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Case Report

Bilineal inheritance of type 1 autosomal dominant polycystic kidney disease (ADPKD) and recurrent fetal loss

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Abstract

We report for the first time a family with type 1 ADPKD in which the marriage between affected non-consanguinous individuals resulted in two live-born heterozygous offspring and two fetuses lost in mid-pregnancy. Given a 25% chance for mutant compound heterozygosity in the offspring of this family, our findings suggest that compound heterozygosity of PKD1 mutations in humans may be embryonically lethal.

Keywords: autosomal dominant polycystic kidney disease (ADPKD); bilineal disease; compound heterozygous; PKD1

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenetic disorder, affecting 1 in 500–1000 persons and accounting for 8–10% of all cases of end-stage renal failure in Western Europe [1–3]. Linkage studies have shown that PKD1 on chromosome 16p13.3 is responsible for ADPKD type 1 (85%) and PKD2 on chromosome 4q21–23 for ADPKD type 2 (15%). Despite the relatively high frequency of PKD1 mutant alleles, no individual with homozygous ($PKD1^{-/-}$) or compound heterozygous ($PKD1^{+/-}:PKD1bis^{+/-}$) mutations of PKD1 has been described.

Material and methods

In the course of ascertaining >400 ADPKD families for genetic studies, we identified a white family in which non-consanguinous marriage between affected individuals was documented (Figure 1). We ascertained the complete pedigree structure of the family over three generations and clinically assessed and genotyped all available members with

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polymorphic markers at PKD1 loci. KG8 and CW2 microsatellite markers were used. All available members of the family were screened at least once by abdominal ultrasonography and the diagnosis of ADPKD was confirmed according to recognized criteria. A detailed obstetrical history of the proband was obtained by an interview with her. Informed consent was obtained from individuals participating in the study.

Results

The pedigree of the family is plotted in Figure 1. Two of the affected members of this family (II3 and II5) developed end-stage renal disease at 40 and 48 years of age, respectively. They were successfully transplanted with a kidney donated from a cadaver donor at the age of 42 and 49 years, respectively. The proband (II6) was diagnosed with PKD when she was 31 years old. In contrast, at a similar age she had severe polycystic kidney and liver disease with creatinine clearance of 81 ml/min. Individuals III6 and III8 were diagnosed with ADPKD at ages 7 years and 3 years, respectively. Disease severity in these individuals was typical of type 1 ADPKD [1,3]. This clinical impression was confirmed by pairwise linkage results, which were consistent with linkage to PKD1. Consistent with linkage results, haplotype inspection showed that the PKD1 haplotype, derived from markers KG8 and CW2, segregated only with affected individuals and not with definitively unaffected members of this family.

The proband (II6), who was involved in the non-consanguinous marriage, had a total of four pregnancies (Figure 1). The second and fourth pregnancies resulted in two offspring (III6 and III8) who are affected with ADPKD. Because both these individuals have inherited only one copy of the putative diseased PKD1 haplotype (paternal), they are predicted to be heterozygotes ($PKD1^{+/-}$). The first and third pregnancies (III5 and III7) were lost at 3 and 4 months of gestation when the proband was 22 and 25 years of age. No apparent cause was identified for either miscarriage, and fetal tissue was not available for further study. According to the proband's testimony, her parents and the parents
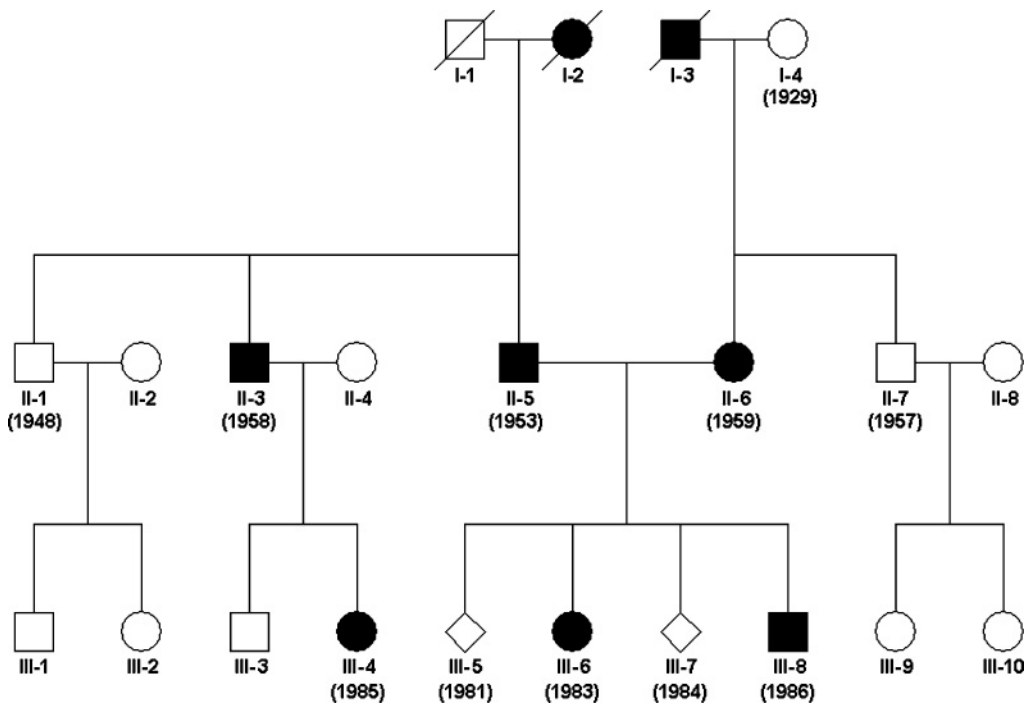
Fig. 1. Pedigree of the family with ADPKD type 1. Affected individuals are denoted by solid symbols. Two spontaneous miscarriages of the proband (II6) are shown as rhombus. The number in parentheses is the year of birth.

of her husband were not relatives and came from different parts of Spain.

Discussion

Given that ADPKD affects 1 in 500–1000 live births, bilineal disease is predicted to occur in 1 in 250 000–1 000 000 marriages in the general population [4]. A potential consequence of bilineal ADPKD is that some of the affected members from these pedigrees may carry two germline mutations. Two scenarios may result. First, in families in which germline mutations of affected parents involve the same polycystic kidney disease gene (i.e. PKD1 or PKD2), homozygous (PKD1$^{-/-}$ or PKD2$^{-/-}$) or compound heterozygous (PKD1$^{+/-}$:PKD1bis$^{+/-}$or PKD2$^{+/-}$:PKD2bis$^{+/-}$) mutations are expected in 25% of offspring. It has previously been reported that in a family with type 1 ADPKD, in a marriage between affected consanguineous individuals, there were two live-born heterozygous offspring and two fetuses lost late in pregnancy, suggesting that homozygosity of PKD1 mutations in humans is embryonically lethal [5]. Second, in families in which germline mutations of affected parents involve one copy each of PKD1 and PKD2, trans-heterozygous (PKD1$^{+/-}$:PKD2$^{+/-}$) mutations in both genes are expected in 25% of offspring. One such family in which trans-heterozygous PKD1 and PKD2 mutations were observed in two affected individuals has been recently reported [6]. The disease associated with the presence of both mutations appears to be more severe than the disease associated with either mutation alone. More recently, a patient with ADPKD has been reported

who was heterozygous for a *de novo* PKD1 variant and homozygous for a novel PKD2 mutation [7]. Her phenotype was more severe than that for PKD1. This could be attributed to her homozygous PC2 mutated protein. However, the scenario involving compound heterozygous mutations of PKD1, which is predicted to be more common, has not been described to date. This raises the possibility that homozygous and compound heterozygous mutation combinations may be lethal in humans. Indeed, recent studies of both Pkd1 and Pkd2 knockout mice support this contention [8,9]. Mice with heterozygous inactivation of either Pkd1 and Pkd2 develop focal cysts later in life. In contrast, mice with homozygous inactivation of either Pkd1 or Pkd2 die, either in utero or perinatally, with massive polycystic kidneys.

A major point of interest in our family is whether the miscarriages of our proband might represent mutant PKD1 compound heterozygotes. However, a limitation of our study is that direct DNA-based verification was not possible because fetal tissue was not available. Based on Mendelian segregation, the risk for disease transmission from the non-consanguineous marriage of our proband and her husband to their offspring is 75% (i.e. 50% risk for heterozygotes plus 25% risk for compound heterozygotes). Conversely, the risk for maternal age-adjusted fetal loss from an unselected cohort of white pregnancies is ∼3.5% [10]. Thus, the probability of PKD1-diseased compound heterozygotes for each of the miscarriages in this family is approximately eightfold greater than the population risk from non-consanguineous marriages. The increased risk for fetal wastage, presumably reflect an increased probability of lethal recessive genes in the offspring.

Recent studies have suggested that individual cyst formation in ADPKD is a cellular recessive two-hit event requiring inactivation of both copies of a PKD gene through germline and somatic mutations within an epithelial cell [11]. A trans-heterozygous variant of the two-hit mechanism, with germline mutation at one polycystin gene coupled with somatic mutation at the other, is supported by observations of somatic PKD1 mutations in kidney cysts of patients with germline PKD2 mutations, and vice versa [12,13]. Since the somatic PKD mutations constitute the rate-limiting step for individual cyst formation, the frequency of such mutations is predicted to determine both the number of cysts eventually formed and the disease severity [14]. In the individuals with compound heterozygous mutations, all cells have already suffered a 'first hit' in both PKD loci. Thus, mutant PKD1 compound heterozygosity is expected to be associated with a severe phenotype. The increased disease severity may simply reflect the fact that all the cells in these individuals have two loci that could be involved in the somatic 'second hits'. Our findings in this family are confirmatory of this possibility since the two offspring who were affected with ADPKD type 1 were heterozygous. It is possible that the two fetuses lost in mid-pregnancy were compound heterozygotes. These data provide the most compelling evidence in support of our contention that PKD1 compound heterozygosity may be embryonically lethal.

In summary, we report for the first time a clinically proven situation of bilineal inheritance and probably compound heterozygosity in a PKD1 family. Based on the arguments presented, our findings suggest that compound heterozygosity of PKD1 mutations in humans may be embryonically lethal.

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