Founding mutations explains hot spots of polycystic kidney disease in southern Spain

Carmen García Rabaneda1,5, Francisco Perea2, María Luz Bellido Díaz2,5, Ana I. Morales García4,5,7, Margarita Morales Atienza2,5, Rafael J. Esteban de la Rosa3,5-7

1 Servicio de Análisis Clínicos, Hospital Universitario San Cecilio, Granada, Spain
2 Servicio de Análisis Clínicos e Inmunología, UGC Laboratorio Clínico; Hospital Universitario Virgen de las Nieves, Granada, Spain
3 Servicio de Nefrología, Hospital Universitario Virgen de las Nieves, Granada, Spain
4 Servicio de Nefrología, Hospital Universitario San Cecilio, Granada, Spain
5 Grupo de Estudio de la Enfermedad Poliquística Autosómica Dominante (GEEPAD).
6 Asociación Amigos del Riñón
7 Instituto de Investigación Biosanitario de Granada (IBS.GRANADA)

Correspondence to:
Carmen García Rabaneda
Email: carmen.garcia.rabaneda.sspa@juntadeandalucia.es

© The Author(s) 2020. Published by Oxford University Press on behalf of ERA-EDTA.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
ABSTRACT

Our group identified two pathogenic variants on the PKD1 gene, c.10527_10528delGA and c.7292T>A from unrelated families. They came from two small counties in Granada, with 61 and 26 ADPKD individuals affected.

To determine a common ancestor, healthy and ADPKD individuals from these families were genotyped by analyzing four microsatellites located on chromosome 16. Our study identified a common haplotype in all ADPKD individuals.

These findings underpin our hypothesis of the founder effect and explains why there is a high frequency of ADPKD in small regions. Determining hot spots of ADPKD will help to better plan health care in the future.

Keywords: ADPKD, common ancestor, disease-associated haplotype, founding mutation, hot-spots, southern Spain
BACKGROUND

We point out two pathogenic variants on PKD1 gene, causing ADPKD, with a geographic location in two small counties in Southern Spain, Loja and La Alpujarra in Granada. We could not find a link among genograms of any of these families.

There is evidence of historical isolation for the population studied, which could have favored a considerable genetic drift. The presence of the same mutation and the disease associated-haplotype conservation in families not directly related is probably the consequence of a bottleneck in the founding of this population. A high frequency of ADPKD in these counties by these two PKD1 variants could be explained by a founding effect. To prove our hypothesis, we performed a molecular study of ancestrality to determine whether the families shared disease-associated haplotype.

CASE REPORT

We analyzed samples from 21 ADPKD patients who have been genetically identified as c.10527_10528delGA mutation carriers and 4 healthy individuals from 10 families from the Loja area. Samples from 4 ADPKD patients are a carrier of the pathogenic variant c.7292T>A. 2 families from Alpujarra county were analyzed. We also performed the haplotype analysis of 18 healthy random individuals used as control. In the Loja area, a pathogenic variant in exon 35 of the PKD1 gene (c.10527_10528 delGA p.) is described. This variant affects 61 ADPKD individuals belonging to 10 unrelated families. In the Alpujarra area, a variant in exon 18 of the PKD1 gene (c.7292T>A) is described as pathogenic (1). This variant was identified in 26 individuals from 4 unrelated families.

The haplotype shared in all affected members in the Loja area was: D16S663 156, D16S291 242, D16S3252 187, and D16S251 154. The haplotype was shared by different families between affected members unrelated. In the Alpujarra area, we found a different haplotype shared by all ADPKD unrelated patients and was as follows: D16S663 156, D16S291 240, D16S3252 193, and D16S251 154. The family segregation of the haplotype is coincident with the disease as shown on the family tree in figure 1. Linkage analysis is showed in additional material table 2.

DISCUSSION

From 2010 to 2019, 23±5 (16-29 range) new cases/year have been diagnosed of ADPKD in our Health Area; an incidence of 2.35 cases / 10^5 inhabitants-year (interval of 1.73 - 3.05 cases / 10^5 inhabitants-year) is estimated (2). We identified 1184 patients, many of them have been genetically tested, especially in recent years due to the development of new analytical strategies(9). Most variants in the PKD1 gene are family-specific; some of them recur in unrelated families because of sequence
characteristics that make DNA prone to mutation. But some of these familiar pathogenic variants are so-called founder mutations. Founder mutations are common in Mendelian disorders and have been described in genetically isolated populations as well as in populations with a migratory history (3). These mutations arose in single individuals and fanned out by succeeding generations and therefore show a high frequency in specific ethnic groups.

Although there is no world map on the distribution of ADPKD variants, we observed in Granada hot spots with a high frequency of disease, where health intervention can be decisive (4). Due to the high prevalence of these mutations, made us suspect a possible ancestor with a founding effect.

For ancestral allele identification for a variant in a population with N individuals, two types of haplotypes exist: haplotype harboring a newly emerged allele and a haplotype harboring an ancestral allele. After an allele has emerged and survived, the frequency of the haplotype harboring the newly emerged allele may increase in the population over time. Originally, the haplotype containing the newly emerged allele is monomorphic; over time, the haplotype diversity increases due to mutation and recombination. If the variant survives for a sufficiently long time, both haplotypes become indistinguishable in terms of their diversities. Until then, the haplotype harboring the newly emerged allele shows less diversity leading to a smaller population mutation parameter, than the original haplotype. Ancestral alleles can be identified by measuring the diversity of each haplotype and comparing the results(3).

The most suitable, easy, and rapid to perform is the linkage study using microsatellite markers flanking gene, in our case *PKD1* gene. Marker informativeness is population dependent and the appropriateness of markers should be assessed in local populations(5). More information is showed in table 1,3 and figure 2 in additional material.

The presence of a common haplotype in ADPKD families who come from small counties underpin our founding mutation hypothesis and explains why there is a high frequency of ADPKD. For this reason, determining hot spots of ADPKD in worldwide may allow the development of better and targeted health intervention strategies in the future.

**PATIENT CONSENT**
Ethics Statement Individuals were recruited at Virgen de las Nieves Hospital during 2010-2019 and enrolled in the clinical and genetic study.
ACKNOWLEDGEMENTS

We thanks the invaluable collaboration from the doctors Lisbeth Sousa Silva and Miguel Ángel García González because of performing genotyping of some samples in their NefroCHUS laboratory. The doctor Antonio Rodriguez-Nicolás by calculating mean heterozygosity and PIC, also the doctor Francisco Ruiz Cabello for his contribution to performing the linkage analysis. And to the doctors Juan Antonio Bravo Soto y María García Valverde for the clinical data collected from the year 2010 until now and belong to the GEEPAD register.

FIGURE 1: Analyzed markers on chromosome 16p in families from Loja A, and Alpujarra B. The disease-associated haplotype is marked with a black line. An individual with a black dot indicates this is a verified pathogenic variant carrier, while a non filled dot indicates a verified non-mutation carrier.

REFERENCES

1. García-Rabaneda C, et al. Nueva mutación asociada a poliquistosis renal autosómica dominante con efecto fundador localizada en la Alpujarra de Granada. Nefrologia. 2020. https://doi.org/10.1016/j.nefro.2020.03.003
2. Informe anual 2020 del registro del Grupo de Estudio de la Enfermedad Poliquística Autosómica Dominante (GEEPAD) https://www.renalamigos.com/wp-content/uploads/2020/05/20-INFORME-ANUAL-REGISTRO-GEEPAD-v.3.pdf
3. Park L. Ancestral alleles in the human genome based on population sequencing data. PLoS One. 2015;10(5):e0128186. Published 2015 May 28. doi:10.1371/journal.pone.0128186
4. Morales García AI, Martínez Atienza M, García Valverde M, Jimenez JF, Martínez Morcillo A, Esteban de la Rosa MA, et al. Overview of autosomal dominant polycystic kidney disease in the south of Spain. Nefrologia. 2018;8(2):190–196. doi:10.1016/j.nefro.2017.07.002

5. Fatehi R, Khosravi S, Abedi M, Salehi R, Gheisari Y. Heterozygosity analysis of polycystic kidney disease 1 gene microsatellite markers for linkage analysis of autosomal dominant polycystic kidney disease type 1 in the Iranian population. J Res Med Sci. 2017;22:102. Published 2017 Sep 26. doi:10.4103/jrms.JRMS_136_17