P- ISSN 1991-8941 E-ISSN 2706-6703 *Journal of University of Anbar for Pure Science (JUAPS)* Open Access
2011,(5), (2) :11-19

Genetic pattern and penetrance of polycystic kidney disease in the Western region of Iraq

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ARTICLE INFO

Received: 2 / 6 /2010
Accepted: 14 / 3 /2011
Available online: 14/6/2012
DOI: 10.37652/juaps.2011.44107

Keywords:
Genetic pattern ,
penetrance ,
polycystic kidney disease ,
Western region of Iraq.

ABSTRACT

The aims of this study are to identify the genetic pattern, estimation of gene frequency, penterance, prevalence of PKD, and to furnish an appropriate plan for genetic counselling specific for these families under investigation. A total of 41 families reside in the western region of Iraq were included in this study. This study showed that PKD is inherited as an autosomal dominant disease due to the defects in PKD1 gene. Gene frequency was 0.003 and 0.997 for p and q respectively. Genotype frequency was 0.000009, 0.005982 and 0.994009 for p2, 2pq and p2, respectively. The prevalence of the disease is 3.7/1000. The mutation was originated outside this family. The individual numberthree from parent generation (Generation- I-3) who is the patient which brought this defected gene to all of her descendants. Gene flow of the defected gene into these families increased the frequency of p gradually.

Introduction

Polycystic kidney disease (PKD) is a common multisystemic disease (1). It is characterized by the progressive development and enlargement of multiple fluid-filled cysts in the kidney, liver and pancreas that may ultimately lead to end-stage renal disease (ESRD) (2&3). It is believed that the crowding cysts in the kidney lead to the ESRD, but the kidney damage seen in PKD is actually from the attempts of immune system to rid the kidney of cysts, instead progressively destroys the formerly healthy kidney tissue (4).

Autosomal dominant PKD (ADPKD) is the most common monogenic genetic disease in humans, with a frequency ranging from

1:400 to 1:1000, in which most of the patients suffer from ESRD after the fourth decade of life (5-11), whereas another form of the disease is the autosomal recessive (ARPKD) in which the patients suffer from renal failure and liver fibrosis in early childhood between ages 1 and 20 years. The estimated prevalence is only 1/10000 – 1/ 40000 (5, 6, 8, 11- 13). Apart from these diseases in which cystic kidneys associated with renal failure are the predominant clinical manifestation, renal cystic disease can also be found in pleiotropic diseases such as the Bardet–Biedl syndrome (BBS), Von Hippel–Lindau disease or the Meckel–Gruber Syndrome (14).

The results of a pilot project (15) which was designed to study some of genetic disease and birth defects in the western region of Anbar province, have been showed a high incidence and variable expressivity with variable age of onset and ESRD in a group of consanguineous families (15). Therefore, PKD was chosen for further investigation and to improve our understanding of renal cystic disease, throughout the investigation of genetic pattern, estimation of gene frequency, penterance and prevalence of PKD. The obtained information

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will be used to furnish an appropriate plan for genetic counselling for those people in need.

Material and methods

The city of Anah has a population of around 21179 (16), it is one of the cities of Alanbar province, located 350 kilometres west of Baghdad. Data for patients and their relatives of families of PKD propositi were collected by questionnaires which Bennent has given in detail (14), and include the 41 families in the study. They are residing in the above city. The PKD patients in this case are defined as one who has been diagnosed as such. The PKD data were complete up to June 2010, the time at which collection of the family data was stopped, a medical-family history questionnaire for renal disorders and medical reports for patients were obtained Table.1 in the Appendix, medical reports issued by professional medical staff, and the population data were taken from the 2010 Vital Statistics of the province-the most recently available statistics (16). Pedigree tree (Figure 1) was constructed according to the rule of construction of human pedigree, and the raw data are summarized in Tables (2) in the Appendix. Estimation of gene frequency, penetrance and prevalence of the incidence of disease has been calculated by the methods which have given in detail (17 -18).

Results and Discussion

ADPKD is not just a kidney disorders, other organs can also be affected. Patients' medical history and reports have not been shown any other problems or disorders which were indicated in Table (1) in Appendix, other than kidney problems and blood hypertension.

On the surface there seems to be a lot of ESRD in this large family which may represent a familial renal genetic disease (Figure 1). To be absolutely certain, it is essential to obtain medical records and death certificates on the family members with disease. Pathology reports and death certificates have been showed that family members who suffer from ESRD was due to the Consequence of polycystic kidney disease (14). The family history is compatible with autosomal dominant (AD) inheritance since the health problems that related to this disease appear in more than one generation, and transmitted from male-to-male. Furthermore, the affected individuals have showed variability in severity of the clinical disease expression, and they have late age of clinical onset (19). The recognition of an AD pattern can be complicated by the variable expressivity and penetrance of the trait. Penetrance refers to the percentage likelihood of the expression of phenotypic effects of the mutant gene that an individual who has inherited it will actually show the disease manifestations in his or her lifetime, whereas, expressivity is the clinical manifestation of the underlying genetic abnormality (14 & 17). Gene penetrance was 100% in second and third generations. Whereas, decreased to be 22.22% in fourth generation. This may be due to the fact that the disease manifestation develops with no noticeable sign in children. Most of the fourth generation peoples are young and less than 20 years of age. These results are in agreement with those of (10-12) who showed that ADPK is genetically heterogeneous and exhibits considerable phenotypic variability.

Genetic background, physical and chemical agents have been shown to modify the phenotypic expression of the gene by affecting on the gene expressivity and penetrance. A treatment of mice carrying tail zigzag mutation with Mitomycin-C decreased the penetrance and expressivity of TZ gene significantly (17).

Peoples who carry the p gene may, or may not, show the phenotypic characters of the disease. This may be due to the physiological development threshold which is needed to determine the gene penetrance for any trait. (20 & 21) suggested that individual does accumulate a sufficient amount of morphogenetic substance will show the character otherwise the individual will not be able to show the character.

Analysis of ADPKD has revealed that this disease is genetically heterogeneous and shows considerable variable expressivity, with at least three different loci are now known to cause ADPKD. PKD1 is the most common, accounting for 85–95% of all ADPKD, PKD2 is responsible for 5–15% of all ADPKD (3, 22 &23), a third gene, PKD3, involved in the causation of ADPKD disease in French-Canadian and Portuguese families (24-26).

A consistent difference in disease severity has been noted between PKD1 and PKD2; PKD1 patients live shorter than PKD2 patients due to an earlier onset of disease and ESRD (median survival 56 vs 71.5 years) (22), have a higher risk of progressing to renal failure, are more likely to have hypertension, tend to be diagnosed at an earlier age (median 44.8 vs 69.1 years), and have more renal cysts at the time of diagnosis (2). Hypertension occurs in 50-75% of patients with PKD prior to renal insufficiency and it is thought to accelerate the decline in renal function (27).

In this setting, the presence of a positive family history of an early ESRD at age forty - fifty years, high progression of renal failure and early diagnosis of hypertension are an essential tool to be certain that the disease in these individuals is due to the defects in PKD1 gene.
Gene frequency was 0.003 and 0.997 for p and q respectively. Genotype frequency was 0.000009, 0.005982 and 0.994009 for p2, 2pq and q2, respectively.

The prevalence of the disease is 3.7/1000; it is higher than estimated incidence of 1/ 500 to 1 /1000 in all ethnic groups worldwide (5-11). The high incidence rate may be due to the system of mating which has been used among these families, and due to the fact that these families come from a small population size at the time were these families founded (28).

The mutation was originated outside this family and outside the country. The proband (Generation- I-3) who brought this defected gene was spread it within her descendants and with offspring of any individual married with that family. She is Syrian origin and does not have any blood relationship with her husband at all.

In addition to that the other reason that jack up the frequency of the incidence of the disease is the marriages among ladies from (G- I-3) relative and with guys from other side. Also, the consanguineous marriages are very common among individual of these families.

Conditions inherited in an autosomal dominant (AD) pattern like ADPKD only one copy of the mutated gene is needed for the expression of the clinical features. Affected individual has a 50:50 chance to pass the gene mutation to each son or daughter.

Because late age of onset of the disease and high frequency of consanguinity marriages, it should be very careful when provide them with any counseling. Since, there is a high chance of heterozygote marriages due to the consanguinity marriages. The chances to pass the mutated gene to each son and daughter are very high and will be in the ratio of 75:25.

Providing genetic counseling and risk assessment for families with PKD and living in our society is complicated, and requires a careful family history and sophisticated genetic testing which is not available in Iraq.

Even though, it can be given some advices that help to distance the complication time.

First of all and the most important one are to overcome the fear of social and economical impact and attend counseling session. Since this disease inherited as an autosomal dominant, therefore the recurrence risks will be as follow: If either parent carries genetic mutation there is 50% probability that their children will inherit this disease. In case of two affected parents, there is 75% chance that their children will be affected with PKD (4). Therefore, they should be aware of this, and family members who at risks should undergo ultrasound and radiography tests to avoid the complication as much as possible by following the physician advices (13). Because there is no test available for the heterozygous, therefore it is preferable to adopt children instead of having offspring with high risk of disease.

The treatment recommendations are by careful control of blood pressure since high blood pressure is very common in patients with PKD (27), the American PKD Foundation indicates that untreated high blood pressure can lead to kidney failure more quickly than if the blood pressure is kept within the normal range (29), prompt treatment of any bladder or kidney infections, lots of fluid and bed rest when blood in the urine is first noted a healthy lifestyle with regard to smoking, exercise, weight control and salt intake.

Finally, the global emergence of genetic diseases is one of the greatest challenges in public health research today. While exciting advancements in molecular technology are rapidly expanding the field of genetic and the capabilities of the genetist elsewhere, it should be noted that limitations of genetic studies of genetic diseases in Iraq still exist. However, with careful planning and attention to study design, methods, conduct, and analytical issues, genetic studies of genetic diseases can yield important and valid results.

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Appendix

Table 1. Medical history questionnaires.

Medical-Family History Questions (14)

Individual's Medical History
What was the age at onset of the renal disorder?
What studies have been done? (obtain documentation of renal function studies, abdominal imaging studies, biopsies)
What is this person's occupation? (could this be a toxic exposure, such as lead poisioning
leading to renal tubular acidosis?)
Individual and Family History Questions
What is the individual's height? What are the heights of the parents and siblings?
Do any of the family members have high blood pressure?
Have any other family members had testing (such as renal studies on the parents)?
Does this individual, or any family members, have other medical conditions such as:
_ Learning disabilities or mental retardation?
_ Any unusual birth marks? (tuberous sclerosis, Fabry disease)
_ Anything unusual about the shape of the hands or feet, or the nails? (periungual fibromas in tuberous sclerosis, nail hypoplasia in nail-patella syndrome)
_ Hearing loss? Commonly seen in many of the inherited renal syndromes. Two of the more common syndromes with hearing loss and renal anomalies are branchio-oto-renal syndrome and Alport syndrome
_ Unusually shaped ears?
_ Preauricular pits? (e.g., branchio-oto-renal syndrome)
_ Ear tags?
_ Visual disorders?
Skeletal anomalies? (several skeletal dysplasias are associated with renal disorders)
Are the parents related as first cousins or closer?

Table 2 **S**ummary of the raw data of the number of PKD and non-PKD individuals by their generation which summarized from pedigree trees.

Generation	Females	Males	Females	Males	Total Affected	Other affected	Dead	Females Married to males	Males married to females
I	2*	1^{a}	1^{*a}	1^{r}	$0^{'}$	1^{1}	1		
II	6**	8^{aa}	4^{*aa}	2^{rr}	$3^{''}$	5^{11}	7	2	9
III	22***	25^{aaa}	22^{*aaa}	0	$25^{'''}$	0	47		
IV	38^{****}	44^{aaaa}	9^{*aaaa}	$29^{''''}$	$9^{'''''}$	35^{1111}	18	2	6
							6		

Unknown sex	Children Less than 5 years of age	Affected	Unaffected	Affected	Unaffected
2	9	1	2	1	3
			10	4	10
			2	0	

Total population= 21179
Total affected individuals = (1+7+47+18+1+1+4)=79

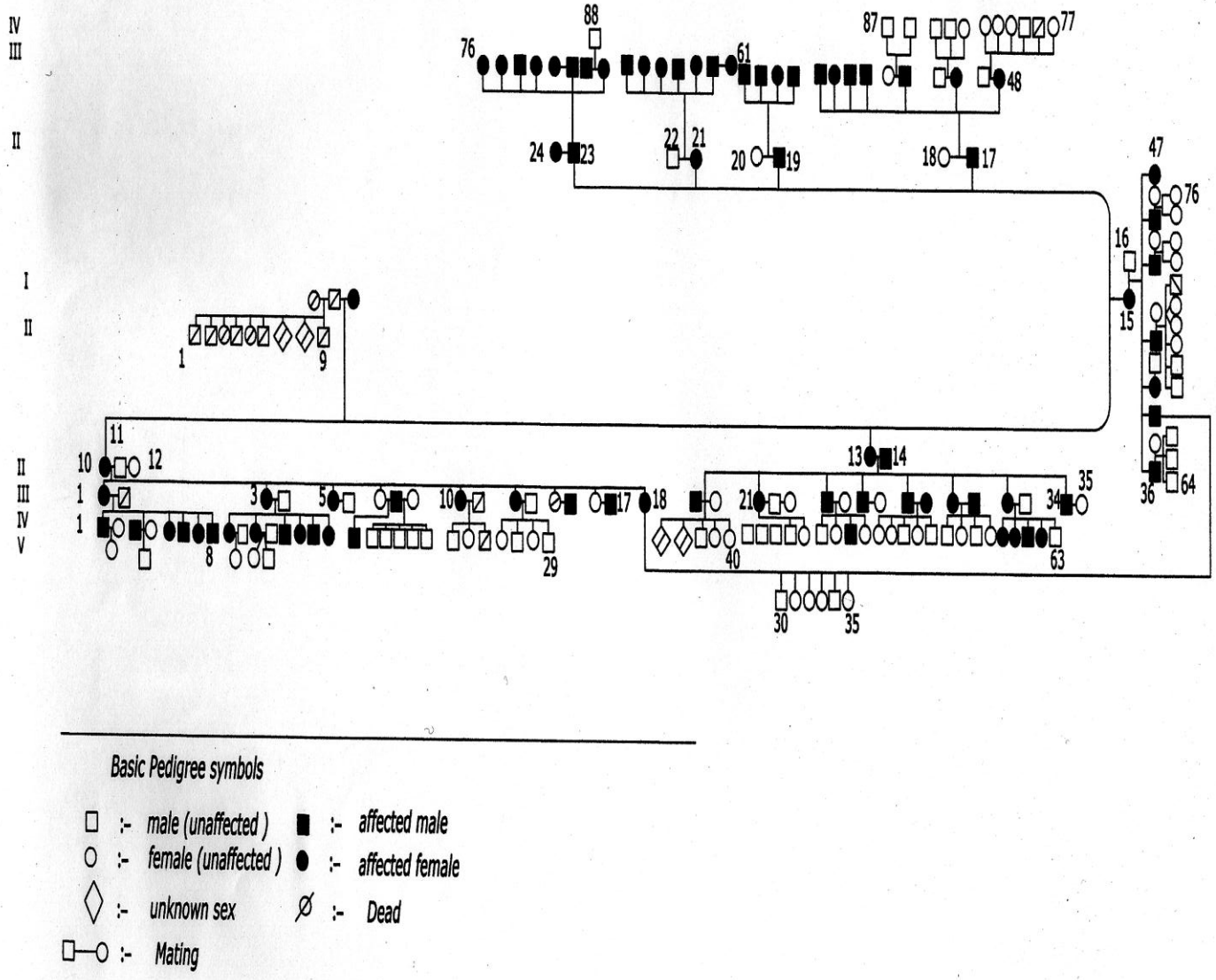
* (1 &3)
** (3,5,10,13 ,15,21)
***(1,3,5,7,10,12,18,21,30,32,39,47,48,50,56,59,64,66,67,69,75,76)
****(5,7,9,11,14,16,24,26,28,31,32,33,35,39,40,45,47,49,50,51,53,56,58,59,60,62,69,70,71,73,74,75,76,77,80,81,82,83)
[a] (2)
[aa](1,2,4,6,9,17,19,23)
[aaa](8,15,17,19,24,26,28,34,36,38,41,43,45,52,54,55,57,58,60,61,63,65,68,71,74)
[aaaa](1,3,6,8,13,15,17,18,19,20,21,22,23,25,27,29,30,34,38,41,42,43,44,46,48,52,54,55,57,61,63,64,65,66,67,68,72,78,79,84,85.86,87,88)
*[a](3)
*[aa](10,13,15,21)

*aaa(
1,3,5,10,12,18,21,30,32,39,47,48,50,56,59,64,66,67
,72,73,75,76)
*aaaa (5,7,9,11,14,16,59,60,62)
(1)
(3,5)
(
24,26,28,31,32,33,35,39,40,45,47,49,50,51,53,56,5
8,69,70,71,73,74,75,76,77,80,81,82,83)
(17,19,23)
(
8,15,17,19,24,26,28,34,36,38,41,43,45,52,54,55,57,
58,60,61,63,65,68,71,74)
(1,3,6,8,13,15,17,48,61)

1(2)
11(1,2,4,6,9)
1111
(18,19,20,21,22,23,25,27,29,30,34,38,41,42,43,44,4
6,52,54,55,57,63,64,65,66,67,68,72,78,79,84,85,86,
87,88)
The consanguineous marriages
II 18x17= ♀ daughter of I-3 sister
II 20x19= ♀ daughter of I-3 sister
II 23x24= ♀ daughter of I-3 sister
II 13x14 = ♂ son of I-3 brother
III 28x29= as shown in the pedigree
III 30x31= ♂ son of II 17x18
III 18x38= ♀ daughter of II 17x18

P- ISSN 1991-8941 E-ISSN 2706-6703 *Journal of University of Anbar for Pure Science (JUAPS)* Open Access
2011,(5), (2) :11-19

Figure 1 . The pedigree of (ADPKD) for the families under investigation



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P- ISSN 1991-8941 E-ISSN 2706-6703 *Journal of University of Anbar for Pure Science (JUAPS)* Open Access
2011,(5), (2) :11-19

النمط الوراثي ونفاذية جين مرض تكيس الكلى المتعدد في المنطقة الغربية من العراق.

لؤي محمد العاني

الخلاصة:

الهدف من هذه الدراسة هو معرفة الجين المسبب لمرض التكيس المتعدد للكلى وتقدير تكرار ونفاذية الجين. كذلك دراسة انتشار المرض في منطقة الدراسة وتهيئة خطة للاستشارة الوراثية لفائدة الافراد الذين هم بحاجة لمثل هذة المعلومات. تمت الدراسة على مجموعة مكونة من ٤1 عائلة يقطنون المنطقة الغربية من العراق وتمتاز هذه العوائل بتكرار حالات الفشل الكلوي وبشكل استثنائي. وقد تم التعرف على سلوكية الجين المسؤلة عن هذا المرض لهذه المجموعة من العوائل والذي كان بسلوكية سائدة ويقععلى كروموسوم جسمي تحت سيطرة الجين PKD1 وبتكرار ٠.٠٠٣ للاليل p و ٠.٩٩٧ للاليل q. اما تكرار الطرز الوراثية فكانت ٠.٠٠٠٠٠٠٩، ٠.٠٠٥٩٨٢، 0.994009 للطرز الوراثية p2 , 2pq, p2 على التوالي.كانت نسبة الاصابة عالية حيث بلغت ٣.٧ / ١٠٠٠مقارنة بنسبة الاصابة لهذا المرض والمسجلة عالميا. الجين الطافر كان في الفرد الثالث من الجيل الاول وكان من خارج العائلة. تكرار الجين الطافر ازداد تدريجيا في هذه العوائل.