Diagnosis of adult polycystic kidney disease by genetic markers and ultrasonographic imaging in a voluntary family register

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Abstract

Diagnosis of autosomal dominant adult polycystic kidney disease (APKD) is possible by ultrasonographic scanning (USS) or by using DNA markers linked to the PKD1 locus. Ultrasonography is complicated by the age dependent penetrance of the gene and linkage studies are subject to recombination errors owing to meiotic crossing over and locus heterogeneity.

This study draws on data collected from a voluntary family register of APKD over 10 years. Records of 150 families were examined, ultrasound reports were obtained from 242 people at 50% prior risk, and 37 families were typed for DNA markers. The fraction of APKD resulting from loci unlinked to PKD1 (designated PKD2 here) was calculated at 2·94% (upper confidence limit 8·62%). Some subjects who were negative on initial scan later gave a positive scan, but there was no example of a definite gene carrier aged over 30 giving a negative scan. In families large enough for linkage analysis, most people who were at 50% prior risk could be given a final risk below 5% or above 95%, by using combined ultrasound and DNA studies.

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Adult polycystic kidney disease is one of the commonest serious autosomal dominant diseases, affecting between 1 in 1000 and 1 in 2500 white people. Renal function is impaired as fluid filled cysts increase in size and number, replacing tissue of the renal cortex with non-functional material and damaging the interstitial cortex. Of all patients requiring kidney transplants, 6% to 10% suffer end stage renal failure as a result of APKD.[1,2] The gradual development of cysts gives the disease a marked age dependent penetrance, and the course is very variable. The risk of end stage renal failure has been estimated as 2% before the age of 40, 23% at the age of 50, and 48% at 73 years.[3]

Few people request prenatal diagnosis of APKD, but presymptomatic screening is important because complications of APKD threaten the health of gene carriers if untreated.[4,5] Presymptomatic diagnosis has been possible for some time through renal imaging. Ultrasonographic scanning is the method of choice, being safe, inexpensive, and non-invasive. A crucial question for genetic counselling is the sensitivity of ultrasound scanning for detecting early manifestations of the disease. In an early study using first generation technology, Bear *et al*[6] analysed data on 17 families from Newfoundland, Canada. For subjects at 50% prior risk of carrying the APKD gene, they reported false negative rates in the second and third decades of 0·25 and 0·12 respectively. In a more recent study in the same families, Bear *et al*[7] have revised their figures for these age classes to 0·08 and 0.

DNA based diagnosis became possible in 1985 when Reeders *et al*[8] showed linkage between the APKD locus (PKD1) and the α globin locus on chromosome 16p13.3. Since then, highly informative markers flanking the PKD1 locus have been defined, allowing accurate presymptomatic diagnosis at any age.[8,9] A problem for DNA marker studies is the existence of families in which APKD does not segregate with 16p markers.[10,11] This unlinked form is called PKD2, but the location of the gene(s) is unknown*. The proportion of unlinked APKD families has been estimated as 4% and 14% in North America and Europe respectively.[12–14] Presymptomatic or prenatal risk estimates are now based on combining age dependent ultrasound data with information from 16p markers, allowing for the possibility that the disease is not linked to PKD1.[15,16]

In the North Western Health Region of the UK a voluntary genetic family register was established in 1980, covering a population of 4 million. We have studied 150 families ascertained through the register. This cohort enables us to estimate the proportion of unlinked (PKD2) kindreds in the study population, to study the reliability of ultrasonographic scanning using modern imaging equipment, and to examine the concordance between USS data and genetic markers. Combining the data permits an overview of the effectiveness of molecular and ultrasonographic techniques combined in presymptomatic and prenatal diagnosis.

Materials and methods

ASCERTAINMENT AND SELECTION OF FAMILIES

All families were ascertained through an index patient referred from a renal unit in the north

* The PKD2 gene has very recently been localised to chromosome 4q (Peters *et al. Nature Genet* 1993;5:359–62, Kimberling *et al. Genomics*, in press).

Table 1 Structure of the data set. Of the 150 family register records examined, 36 families with only one case of diagnosed APKD were excluded from analysis. The total of subjects at 50% risk and those diagnosed affected includes index cases in this table

Families examined	Families excluded	Subjects at 50% risk	Diagnosed APKD clinically or by USS
150	36	1412	522

west of England, who was then contacted by the Regional Genetics Service. Register records and USS reports from 150 families were examined (table 1). Families with only one subject diagnosed were not included in the analysis to prevent phenocopies or new mutations entering the data set. For the multiplex families, all people at 50% prior risk were counted, and total numbers and numbers affected, excluding the index case, were counted for each age group 0–9, 10–19, 20–29, 30–39, 40–49, and 50+.

CALCULATION OF THE PROPORTION OF FAMILIES NOT LINKED TO THE PKD1 LOCUS

Families were typed with two or more of the DNA markers listed in table 2, to find informative flanking markers. Following Sandkuijl (personal communication) we calculated the likelihood of each pedigree using two alternative maps:

$$A---\theta_1---D---\theta_2---B \text{ and}$$
$$D---(\theta = 0{\cdot}5)---A---(\theta_1 + \theta_2)---B$$

where D is the disease and A and B are markers known to flank the PKD1 locus with recombination fractions θ_1 and θ_2 respectively. Linkmap[25] was used to calculate these likelihoods. The ratio of the two likelihoods gives the odds PKD1:non-PKD1 for that family. Some families were informative only for a single marker, in which case Mlink was used. The odds ratio was converted into a probability of non-PKD1 using a prior probability of non-linked disease of 0·14, from the European study.[14]

ULTRASOUND DETECTION RATES

Ultrasonographic reports were noted from persons at 50% prior risk who had no previous history of symptoms to bring them forward for clinical examination. Mostly these were people who volunteered for presymptomatic screening as a result of contact with the Family Register. Index cases and all subjects presenting with symptoms were excluded from the analysis of ultrasound error rates. Subjects were assigned an age class according to the date when they were first examined by ultrasonography. Scan reports were classified as positive, negative, or equivocal. Following Bear *et al*,[6] the criterion for a positive report was at least one cyst in each kidney and one kidney having more than one cyst. Most of the ultrasonographic scans were performed by a single experienced consultant radiologist using either a Hitachi EUB 25M scanner with a 3·5 MHz linear array or an Acuson 128 scanner with a 3·5 MHz linear array or sector probe.

For each age class the frequency of false negative USS diagnosis was estimated by comparing observed and expected rates of positive results. The expected frequency of positive results depends on age. It is always less than 50% because only asymptomatic people are considered. In a group of N people all at 50% prior risk, of whom A have already presented with symptoms, the proportion of gene carriers among asymptomatic people is $\{(\frac{1}{2}N)-A\}/(N-A)$. This was compared with the proportion of people examined whose scan was positive (equivocal scans were counted as negative for this purpose).

A 95% confidence interval was calculated for the observed rate of positive scans (observed $\pm 1{\cdot}96 \times \sqrt{(pq/n)}$, where $\sqrt{(pq/n)}$ is the binomial standard deviation). Complementing this statistical approach to detecting false negatives, individual cases were noted where the diagnosis had changed on repeated scans.

CONCORDANCE BETWEEN USS AND GENETIC MARKERS

High risk and low risk haplotypes were assigned by inspection in each family. Marker and ultrasound data were classed as conflicting when somebody inherited a haplotype non-recombinant for markers spanning the PKD1 locus, but did not have the expected scan result. Cases where there was a marker–marker recombinant, so that the haplotype could not be unambiguously defined as high risk or low risk, were not counted as conflicting.

CALCULATION OF INDIVIDUAL RISKS

Individual risks combining marker and ultrasound information were calculated for 65 asymptomatic subjects from 30 families. Risks were calculated using Mlink, using conservative liability classes based on the study of Bear *et al*[7] (all asymptomatic persons under 20 years a risk of 0·5 of having the APKD gene and allowing an error rate of 0·08 for persons over 20 years with negative USS). The Mlink risk was then modified to allow for the possibility that the disease was not PKD1. If the risk of PKD2 in the family is x %, this adds a risk of false results of $^{x}/_{2}$ %, since half the time the 16p markers will segregate with the unlinked disease just by chance.

Table 2 Genetic markers used in this study

Locus name	Marker name	Marker type	Alleles	Distance from PKD1 (cM)	Reference
D16S85	3'αHVR	VNTR	Many	5	17
D16S84	GGG1	RFLP	3	1	18
D16S145	pNL56S	RFLP	4	1	19
D16S283	SM7	$(CA)_n$	11	1	20
D16S291	16AC2.5	$(CA)_n$	10	1	21
—	SM6A	$(CA)_n$	6	1	*
D16S125	p26-6	RFLP	2	1	22
D16S94	VK5	RFLP	2	1	23
	VK5AC	$(CA)_n$	5	1	23
D16S80	p24-1	RFLP	3	5	24

Marker types: RFLP, restriction fragment length polymorphism; VNTR, variable number of tandem repeats; $(CA)_n$, microsatellite. Marker order: 16pter-D16S85-(D16S84,D16S145)-PKD1-(D16S283, D16S291, SM6A)-D16S125-D16S94-D16S80-16cen.
* P Harris, personal communication.

Table 3 Probability for each family that APKD is not linked to the PKD1 locus. Markers are listed in table 2. The final column combines the odds ratio with a prior probability of 0.14

Family	*Distal marker*	*Proximal marker*	*Odds linked:not linked*	*Probability non-linked*
100	S85	S125	10·18:1	0·0144
101	S85	S125	16·33:1	0·0091
102	S85	S283	34·43:1	0·0044
104	S85	S125	3·76:1	0·0405
106	S85	S80	1502·09:1	0·0001
108	S85	S125	1·04:1	0·1256
109	S85	S125	3·58:1	0·0528
117	S85	S80	1·80:1	0·0766
123	S85	S283	1:1·17	0·1488
125	S85	S283	1·83:1	0·0754
126	S85	S125	33·52:1	0·0045
138	S85	S125	1·69:1	0·0812
145	NI	NI	1:1	0·1300
148	S85	S80	21·72:1	0·0068
158	S85	S80	1·53:1	0·0890
159	S85	S125	6·91:1	0·0211
168	NI	NI	1:1	0·1300
169	S85	S125	1·59:1	0·0859
172	S85	S283	3·56:1	0·0403
177	S85	S283	3·38:1	0·0424
181	S85	S283	3·58:1	0·0731
184	S85	S125	1·97:1	0·0705
800	S85	S94	7·53:1	0·0194
802	S84	S94	11·71:1	0·0126
813	S84	S94	23·39:1	0·0063
814	S85	S80	12·28:1	0·0120
817	S84	S28	1·90:1	0·0751
818	S85	NI	1:1·46	0·1790
819	S85	S80	1·81:1	0·0763
822	S85	S125	1·83:1	0·0755
823	NI	NI	1:1	0·1300
824	S85	S283	1·83:1	0·0755
825	S85	SM6A	1:347	**0·9811**
829	S85	S125	1·83:1	0·0755
837	S85	S125	1·27:1	0·1053
838	NI	S291	1·68:1	0·0817
848	S84	S125	2·00:1	0·0686

NI = not informative.

Results

DNA MARKER STUDIES: LOCUS HETEROGENEITY

Of 37 families, 32 were informative for flanking markers, two families were informative for only a single marker, and three were completely uninformative. In total 179 subjects born at 50% risk of APKD were typed. Applying the test for locus heterogeneity (table 3), family 825 emerges as almost certainly unlinked and families 123 and 818 have odds of between 1·1 and 1·5 in favour of non-linkage to PKD1 (translating into posterior probabilities of 0·15 and 0·18 respectively). No other informative family has any significant probability of being unlinked. Thus 1 out of 34 of our families probably has non-PKD1 disease.

OBSERVED AND EXPECTED POSITIVE SCANS

Table 4 sets out the findings in each age group. Except in the 0–9 year olds and the small number scanned over the age of 50, the observed frequency of positive scans was at least as high as the expected proportion of gene carriers, calculated as explained above. Thus this global calculation gives no evidence of a significant number of false negative scans after the age of 10. Table 5 shows scan results from 39 subjects who had two or more USS separated by one year or more. Twenty-nine of the 39 subjects had negative first scans confirmed on repeat. Ten changed scan status: either the first scan was equivocal and the second positive, or the first scan was negative and the second positive or equivocal. The ages at first and second scans are shown. Two more people were excluded from this analysis because their two scans were probably not done on comparable instruments. These rates of change cannot be assumed to apply generally, because there may have been suspicions which indicated a repeat scan.

Table 4 The results of ultrasonographic screening. See Methods section for methods of calculation

Age class	*No*	*No affected*	*USS examination*				*USS +ve rate*	
			No	+ve	−ve	?	Exp	Obs ± 95%CI
0–9	149	3	17	4	10	3	0·490	0·235 ± 0·201
10–19	156	20	53	32	17	4	0·426	0·604 ± 0·132
20–29	198	39	96	44	50	2	0·377	0·458 ± 0·100
30–39	165	50	51	21	30	0	0·283	0·412 ± 0·135
40–49	126	54	15	3	12	0	0·125	0·200 ± 0·202
>50	348	75	10	3	7	0	0·363	0·300 ± 0·284
Total	1142	241	242	107	126	9		

Table 5 Results of sequential scanning. Numbers of people whose scan diagnosis changed (from negative to equivocal or positive, or from equivocal to positive) as a proportion of the total number of people who had sequential scans

	Age at subsequent scan			
Age at first scan	*0–9*	*10–19*	*20–29*	*30–39*
0–9	1/2	0/0	0/0	0/0
10–19		2/4	2/12	1/1
20–29			2/11	1/3
30–39				1/6

COMPARISON OF DNA AND ULTRASOUND RESULTS

Table 6 shows the findings in 78 subjects with informative DNA and ultrasound results. There were five evident discrepancies. Two of these were from family 825 which is probably segregating the unlinked disease (see above). Two, from two different families, inherited a high risk haplotype but were negative on scan (table 6). One further person (subject 33 in family 106) had a low risk haplotype and an equivocal scan.

Discussion

STRUCTURE OF THE FAMILY SET

Of 150 families studied, 114 had two or more affected cases. The remaining 36 families each contained only one affected person. These were excluded because of the risk that there was a new mutation to APKD, or a disease distinct from APKD. Most of these cases are probably the result of APKD but appear sporadic because of a mild phenotype and the

Table 6 Comparison of findings by scan and DNA markers. One person (subject 33 in family 106) with a low risk haplotype but an equivocal ultrasound finding has been classed as negative

Age group	*PKD1 haplotype*	*+ve on scan*	*−ve on scan*
<30 years	High risk	27	2*
	Low risk	1*	28
>30 years	High risk	1	1
	Low risk	0	20
Total	High risk	28	3
	Low risk	1	48

* These categories each include one subject from family 825 which is probably segregating PKD2.

failure of the gene to manifest as a diagnosed complaint.

PROPORTION OF FAMILIES NOT LINKED TO PKD1

One out of 34 informative families (table 3) probably has the unlinked disease, giving a rate of 0·029 (upper 95% confidence limit 0·086). This latter figure (0·086) has been used as the prior probability in subsequent individual risk calculations. Our figure agrees with estimates from North America (0·04)[12] and Scotland (0·03),[26] but is lower than the European estimate of 0·14.[14] Parfrey *et al*[13] suggested that the unlinked disease shows a milder course than PKD1. This would lead to an increased proportion of non-PKD1 disease among "sporadic" cases and kindreds with low numbers of clearly affected subjects. These families are less suitable for linkage analysis. Thus it is possible that there is a selective bias against the inclusion of non-PKD1 families in linkage based clinical studies.

FALSE NEGATIVE RATE OF ULTRASONOGRAPHY

Realistic genetic counselling of family members at risk of APKD requires knowledge of the risk that a gene carrier will give a negative ultrasonograph. This error rate comes partly from failure to see cysts which are there, and partly from late development of cysts. The rate of development might be different in PKD1 and PKD2. The most quoted error rates come from the work of Bear *et al*[6] on 17 kindreds in Newfoundland. In the second and third decades these rates were calculated as 25% and 12% respectively. Scanning technology has improved since that study. The more recent study of Bear *et al*[7] (based only on families with linkage results suggesting PKD1) revised the error rates to 8% in the second decade and approaching zero in the third decade and thereafter.

Our data broadly agree with these updated findings of Bear *et al*.[7] Statistically we did not see false negative scans after the age of 10, although anecdotally there were cases. We calculated 95% confidence intervals as explained above for the observed positive rate. Throughout the 10–39 age groups, the lower confidence limit of observed positives was equal to or greater than the expected frequency (table 4); thus this approach does not point to the presence of a significant false negative rate. These statistics are based on small numbers and on certain assumptions. We necessarily calculated the expected rate from the whole of the age group, including people not scanned. We assumed that the proportion of gene carriers in the subset examined by USS was the same as among the whole age group. This assumption might be wrong: some people may have presented for screening because they had noticed symptoms, or conversely people with minor symptoms might have declined screening to avoid confirming their fears. In the absence of data, it is impossible to say whether either of these biases occurred. Anecdotally we have detected false negative tests in certain subjects over 10 years old, from the data on repeat scans (table 5) and from the comparison of genetic marker data with ultrasonography (table 6). Table 5 shows 10 asymptomatic subjects whose scan status changed on repeat examination. Seven out of these 10 subjects developed imageable renal cysts or an abnormal cortex appearance (equivocal finding) in the second or third decades. We discourage screening in asymptomatic children, hence the small number scanned in the 0–9 age group, who otherwise would no doubt have produced many cases of changed scan reports. Clearly a negative scan before the age of 30 does not exclude risk of APKD.

CONCORDANCE BETWEEN GENETIC MARKER AND ULTRASONOGRAPHIC DATA

The concordance between genetic marker and USS data in our series is strong (table 6) although there were a number of conflicts. Two members of family 825 show non-concordance. One is clearly affected and one is unaffected. The disease in this family is probably not PKD1 (table 3). Three other cases of non-concordance have occurred. Subject 4 from family 138 is aged 26 and has inherited high risk close flanking markers despite having four negative USS between the ages of 18 and 24. Mlink[17] gives this subject a >98% risk of carrying the APKD gene despite the conflicting information. Non-penetrance is the likely explanation of this false negative result. In family 814, subject 8 has had two negative scans at the age of 52, yet she has the same high risk haplotype as her affected sib. The disease in this family is almost certainly PKD1 (table 3). However, their parents are dead, so an alternative to non-penetrance is that the affected parent was homozygous for these marker alleles. Person 33 from family 106 was originally diagnosed as affected but has the low risk haplotype. This large family, which has previously been described,[15] has unambiguous PKD1. Reassessment of the ultrasound data showed the cysts were observed in only one kidney (so this case did not meet the diagnostic criteria of Bear *et al*), and the subject has not reported any symptoms. The likely explanation is a false positive assignment of APKD. Reeders *et al*[27] have calculated that the false positive rate of ultrasonographic diagnosis may be as high as 2%.

Table 5 includes very few people aged over 30 who had a high risk haplotype that could be compared with USS. In almost all of these small families, two affected people are "used up" to establish the linkage phase of the markers; therefore there are often no other affected people who can be scored independently.

In summary, among the USS negative group there are 3/51 cases with a high risk of APKD from DNA studies. One case can be explained by genetic heterogeneity, leaving one or possibly two cases apparently the result of failure of gene carriers to manifest renal cysts. The rate of false negative scans was 1/29 or 0·034 (upper confidence limit 0·10) in the

Table 7 The final risks for subjects at 50% prior risk of APKD based on scan findings and DNA marker analysis

Family	*Person*	*Markers used*	*Age at scan*	*Scan result*	*Risk by Mlink*	*Prob PKD2*	*Overall risk*
100	04	S85/S125	50	−ve	0·00466	0·0144	0·01186
	06	S85/S125	48	−ve	0·00466		0·01186
	18	S85/S125	—	ND	0·99906		0·99186
	20	S85/S125	22	−ve	0·00008		0·00728
101	13	S85/S125	19	−ve	0·00061	0·0091	0·00516
	14	S85/S125	—	ND	0·95262		0·94807
	15	S85/S125	5	−ve	0·00061		0·00516
	16	S85	20	−ve	0·00753		0·01208
	17	S85	19	−ve	0·05433		0·05888
104	05	S85/S125	50	−ve	0·01016	0·0405	0·03041
106	16	S84	27	−ve	0·00087	0·0001	0·00097
	17	S85/S80	—	ND	0·00276		0·00281
	19	S85/S80	—	ND	0·00276		0·00281
	21	S85/S80	35	−ve	0·00031		0·00036
	22	S85/S80	25	−ve	0·00104		0·00109
	23	S85/S80	30	−ve	0·00031		0·00036
	25	S85/S125	—	ND	0·00236		0·00251
	26	S85/S125	—	ND	0·99716		0·99711
	27	S85/S125	22	−ve	0·00005		0·00010
	30	S85/S80	23	−ve	0·01169		0·01174
	33	S85/S125	21	?	0·00055		0·00060
109	04	S85/S125	27	−ve	0·00115	0·0528	0·02755
117	03	S85/S125	22	−ve	0·01135	0·0766	0·04965
123	05	S85/S283	24	−ve	0·00456	0·1488	0·07896
125	03	S85	23	−ve	0·00018	0·0754	0·03788
126	05	S85/S125	36	−ve	0·00008	0·0045	0·00233
	18	S85/S125	22	−ve	0·01496		0·01721
138	04	S85/S125	26	−ve	0·99392	0·0812	0·95332
	05	S85/S125	21	−ve	0·00005		0·04065
	07	S85/S125	19	−ve	0·00382		0·04442
145	05	S85/S125	32	−ve	0·08000	0·0862	0·12310
148	08	S85	18	?	0·00513	0·0068	0·00853
	13	S85	23	−ve	0·00026		0·00366
158	04	S85/S80	38	−ve	0·00721	0·0890	0·05171
	05	S85/S80	32	−ve	0·15279		0·19729
159	03	S84/S125	29	−ve	0·00004	0·0211	0·01059
	04	S84/S125	31	−ve	0·00004		0·01059
	06	S84/S125	25	−ve	0·00001		0·01056
	07	S84/S125	22	−ve	0·00001		0·01056
168	03	S85/S125	18	−ve	0·00212	0·0862	0·04522
172	03	S85/S283	42	−ve	0·00138	0·0403	0·02153
177	03	S85/S283	33	−ve	0·00005	0·0424	0·02125
	04	S85/S283	33	−ve	0·00005		0·02125
181	05	S85/S283	42	−ve	0·00100	0·0731	0·03755
	08	S85/S283	17	−ve	0·02500		0·06155
800	05	S85/S283	36	−ve	0·00038	0·0194	0·01008
	10	S85/S283	—	ND	0·50478		0·51448
802	06	S85/S125	35	−ve	0·50070	0·0126	0·50700
	08	S85/S125	30	−ve	0·04475		0·05105
813	05	S84/S94	47	−ve	0·00097	0·0063	0·00254
	08	S84/S94	28	−ve	0·00001		0·00316
	09	S84/S94	23	−ve	0·00001		0·00316
814	03	S85/S80	33	−ve	0·00025	0·0120	0·00625
	04	S85/S80	30	−ve	0·00025		0·00625
	05	S85/S80	30	−ve	0·00025		0·00625
	08	S85/S80	52	−ve	0·77191		0·77791
817	03	S84/S283	20	−ve	0·00004	0·0751	0·03759
819	04	S85/S80	28	−ve	0·00137	0·0763	0·03952
822	05	S85/S125	40	−ve	0·00030	0·0755	0·03805
823	04	S85	19	−ve	0·15758	0·0862	0·20068
824	03	S84/S283	33	−ve	0·00004	0·0755	0·03779
829	04	S85/S125	36	−ve	0·00018	0·1235	0·06193
838	04	S85/S145	—	ND	0·00059	0·0817	0·04144
848	04	S84/S125	—	ND	0·00020	0·0686	0·03450
	06	S84/S125	—	ND	0·50000		0·50000

third decade and 1/20 or 0·05 (upper confidence limit 0·14) in the fourth decades and above. There was one reported false positive scan, but this did not strictly meet the criteria for a positive diagnosis.

CALCULATION OF INDIVIDUAL RISKS

Table 7 shows that the methods described here can effectively shift the carrier risk for persons at 50% prior risk of APKD. In this sample of register families, 80% of subjects could be placed in a low (<5%) or high (>95%) risk category. For smaller families where linked markers cannot be used, ultrasound scanning is still highly reliable for people over 30 years old. Genetic heterogeneity is not a serious problem in most families. Risks calculated by Mlink are altered by no more than 4·5% (half the upper confidence limit of the proportion of unlinked disease) in families not informative for flanking markers. Of the three families showing a raised probability of PKD2, only one showed a high likelihood. In the other two families, risks to subjects who had inherited a low risk PKD1 haplotype were raised by approximately 9% and 7·5% respectively.

Hopefully the PKD1 gene will be cloned in the near future and mutations characterised. This may still not remove the need for ultrasound and DNA marker studies, if it turns out, as with so many other disease genes, that a wide variety of different mutations occur in the population. Furthermore, differentiating the two or more loci for APKD may still be problematical. In this situation linkage analysis with close markers will continue to be a useful test. In addition ultrasonography will remain a cheap, relatively accurate, and widely available screening tool.

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