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Exceptional Case

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Founding mutations explains hotspots of polycystic kidney disease in Southern Spain

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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 autosomal dominant polycystic kidney disease (ADPKD) individuals affected. To determine a common ancestor, healthy and ADPKD individuals from these families were genotyped by analysing 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 explain why there is a high frequency of ADPKD in small regions. Determining hotspots of ADPKD will help to better plan healthcare in the future.

Keywords: ADPKD, common ancestor, disease-associated haplotype, founding mutation, hotspots, Southern Spain

BACKGROUND

We point out two pathogenic variants on *PKD1* gene, causing autosomal dominant polycystic kidney disease (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

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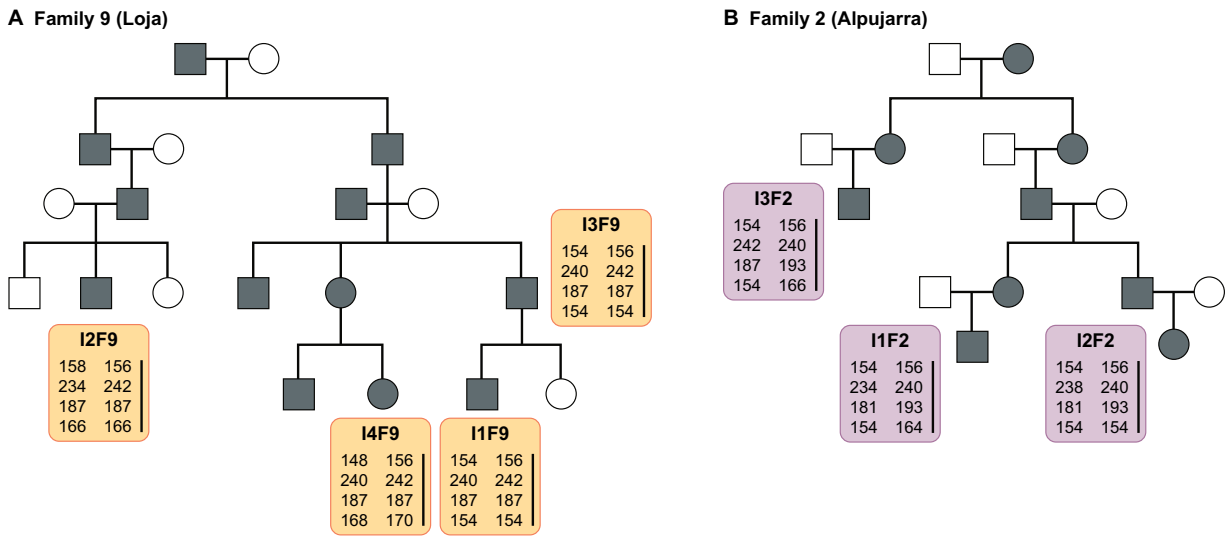

FIGURE 1: Analysed markers on chromosome 16p in families from Loja (A) and Alpujarra (B). The disease-associated haplotype is marked with a black line. An individual with a black dot indicates this is a verified pathogenic variant carrier, while a non-filled dot indicates a verified non-mutation carrier.

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 analysed 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 four ADPKD patients are a carrier of the pathogenic variant c.7292T>A. Two 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 four 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 (Supplementary data, Table S2).

DISCUSSION

From 2010 to 2019, 23 ± 5 (16–29 range) new cases/year have been diagnosed with 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 whom have been genetically tested, especially in recent years due to the development of new analytical strategies. 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. However, 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 hotspots with a high frequency of disease, where health intervention can be decisive [4]. The high prevalence of these mutations, led us to 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: a haplotype harbouring a newly emerged allele and a haplotype harbouring 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 harbouring 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 the *PKD1* gene. Marker informativeness is population dependent and the appropriateness of markers should be assessed in local populations [5]. More information is showed in Supplementary data, Tables S1 and S3, and Figure S2.

The presence of a common haplotype in ADPKD families who come from small counties underpins our founding mutation hypothesis and explains why there is a high frequency of ADPKD. For this reason, determining hotspots of ADPKD

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 2010–19 and enrolled in the clinical and genetic study.

FUNDING

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

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SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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