

our series, markers of bone turnover were not directly measured, since diagnosis-related groups did not cover a workup for metabolic bone disease, including markers of bone turnover, for the care of patients with fractures. Microfractures, inadequate mineralization, and outdated collagen are several candidate causes. Although the fractures reported by Lee et al. healed with continued bisphosphonate treatment, an anabolic agent such as parathyroid hormone (1-34) may be preferable. Parathyroid hormone not only has activated bone-formation markers in trials in humans but has also enhanced the healing of fractures in studies in animals.^{1,2}

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Perinatal Deaths in a Family with Autosomal Dominant Polycystic Kidney Disease and a *PKD2* Mutation

TO THE EDITOR: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common mendelian disorders, affecting approximately 12.5 million persons worldwide.^{1,2} Clinical symptoms usually do not arise until adulthood. ADPKD2 is generally considerably milder than ADPKD1. About 2 to 5% of patients have early-onset ADPKD, which at times is clinically indistinguishable from autosomal recessive polycystic kidney disease (ARPKD).³ To date, ADPKD with early manifestations has been thought to be strictly confined to persons with ADPKD1.²

We now report on a four-generation family carrying a mutation in the gene for ADPKD2 (*PKD2*) with previously undetected disease. In the present generation, however, perinatal death due to polycystic kidney disease occurred in the mother's second and third pregnancies, the first having resulted in a healthy girl. The second pregnancy was complicated by oligohydramnios and massively enlarged hyperechogenic fetal kidneys; a boy born at 30 weeks of gestation died shortly after birth from respiratory insufficiency. The third pregnancy was complicated from 20 weeks of gestation forward; a girl born at 34 weeks of gestation died shortly after birth.

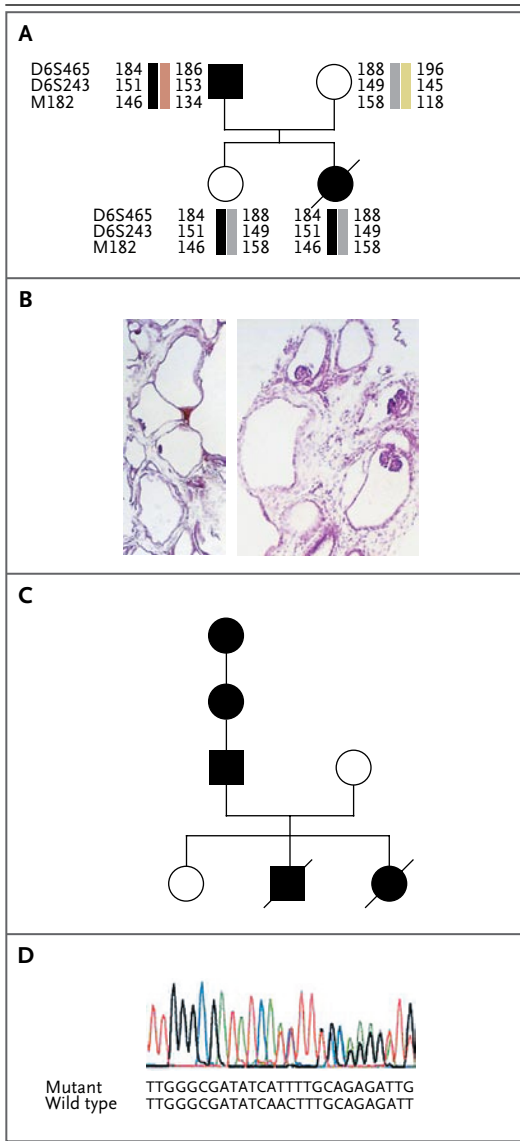
Linkage analysis of the gene for ARPKD (*PKHD1*) revealed identical haplotypes in the healthy daughter and the affected daughter, making ARPKD very unlikely (Fig. 1A). Histologic studies unexpectedly

showed glomerular cysts that were suspicious for ADPKD (Fig. 1B). Abdominal ultrasound studies in the parents revealed no cysts in the 31-year-old mother but two cortical cysts in the left kidney and three cysts in the right kidney in the 32-year-old father. Ultrasound studies in other family members showed bilateral renal cysts in the paternal grandmother and in the 80-year-old paternal great-grandmother (Fig. 1C). However, none of these adults had any clinical symptoms. Analysis of the fetal DNA for *PKD1* and *HNF1β* did not show a pathogenic mutation, but *PKD2* sequencing revealed a novel frameshift mutation, c.1934_1935del insT (p.Asn645fs), in exon 9 (Fig. 1D) that is thought to lead to premature truncation of the encoded polycystin-2 protein and that was not present among 200 ethnically matched control chromosomes. This mutation segregated with the phenotype, further validating its pathogenicity.

These cases emphasize the need for ultrasound studies in the parents and, if the parents are young, the grandparents of a child with polycystic kidney disease of unknown type.⁴ The high risk of recurrence of ADPKD with early manifestations in affected families suggests a common familial modifying background for early and severe disease expression (e.g., mutations or variants in genes encoding other cystoproteins).⁵ Definition of the underlying mechanisms might provide further insights into polycystic kidney disease. This family

Figure 1. Linkage Analysis for ARPKD in the Unaffected and Affected Daughters of a Family with the *PKD2* Mutation, Histologic Findings in a Renal-Biopsy Specimen from the Affected Daughter, the Family Pedigree, and a Sequence Chromatogram Showing the *PKD2* Mutation.

Panel A shows the results of linkage analysis for autosomal recessive polycystic kidney disease (ARPKD) in the healthy daughter and the deceased affected daughter, with genetic markers closely flanking the *PKHD1* gene on chromosome 6p12. The microsatellite marker D6S465 is located distally to the *PKHD1* gene; D6S243 is an intragenic marker, and M182 is located proximally to the *PKHD1* gene. Squares denote males, circles females, open symbols unaffected family members, and solid symbols affected family members; the slash indicates the deceased daughter. The recombination rates of the flanking informative markers are about 1.2 cM. Haplotypes are incompatible with linkage to this locus, because the healthy daughter bears the same parental *PKHD1* haplotypes as the affected daughter. A DNA sample from the family's first affected child was not available. In Panel B, a renal-biopsy specimen from the deceased affected daughter shows glomerulocystic kidney disease (hematoxylin and eosin), which is suggestive of an early manifestation of ADPKD. Residual glomerular structures can be seen in some of the cysts. Panel C shows the four-generation pedigree of the described family. The sequence chromatogram in Panel D shows the *PKD2* mutation c.1934_1935del insT (p.Asn645fs), which segregates with the disease status in this family over four generations. The chromatogram depicts the deletion of two nucleotides (del AC) and a 1-base-pair insertion (ins T) predicted to result in a premature stop. Wild-type and mutant *PKD2* sequences are shown below the chromatogram.



history emphasizes that early manifestations of polycystic kidney disease may occur, even in families with ADPKD2 and that this is information that should be shared with affected persons and their families.

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