals with identical mutations also invokes the role of ‘modifier genes’ in the pathogenesis of the disease.

In this study, we performed a genome-wide search for linkage in Somali kindred with 12 children, eight of whom presented with CAKUT. We identify a new non-syndromic recessive gene locus for CAKUT on chromosome 8q24 and report fine mapping to a 2.5-Mb genetic interval. This 2.5-Mb interval on chromosome 8q24 contains only one annotated gene called *KH domain containing, RNA binding, signal transduction associated 3* (*KHDRBS3*). *KHDRBS3* is an RNA-binding protein that plays a role in the regulation of alternative splicing and influences mRNA splice site selection and exon inclusion [34,36]. It may also play a role as a negative regulator of cell growth and inhibits cell proliferation. In the tissues, it is expressed in testis, skeletal muscle and brain. In the kidneys, it is expressed in podocytes and the glomerular epithelial cells [37].

Materials and methods

Patient recruitment

Blood samples and clinical data were obtained after informed consent from the parents and 12 children, eight of whom were affected with CAKUT. Ethnic origin of this family was Somali. The pedigree is depicted in Figure 1. The affected individuals showed a diverse spectrum of CA-

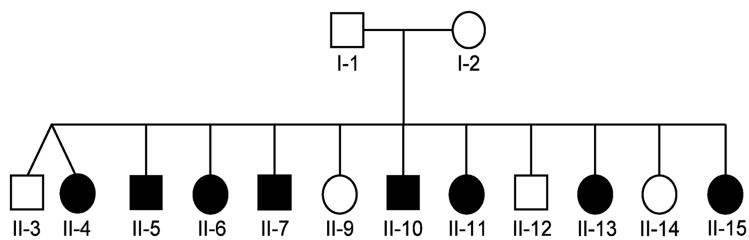


Fig. 1. Pedigree of the Somalian kindred with CAKUT (circles denote females, squares denote males; filled symbols represent affected individuals; Individuals II-3 and II-4 are dizygotic twins).

Table 1. Clinical characteristics on the eight individuals with CAKUT from Somalian family

Individual	Age of diagnosis	VUR		UPJO		Renal agenesis	Further findings
		Left	Right	Left	Right		
II-4	9 years			+	+		
II-5	10 years			+	+		Duplicate left pyelon
II-6	6 years				+	+ (left)	
II-7	1 month		+ ^a			+ (left)	Remnant left ureteral ostium
II-10	<i>in utero</i>			+	+		
II-11	5 days	+	+				
II-13	5 days			+	+		
II-15	1 day		+	+			Right Hutch diverticulum, malrotated left kidney

VUR—vesicoureteral reflux, UPJO—ureteropelvic junction obstruction.

^aPresumed diagnosis before surgery in Somalia.

KUT as follows: unilateral renal agenesis, kidney malrotation, severe ureteropelvic junction obstruction, duplication of the pyelon, VUR grades II–V, Hutch diverticulum and remnant ureteral ostium. The clinical findings in this family have been described previously [38]. However, while updating the pedigree data from the previous publication, it was revealed that Individual II-4 is also affected. Furthermore, Individuals II-3 and II-4 were found to be dizygotic twins. Diagnosis was established by pediatric nephrologists and pediatric urologists. The affected status in an individual was defined by the presence of at least two out of the following malformations: unilateral renal agenesis, severe ureteropelvic junction obstruction, VUR grade III or higher. The findings were confirmed by abdominal ultrasounds, intravenous urogram (IVU) and renal scans. Further, clinical characteristics of the affected individuals are shown in Table 1. Age at detection of CAKUT ranged from 0 to 10 years. The mother of the affected individuals is healthy with completely normal renal ultrasound. Though the father was unavailable for the study, he is also known to be healthy with no medical records or history of hospitalization.

Genome-wide linkage analysis

Genomic DNA was isolated from blood samples according to manufacturer's instructions (Puregene Gentra Systems). For the genome-wide search for linkage, DNA was available from eight affected siblings, three apparently unaffected siblings and the parents. No DNA was available from Individual II-3. Family history revealed that the maternal grandmother, her brother and her sister were also affected by an unspecified urinary tract malformation. Clinical data from these individuals were unavailable. We performed genome-wide scans for linkage on the eight affected children and both parents using a 50K single-nucleotide polymorphism (SNP) arrays (GeneChip) from Affymetrix, Inc (50K *Hind* Array). As neither parent is affected and as it is not known whether they are consanguineous, the results of the genome-wide search for linkage were analysed under a recessive model of inheritance alternatively, with and without the assumption of consanguinity.

Since many cases of urinary tract malformations are oligosymptomatic and therefore unrecognized due to incomplete penetrance or variable ex-

pressivity [4], only affected individuals were evaluated for Logarithm of the ODDs (LOD) score analysis, and apparently unaffected individuals were coded as unknown affected status ('affecteds-only strategy'). Parametric linkage analysis was performed by a modified version of the program GENEHUNTER 2.1 [39,40] and by the program ALLEGRO [41]. Haplotypes were reconstructed with ALLEGRO and presented graphically with HaploPainter [42]. All data handling was performed using the graphical user interface ALOHOMORA [43].

Mutation analysis

For all the affected-only individuals of this family, exon PCR and direct sequencing was performed in the candidate gene *KHDRBS3*, the only annotated gene present in the 2.5-Mb interval on chromosome 8q24. Sequences were aligned and evaluated with the SEQUENCHER™ software (Gene Codes Corporation, Ann Arbor, MI).

Results

Haplotype analysis data from the genome-wide search for linkage excluded the known loci for urinary tract malformations on chromosomes 1p13 [21], 6p21 [22–24], 19q13 [25], 10q26 [26], 13q33–34 [27] and the chromosomal regions containing candidate genes such as *EYAI*, *SIX1*, *SIX5*, *TCF2*, *PAX2*, *BMP4*, *SIX2*, *UPIII*, *SALL1* and others. The genome-wide search under the non-consanguineous recessive model yielded a single region with a significant maximum parametric LOD score of ($LOD_{max} = 4.2$) on chromosome 8q24 (Figure 2A). There was no additional alternative suggestive locus anywhere in the genome (Figure 2A). Haplotype analysis revealed that in the region

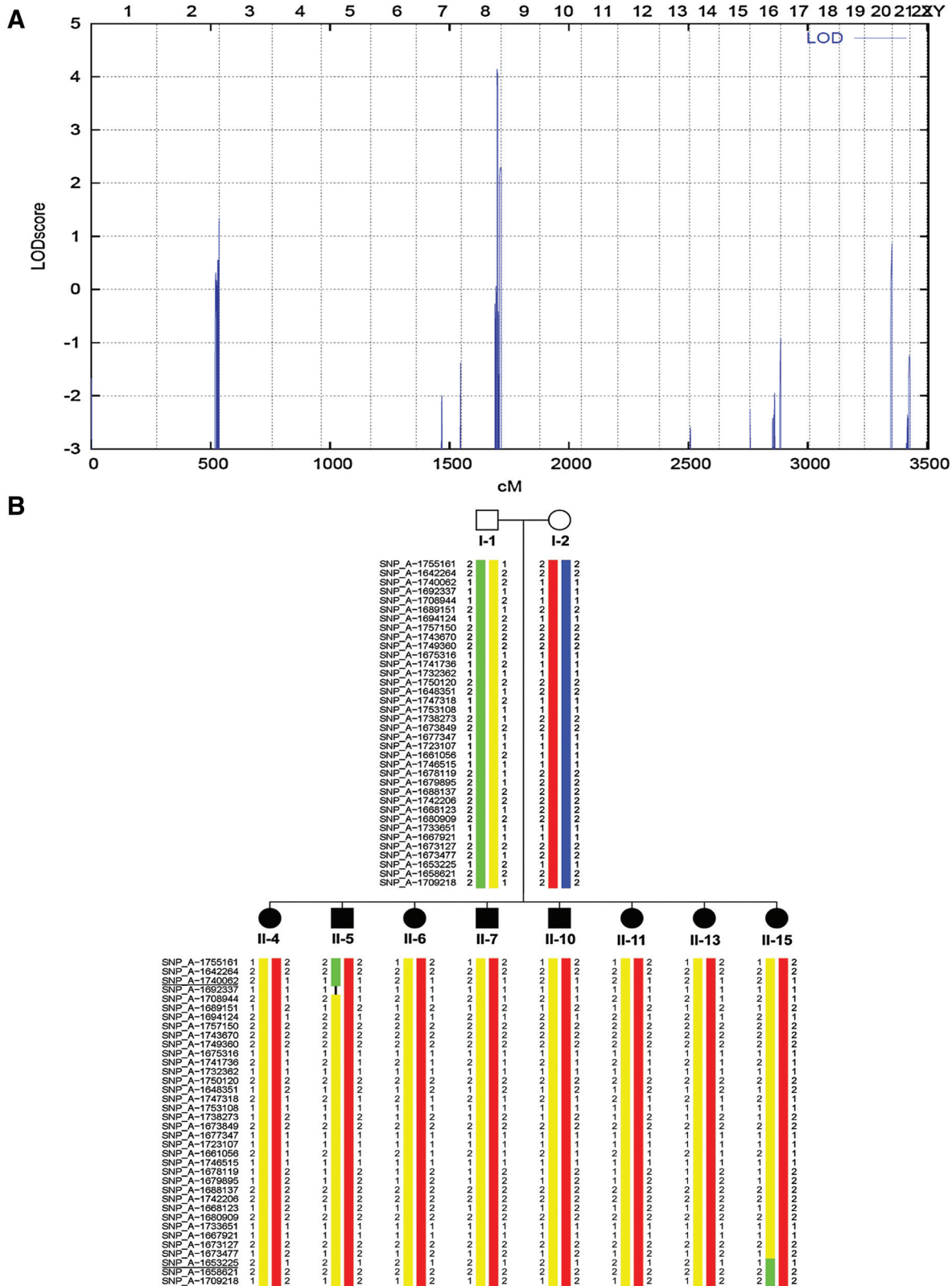


Fig. 2. (A) Parametric multipoint LOD score profile across the human genome, calculated in the eight affected individuals for a non-consanguineous model. Parametric LOD scores are on the y-axis in relation to genetic position on the x-axis. Human chromosomes are concatenated from p-terminal (left) to q-terminal (right) on the x-axis. Note the significant maximum LOD score of 4.2 on human chromosome 8, defining a new gene locus (CAKUT 8) for CAKUT on chromosome 8q24. (B) Haplotypes of the affected children and parents on chromosome 8q24. Only data from affected children are shown. All children have inherited the same paternal (represented in yellow) and maternal (represented in red) haplotype. Recombination breakpoints in Individuals II-5 and II-15 define the proximal and distal boundaries, respectively, of the critical interval. Flanking markers *SNP_A-1740062* and *SNP_A-1653225* are underlined.

of chromosome 8q, all eight affected children carried the same maternal haplotype (Figure 2B). The proximal flanking marker *SNP_A-1740062* and distal flanking marker *SNP_A-1653225* were defined by recombination events in Individuals II-5 and II-15, respectively, which delimit a critical genetic interval of 2.5-Mb physical distance. No mutation was found by directly sequencing all exons of the only annotated gene, *KHDRBS3*, within the region (data not shown).

Discussion

Employing an SNP array mapping strategy, we identified by genome-wide linkage analysis a new gene locus for non-syndromic recessive CAKUT, mapping it to chromosome 8q24. According to the University of California Santa Cruz Genome Browser, the interval between markers *SNP_A-1740062* and *SNP_A-1653225* spans a physical distance of approximately 2.5 Mb.

In this Somalian family, as eight out of 12 children are affected, the mode of inheritance is more likely to be an autosomal dominant trait, which would then imply that one of the parents was affected. However, both, the father and the mother of the affected children, are known to be healthy with no clinical history. Their consanguinity is also unknown. In light of healthy parents, we thus consider the mode of inheritance as an autosomal recessive trait and believe that the high rate of affected children is the result of a random genetic effect.

In addition to the 12 children shown in the pedigree (Figure 1), there are four more non-affected children who are from a different father (data not shown). The fact that all four children from a different father are healthy also supports the autosomal recessive model of inheritance of the disease.

We thus consider an autosomal dominant or codominant transmission (with incomplete penetrance and variable expressivity in the parents) unlikely, although based on the data presented, it cannot be ruled out with absolute certainty. The evaluation of the total genome search for linkage based on this dominant model of inheritance did not yield a significant LOD score (data not shown).

In summary, by total genome search for linkage, we mapped a new recessive locus (CAKUT1) for CAKUT to chromosome 8q24. The critical genetic region is flanked by markers *SNP_A-1740062* and *SNP_A-1653225* by the criterion of lack of consanguinity in parents. Mutational analysis of *KHDRBS3*, the only known gene within the 2.5-Mb interval, did not reveal any mutations. There is a slight possibility that we might be missing a disease-causing mutation in the promoter region of this gene, but it is very unlikely. Large-scale analysis of the entire critical genetic region will be necessary to identify the disease-causing gene. The identification of the gene mutated in the CAKUT phenotype will provide further insights into the molecular basis of urinary tract infections and into the development of the kidney and urinary tract.

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Conflict of interest statement. None declared.

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An unusual cause of hypertension and renal failure: a case series of a family with Alagille syndrome

Rajesh Shrivastava¹, Andrew Williams¹, Ashraf Mikhail¹, David Roberts³, Martyn Richards² and Vandse Aithal¹

¹Morrison Hospital, Renal Medicine, Swansea, United Kingdom, ²Morrison Hospital, Cardiology, Swansea, United Kingdom and ³Morrison Hospital, Radiology, Swansea, United Kingdom

Correspondence and offprint requests to: Rajesh Shrivastava; E-mail: rajesh.shrivastava@swansea-tr.wales.nhs.uk

Abstract

Alagille Syndrome (OMIM 118450) is a multisystem developmental disorder inherited in an autosomal dominant pattern with variable expression. It commonly manifests in children with early cholestatic jaundice due to paucity of interlobular biliary ducts. Renal involvement is less

common but can take various forms including renovascular disease, renal agenesis or hypoplasia, cystic renal disease, mesangiolipidosis, tubulointerstitial nephritis and renal tubular acidosis. We describe a family of Alagille syndrome with JAG 1 mutation running through at least two generations, affecting four members with variable