A genome-wide scan for genes involved in primary vesicoureteric reflux

H Kelly, C M Molony, J M Darlow, M E Pirker, A Yoneda, A J Green, P Puri, D E Barton

Background: Vesicoureteric reflux (VUR) is the retrograde flow of urine from the bladder into the ureters. It is the most common urological anomaly in children, and a major cause of end-stage renal failure and hypertension in both children and adults. VUR is seen in approximately 1–2% of Caucasian newborns and is frequently familial.

Objective and methods: In order to search for genetic loci involved in VUR, we performed a genome-wide linkage scan using 4710 single-nucleotide polymorphisms (SNPs) in 609 individuals from 129 Irish families with >1 affected member.

Results: Nonparametric linkage (NPL) analysis of the dataset yielded moderately suggestive linkage at chromosome 2q37 (NPL\textsubscript{max} = 2.67, p<0.001). Analysis of a subset without any additional features, such as duplex kidneys, yielded a maximum NPL score of 4.1 (p=0.001), reaching levels of genome-wide statistical significance. Suggestive linkage was also seen at 10q26 and 6q27, and there were several smaller peaks.

Conclusion: Our results confirm the previous conclusion that VUR is genetically heterogeneous, and support the identification of several disease-associated regions indicated by smaller studies, as well as indicating new regions of interest for investigation.

Vesicoureteric reflux (VUR, OMIM 193000) is the retrograde flow of urine from the bladder along the ureter towards the kidneys. VUR is common, occurring in an estimated 1–2% of Caucasian newborns and is a major cause of end-stage renal failure and hypertension in both children and adults. An estimated 30–50% of children presenting with urinary tract infections (UTI) have VUR, and the reflux of infected urine can cause pyelonephritis and resultant permanent renal damage. Anatomically, primary vesicoureteric reflux arises from a submucosal ureter that is of insufficient length, or a ureteric orifice that is too wide to allow for the operation of a proper valvular mechanism. VUR occurs frequently in families: approximately half of the offspring will be affected but the mode of inheritance is unknown. Micturating cystourethrography (MCUG) in children may be performed because of UTI or suspicion of renal-tract anomalies from prenatal ultrasonography, and in either case both VUR and renal tract anomalies, including duplex renal systems, are commonly found. Furthermore, VUR is more common in those with duplex than with single renal tracts, and duplex kidneys are commonly found in those with VUR. In both mice and humans, individuals with various renal tract defects, including VUR, occur in the same sibships, indicating that mutations of the same genes can cause both renal developmental anomalies and VUR, with considerable phenotypic variation, for reasons yet to be identified.

To date, the only genes identified as mutated in VUR have been in cases with other anomalies, or in families in which other anomalies were segregating. Hu et al observed VUR among other features in mice in which the gene for uroplakin III (locus UPK3A) had been homozygously inactivated. Linkage and mutation screening studies of UPK3A and other members of the uroplakin family (Kelly et al, unpublished data) in humans did not show evidence for their involvement in VUR, but mutations in UPK3A have now been found in some cases of renal aplasia, hypoplasia and dysplasia, including some with VUR. The PAX2 gene has been shown to be mutated in renal-coloboma syndrome, which includes VUR as part of a complex phenotype, and in renal hypoplasia and VUR without eye defects, but has not been found to be mutated in uncomplicated VUR. Investigation of a patient with multiple congenital anomalies, including severe bilateral VUR, found a Y;3 translocation that disrupted ROBO2, and investigation of this gene in 124 families with VUR with potential autosomal dominance revealed mutations in two families. Both index cases had bilateral VUR (one having hypoplastic kidneys and nephropathy, the other having a unilateral duplex system), and most affected relatives in both families had renal anomalies. Inheritance in all of the above cases appeared to be autosomal dominant, but mutations in these genes account for a very small proportion of VUR in general.

Attempts at mapping other genes for VUR have included genome-wide scans of small numbers of multi-generation families (the latter yet to be reported in full), or individual or small collections of cases with chromosomal rearrangements, although most patients in the latter group also had other renal tract anomalies. These studies identified several possible loci, and indicated that the disease is genetically heterogeneous. Several candidate-gene studies to confirm some of these and other loci possibly involved in VUR have been unsuccessful.

In this paper, we present the results of a genome-wide linkage scan with 4710 SNP markers and 129 families, each with ≥2 individuals who meet the criteria for a diagnosis of primary VUR.

METHODS

Subjects

The samples for this study were collected at Our Lady’s Children’s Hospital Crumlin, and the National Children’s Hospital, Dublin 12, Ireland; Children’s Hospital Crumlin, Dublin 12, Ireland; and the National Centre for Medical Genetics, Our Lady’s Children’s Hospital Crumlin, Dublin 12, Ireland; and the National Centre for Medical Genetics, Our Lady’s Children’s Hospital Crumlin, Dublin 12, Ireland.

Abbreviations: HLOD, heterogeneity logarithm of odds; OMIM, Online Mendelian Inheritance in Man; MCUG, micturating cystourethrography; NPL, nonparametric linkage; SNP, single-nucleotide polymorphism; TDT, transmission disequilibrium test; UTI, urinary tract infections; VUR, vesicoureteric reflux

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Hospital, Tallaght, both in Dublin, Ireland. Ethics approval was granted, and informed consent was obtained from all subjects and/or their parents. Families with ≥2 affected siblings with primary VUR of any grade were collected. All families are Caucasian and the majority considered to be of homogeneous Irish ancestry. All index cases were referred because of recurrent UTIs and diagnosed by MCUG. Siblings of index cases were screened by MCUG. Three parents and one grandparent of affected children were classed as affected because they had been diagnosed with primary VUR in the past; others with merely a history of renal problems were classified as of unknown affectedness status. Patients with VUR secondary to other conditions were not collected. Note: most authors agree that secondary VUR can result from bladder dysfunction (neurogenic bladder and non-neurogenic neurogenic bladder (Hinman–Allen syndrome)), posterior urethral valves, or ureterocoele, but some authors include complete duplex renal systems as a cause, and some count some cases with duplex systems as primary and some as secondary. All families included in our study were considered to exhibit primary VUR. It was noted that in one of the excluded families, only one of the affected members had a posterior urethral valve, and in one of the included families, one of the affected members had a ureterocoele. From a developmental genetics point of view, both types of condition could probably safely be included (see Introduction and Discussion).

Genotyping

Samples were sent to Illumina (San Diego, California, USA) for genotyping. The panel (linkage panel III) consisted of 4753 SNP markers, with an average distance between markers of 600 Kb. In total, 626 DNA samples from 133 families were genotyped, but 4 families were subsequently removed because exclusion of members giving non-mendelian results left only one affected member. The following figures for the remaining 129 families refer only to genotyped individuals. They included 255 parents (3 affected, 5 unaffected, and 247 with unknown affectedness status), 283 affected siblings (117 male and 166 female), 37 unaffected siblings (17 male and 20 female), 32 siblings with unknown affectedness status (14 male and 18 female) and 2 grandparents (one affected and one of unknown status). There were 107 families with 2 genotyped affected children, 20 with 3, 1 with 4 and 1 with 5, giving 183 affected sibling pairs in total. Six samples gave no genotype results, thus 638 samples (620 samples + 18 replicates) were genotyped in total. After cleaning the data for mendelian errors and departures from Hardy–Weinberg equilibrium (ie removing obvious genotyping errors) with Pedstats software, 4710 SNPs were used in the analysis. Of the possible 3 004 980 genotypes, 3 002 877 were reported, giving a success rate of 99.93%. The mean heterozygosity over all markers was 46.1%.

Statistical analysis

Both non-parametric and parametric linkage analysis for the scan was performed using MERLIN V.1.0.1.10.3 (http://www.sph.umich.edu/csg/abecasis/Merlin). NPL scores were based on a procedure for converting scores for individual inheritance vectors into Z scores for single or multiple pedigrees, which are used to construct a likelihood ratio test for linkage and define a (NPL) LOD score statistic. The dataset was prepared for analysis using MEGA2 software (http://www.megasoftware.net/) and markers in tight LD (D’>0.7) were removed from the dataset prior to analysis using the SNPLINK program (http://www.icr.ac.uk/research/sections/cancer_genetics/cancer_genetics_teams/molecular_and_population_genetics/software_and_databases/index.shtml). The resultant panel consisted of 3861 markers. Although all patients included in the study had primary VUR, 25 families included patients with additional phenotypic features. These features were mainly duplex kidneys (20 families, in most of which only one of

Figure 1  Layout plots of nonparametric linkage (NPL) scores from the genome scan. (A) Full dataset; (B) uncomplicated dataset. The vertical axis shows NPL scores. Plots are scaled vertically to show the maximum peak (4.10) in the uncomplicated dataset.
the patients with VUR had a duplex system) but also included fused kidneys, renal hypoplasia, large ureteroceles, branchial cleft remnants, or mental retardation with abnormal faces. After the initial scan, these families were removed to create a subset for further analysis. The reduced set consisted of 104 families, comprising 480 members.

A genetic model of inheritance for VUR has been proposed both in segregation studies and in studies of large multi-generational families. A single model was tested in the parametric analysis, which corresponded to an autosomal dominant mode of inheritance with a disease frequency of 0.01 and incomplete penetrance according to the previously proposed genetic model. Power for the complete cohort is 79% (\( \alpha = 0.05 \)), given the genetic model, and is estimated as 1 - 0.33 = 0.67, 0.9 of the disease frequency and 0.8 of the penetrance. This is likely to be an overestimate in general, as power will have fluctuated substantially based on marker and multilocus informativeness, increasing \( \alpha \), or the sample size reduction, as in our uncomplicated cohort setting. For parametric analysis, heterogeneity was investigated using the heterogeneity logarithm of odds (HLOD) statistic. Abreu et al. suggest that an HLOD of 2.90 (NPL = 3.18) was suggestive of linkage, and p = 0.001 and a LOD score of 2.2 (NPL = 3.18) was suggestive of linkage, and p < 0.001 and a LOD score of 3.6 (NPL = 4.08) was considered significant linkage.

### Table 1

<table>
<thead>
<tr>
<th>Location</th>
<th>SNP markers</th>
<th>Interval (cM)</th>
<th>Interval (Mbp)*</th>
<th>Width (Mbp)</th>
<th>LOD</th>
<th>Maximum NPL</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q23.2–q25.2</td>
<td>rs1053074</td>
<td>rs1923626 152–175</td>
<td>158.3–175.3</td>
<td>17.05</td>
<td>-18.10</td>
<td>2.10</td>
<td>1 ( \times 10^{-4} )</td>
</tr>
<tr>
<td>2q37.2–q37.3</td>
<td>rs869214</td>
<td>rs16747 246–261</td>
<td>235.6–242.4</td>
<td>6.79</td>
<td>-15.33</td>
<td>2.67</td>
<td>2 ( \times 10^{-4} )</td>
</tr>
<tr>
<td>3p13–q21.2</td>
<td>rs7064</td>
<td>rs713161 96–131</td>
<td>126.3–127.4</td>
<td>1.1</td>
<td>-17.36</td>
<td>1.36</td>
<td>6 ( \times 10^{-3} )</td>
</tr>
<tr>
<td>3q26.31</td>
<td>rs2064718</td>
<td>rs753293 177–178</td>
<td>175.0–176.6</td>
<td>1.6</td>
<td>-20.8</td>
<td>0.98</td>
<td>0.02</td>
</tr>
<tr>
<td>4p16.1–p15.31</td>
<td>rs1981635</td>
<td>rs279918 18–30</td>
<td>10.2–20.1</td>
<td>9.9</td>
<td>-19.77</td>
<td>1.33</td>
<td>7 ( \times 10^{-3} )</td>
</tr>
<tr>
<td>6q24.1–q27</td>
<td>rs191992</td>
<td>rs756519 146–188</td>
<td>142.6–170.7</td>
<td>28.1</td>
<td>-9.16</td>
<td>2.55</td>
<td>3 ( \times 10^{-4} )</td>
</tr>
<tr>
<td>7q26.1–q26.3</td>
<td>rs1547958</td>
<td>rs1343750 165–179</td>
<td>112.8–134.9</td>
<td>22.1</td>
<td>-11.38</td>
<td>2.35</td>
<td>5 ( \times 10^{-4} )</td>
</tr>
<tr>
<td>10q25.2–q26.3</td>
<td>rs1327551</td>
<td>rs880340 120–165</td>
<td>150.3–155.2</td>
<td>4.94</td>
<td>-14.94</td>
<td>2.19</td>
<td>7 ( \times 10^{-4} )</td>
</tr>
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<td>13q32.3–q33.3</td>
<td>rs981900</td>
<td>rs1876273 100–108</td>
<td>105.3–107.4</td>
<td>2.12</td>
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<td>1.47</td>
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</tr>
<tr>
<td>16q24.1–q24.3</td>
<td>rs454087</td>
<td>rs6577 107–123</td>
<td>83.1–88.6</td>
<td>5.5</td>
<td>-4.02</td>
<td>1.36</td>
<td>7 ( \times 10^{-3} )</td>
</tr>
<tr>
<td>20p11.2–p11.23</td>
<td>rs742920</td>
<td>rs761461 30–41</td>
<td>11.0–18.2</td>
<td>7.25</td>
<td>-17.73</td>
<td>2.09</td>
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</tr>
<tr>
<td>21q22.3</td>
<td>rs234705</td>
<td>rs235310 53–56</td>
<td>42.8–45.1</td>
<td>2.3</td>
<td>-25.69</td>
<td>1.35</td>
<td>6 ( \times 10^{-3} )</td>
</tr>
</tbody>
</table>

LOD, logarithm of odds; NPL, nonparametric linkage.

Results

### Table 2

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>cM</th>
<th>HLOD</th>
<th>( \alpha )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>169</td>
<td>1.45</td>
<td>0.29</td>
</tr>
<tr>
<td>2</td>
<td>260</td>
<td>2.90</td>
<td>0.40</td>
</tr>
<tr>
<td>3</td>
<td>129</td>
<td>1.55</td>
<td>0.29</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>1.64</td>
<td>0.29</td>
</tr>
<tr>
<td>5</td>
<td>115</td>
<td>1.31</td>
<td>0.25</td>
</tr>
<tr>
<td>6</td>
<td>163</td>
<td>3.55</td>
<td>0.42</td>
</tr>
<tr>
<td>7</td>
<td>172</td>
<td>1.84</td>
<td>0.33</td>
</tr>
<tr>
<td>10</td>
<td>154</td>
<td>1.78</td>
<td>0.36</td>
</tr>
<tr>
<td>13</td>
<td>104</td>
<td>1.37</td>
<td>0.29</td>
</tr>
<tr>
<td>20</td>
<td>38</td>
<td>1.25</td>
<td>0.29</td>
</tr>
</tbody>
</table>

All areas giving heterogeneity logarithm of odds (HLOD) scores >1.2 are reported.

Under the proposed genetic model, parametric analysis of the UCS provided a number of regions with only moderately negative LOD scores, in contrast to the strongly negative LOD

All areas giving heterogeneity logarithm of odds (HLOD) scores >1.2 are reported.
scores obtained across the entire genome observed in the parametric analysis of the full set. Some of the regions, where the degree of “rejection” decreased in the UCS versus the FS parametric analysis, overlapped with some of those highlighted in the nonparametric analysis (tables 1 and 3).

Again, significant HLOD scores were coincident with significant or suggestive NPL scores, with HLODs of 3.37 and 3.28 for 2q37 and 6q27, respectively. As the overall number of families decreased, the proportion of linked families increased to as much as 0.5 in these regions (table 4); elsewhere, there were more modest changes. Individual familial LOD scores were obtained; it seemed from these that there was no significant enrichment or association for uncomplicated status for reduced dataset

**DISCUSSION**

This is by far the largest linkage study of VUR yet undertaken, in terms both of families and markers tested. The results from the scan revealed 10–15 regions of varying sizes and levels of support or significance across the genome. It is likely that some of these regions will not be replicated, but the smaller ones should not necessarily be rejected out of hand.

The genetics of VUR reflect the complexity of the development of the urinary tract. VUR results from poor function of the vesicoureteric valve. The development of the renal tract in the embryo begins with the formation of the ureteric bud, an outgrowth of the mesonephric (Wolffian) duct. Reciprocal signalling between the ureteric bud and the metanephrogenic mesenchyme stimulates the ureteric bud to grow to form the kidney. The part of the mesonephric duct between the urogenital sinus and the newly developed ureter is removed by apoptosis, whereupon the freed end of the ureter inserts into the bladder wall and the vesicoureteric valve is formed. The precise position at which the UB grows out from the mesonephric duct is critical for the development of the whole urinary tract and many genes are involved in the control of this process.

Additional exploratory association testing using the TDT gave no significant results after correction for multiple testing. None of the most significant association results (p<0.01) before correction were located in the regions supported by the linkage analysis.

**Table 4** Heterogeneity logarithm of odds scores for reduced dataset

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>cM</th>
<th>HLOD</th>
<th>α</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>168</td>
<td>1.30</td>
<td>0.31</td>
</tr>
<tr>
<td>2</td>
<td>260</td>
<td>3.37</td>
<td>0.50</td>
</tr>
<tr>
<td>3</td>
<td>177</td>
<td>1.40</td>
<td>0.34</td>
</tr>
<tr>
<td>6</td>
<td>163</td>
<td>3.28</td>
<td>0.45</td>
</tr>
<tr>
<td>7</td>
<td>172</td>
<td>1.37</td>
<td>0.34</td>
</tr>
<tr>
<td>10</td>
<td>154</td>
<td>2.19</td>
<td>0.48</td>
</tr>
<tr>
<td>13</td>
<td>23.2</td>
<td>1.32</td>
<td>0.30</td>
</tr>
<tr>
<td>20</td>
<td>38</td>
<td>1.36</td>
<td>0.32</td>
</tr>
</tbody>
</table>

HLOD, heterogeneity logarithm of odds.
ignored as artefacts; at least those that show agreement with results of earlier studies should be given further consideration. Peaks in our study that coincided or overlapped with areas identified in other studies are illustrated in fig 2. A peak (NPL 1.47 in the full set, 1.55 in the uncomplicated set) in 13q33 coincides with a region identified by interstitial deletion mapping in children with renal anomalies, some of whom had VUR. Similarly, in a study of patients with terminal deletions of 10q26, a location at which we identified a peak NPL of 2.35 (full set) and 2.89 (uncomplicated set), all cases had

![Figure 2](http://jmg.bmj.com/)

**Figure 2** Comparison of regions suggestive of linkage in this study with those identified in other studies. (A) chromosome 1; (B) chromosome 2; (C) chromosome 3; (D) chromosome 10. The vertical line indicates the position of the peak in the uncomplicated set. (E) chromosome 13; (F) chromosome 20. Regions of suggestive evidence for linkage from the full set of families used in this study are shown in red; results from the uncomplicated set are shown in light green. Results from other studies are coded as follows: Feather *et al*., blue; Casas *et al*., brown; Ogata *et al* (renal development region), purple; Ogata *et al* (genital development region), maroon; Vats *et al*., aqua. The chromosomes are drawn to the scale of nucleotides rather than of their cytogenetic lengths.
either urinary-tract anomalies (including VUR), genitai anomalies or both.25

The first genome scan for VUR22 studied seven extended families, whereas our study used 129 families, but ours were only nuclear families, thus it was essentially an affected sibling-pair study. The other difference was that the first study used 375 microsatellite markers, which are highly variable, so that nearly all individuals are heterozygotes and therefore nearly all markers are informative in every family, whereas our study used >10 times as many markers, but they were SNPs with an average heterozygosity of 46%, meaning that each marker will be uninformative in some families. However, SNPs in high density, such as those used here, can provide greater information content and better resolution, and may be less biased by genotyping error rates.44 45 Nonetheless, there is good agreement between the two studies, with coincident or overlapping peaks on chromosomes 1, 3, 13 and 20 (fig 2). Furthermore, there has been a recent report of mosaic monosomy 20 in the renal tract of a child with bilateral VUR27 and the principal peak of the genome scan of Conte et al27 is on 3q, although the exact region has yet to be published.

Our region of greatest significance is in the terminal band of chromosome 2, q37. We have searched the case reports of 77 cases of terminal deletions of 2q (mainly with breakpoints at 2q37, but a few more proximal), plus four unrationyped close relatives with similar phenotypes66–68 (see also Casas et al77 and references therein). Of these 81 cases, 7 were reported to have had urinary tract anomalies,66 67 68 1 of whom was recorded to have bilateral VUR,77 and 3 cases without recorded anomalies were reported to have recurrent UTIs and therefore may also have had VUR.66–69 As this region is gene-rich, even small deletions tend to cause multiple anomalies, and VUR may have been under-reported. One of the candidates at the centre of our region is the transcription factor TWIST2, but the sequence of this human gene is unfortunately incomplete, as there are gaps in both the reference and Celera genome sequences in this region. Other possible candidates are the transcription factor HES6 and the integrin-linked kinase-associated serine/threonine phosphatase, ILKAP, which may participate in the wnt signalling pathway.

Thus we have detected in our families six regions supported by earlier studies, on 1q, 2q 3q, 10q, 13q and 20p (fig 2). However, others of similar significance, on chromosomes 6q, 7q, 16q and 21q, have not been reported previously in genetic studies of VUR in humans (VUR has been reported to be linked to the HLA region on 6p,64 but we had no peak in this region).

Yeung et al65 concluded that mild reflux affects mostly females and a small proportion of males, whereas severe reflux with congenital renal malformation affects almost exclusively males, and our own data are in broad agreement.66 67 It is therefore possible that the relative significances of different regions might be affected by the method of ascertainment of probands. Several studies of VUR have noted a preponderance of males (Yeung et al65 and references therein) whereas our series had more affected female patients. Our index cases were ascertained through UTIs, which, after the first year of life, are more common in female patients, and may therefore give more emphasis to genes causing mild VUR without renal anomalies than does ascertainment by other methods, such as detection of hydronephrosis on prenatal ultrasound.

The former conclusion that VUR is a homogeneous disorder1 60 is no longer tenable; it is clearly heterogeneous. The subgroup of 25 families with additional phenotypic features was too small to analyse on its own. We expected that the removal of this subgroup would cause a reduction in the NPL scores of those regions that we had identified as containing loci associated with renal anomalies, on 2q37, 10q26, and 13q33, but in fact, all scores rose, particularly that on 2q, and there were modest changes, up or down, to the NPL scores of other regions, with the exception of a new peak appearing on 17q. Thus, many of the genes represented by our peaks may be associated with VUR, with or without renal and ureteric anomalies, depending upon the mutation, hence the removal of the subgroup had a rather random effect, by changing the relative proportions of mutated loci left in the sample. Drastic changes in results, such as the appearance of the 17q peak, may have arisen due to fluctuations in the amount of evidence supporting and/or rejecting linkage in the underlying dataset, or due to random chance alone. Without corroborating or even suggestive evidence from additional studies, results such as this 17q peak require replication before any further investigation is warranted.

Our genome scan has revealed a number of large regions (mean intervals of 9.1 and 12.9 MB in the full and uncomplicated sets, respectively) that, when combined together, provide a very large region for follow-up studies. In some regions, there are good candidate genes, but in others, it is much less obvious which gene might be the relevant one. There is almost nothing known about many of the genes revealed by the Human Genome Project, making it difficult to decide which genes to investigate, so that fine mapping is necessary in some regions. Similar genome scans on other groups of patients with VUR should provide valuable replication of these results and help eliminate false positive peaks. In the meantime, we shall be investigating the likely candidates. Our total number of families is now >200 and we have 600 DNA samples available from healthy Irish controls. These will be useful for investigation of which mutations are causative and which are normal polymorphisms, and possibly which common variants are associated with an increased risk of VUR or associated developmental anomalies. The recently published data on copy-number variation in the human genome67 will also be taken into account.

As we have said earlier, VUR results from developmental anomaly and can have serious consequences of hypertension and renal failure, yet in many cases it resolves spontaneously without any damage. VUR is clearly genetically heterogeneous, so genotyping will not provide a simple diagnostic test, but finding the genes will be the first step in the process of understanding the aetiology of the condition. It is to be hoped that it may be possible to identify which mutations are compatible with spontaneous resolution and whether any are related to inevitable renal damage, which will help with prognosis and genetic counselling, and in due course may lead to new forms of treatment.

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Competing interests: None.

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