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Familial clustering of medullary sponge kidney is autosomal dominant with reduced penetrance and variable expressivity

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Medullary sponge kidney (MSK) is a renal malformation typically associated with nephrocalcinosis and recurrent calcium nephrolithiasis. Approximately 12% of recurrent stone formers have MSK, which is generally considered a sporadic disorder. Since its discovery, three pedigrees have been described in which an apparently autosomal dominant inheritance was suggested. Here, family members of 50 patients with MSK were systematically investigated by means of interviews, renal imaging, and biochemical studies in an effort to establish whether MSK is an inheritable disorder. Twenty-seven MSK probands had 59 first- and second-degree relatives of both genders with MSK in all generations. There were progressively lower mean levels of serum calcium, urinary sodium, pH, and volume, combined with higher serum phosphate and potassium from probands to relatives with bilateral, to those with unilateral, and to those unaffected by MSK. This suggests that most affected relatives have a milder form of MSK than the probands, which would explain why they had not been so diagnosed. Thus, our study provides strong evidence that familial clustering of MSK is common, and has an autosomal dominant inheritance, a reduced penetrance, and variable expressivity.

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Medullary sponge kidney (MSK) is a relatively rare renal malformation typically associated with nephrocalcinosis and recurrent renal calcium stones. Incomplete distal renal tubular acidosis, hypocitraturia, and hypercalciuria are very frequent and most likely combine with the distinctive precalyceal cystic anomalies of the Bellini ducts in triggering stone formation.[1]

MSK is generally considered a sporadic disorder, but a few pedigrees have been described with an apparently autosomal dominant inheritance.[2–4] Some nephrologists have also seen a familial clustering of the disease.

In recent papers of ours, we reported on the passage of renal stones in relatives of our probands with MSK,[5] and we documented familial cases of MSK.[6] We also found that MSK could have atypical presenting features (that is, asymptomatic or with a very indolent history of renal calculi).[5] These observations have raised the hypothesis that as MSK patients might go undiagnosed or misdiagnosed, familial aggregations of MSK may not be recognized.

The notion that MSK may be an inheritable disorder has never been investigated systematically. To address this possibility, we identified all our familial cases and evaluated their possible modes of inheritance in one of the largest cohorts of MSK patients ever available, which is currently being followed up in Verona (Italy). Family members of our patients with MSK were systematically screened by means of interviews, biochemical studies, and renal imaging. The results of these analyses are reported in this paper.

RESULTS

From the cohort of 50 probands, we identified MSK in other members in 1 family involving 1 generation, in 18 families involving 2 generations, and in 8 families involving 3 generations (Figure 1). A diagnosis of MSK was considered highly likely in 5 deceased relatives on the basis of their reported history of multiple renal calculi. The diagnosis of MSK in relatives was obtained in 40 cases by intravenous

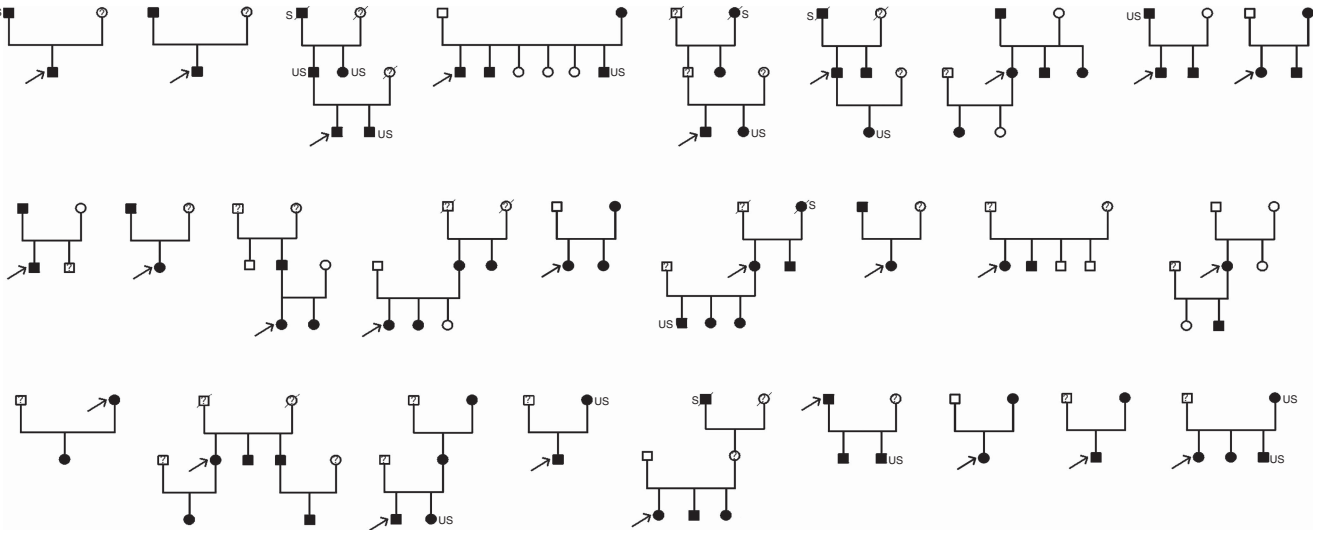

Figure 1 | The pedigrees of 27 families in whom medullary sponge kidney (MSK) was discovered in multiple cases. Crossed symbols refer to deceased subjects. Males and females are shown with squares and circles, respectively. Full black symbols indicate MSK subjects. The arrow points to the proband. A question mark inside the symbol indicates that the corresponding subject was not investigated. Ultrasound (US) and S close to full black symbols denote that the diagnosis of the MSK conditions was done by kidney US or by personal history of stones, respectively. When the full black symbol has no close specification, the diagnosis of MSK was performed by urography or computed tomographic urography. First line, left to right, families 1–9; second line, families 10–18; third line, families 19–27.

(i.v.) urography and in 14 cases by kidney ultrasound (US). In another 4 and 18 relatives, respectively, urography/computed tomographic urography (uro-CT) and kidney US did not disclose any typical features of MSK. On average, 2.8 relatives per proband underwent imaging.

Thus, 27 (54%) of our MSK probands (15 females and 12 males) had 59 out of 81 (73%) first- and second-degree relatives with MSK (29 females). Cases of MSK were identified in all generations in 6 of the 8 families with 3 generations involved in the study (Figure 1).

Among the 54 relatives diagnosed with MSK by urography or kidney US, renal abnormalities were unilateral in 14 cases (an example is shown in Figure 2a and b) and bilateral in 40 cases (Table 1).

Twenty-three MSK probands had no relatives affected: 60 first-degree relatives (a mean 2.6 per proband, a number similar to the number of relatives screened in MSK families) were investigated, all by kidney US, as none had previously undergone renal imaging.

We analyzed the following data in our MSK families using four different groupings: (1) probands; (2) relatives with bilateral MSK; (3) relatives with unilateral MSK; and (4) unaffected relatives.

We found a decreasingly frequent history of urography or uro-CT among the family members in the various groupings, that is, it was most prevalent in probands and in bilateral MSK forms, and least prevalent in unaffected relatives (Table 1).

We found a statistically significant decreasing gradient for the mean levels of serum calcium, urinary sodium, calcium, oxalate, urine pH, and urinary volume in the different groupings of MSK family members, from the probands to their relatives with bilateral MSK, to those with unilateral MSK, and to the unaffected relatives (Table 2a and b). In particular, although it was still within the normal range, serum calcium was slightly higher in MSK probands and decreased progressively across the four groupings.

Serum phosphate concentrations were slightly lower in probands and showed a significant, increasing gradient in mean levels from the probands to their relatives with bilateral MSK, to those with unilateral MSK, and to unaffected relatives. A similar profile was seen for serum potassium, which was also marginally reduced in probands.

The main results did not change after adjusting the regression model for familial clustering: the disease severity trend remained significant for plasma potassium, calcium, and phosphate, and for urinary sodium, calcium, oxalate, pH, and volume, suggesting that the association between disease status and these parameters was not influenced by other variables that might exist in familial clusters (for example, dietary habits).

The intraclass correlation coefficients and the amount of variance for each variable explained by disease status are given in Table 3a and b. After accommodating the regression model for familial clustering, the main results did not change.

DISCUSSION

This is the first study to systematically analyze the familial aggregation pattern of MSK, a condition that is generally considered sporadic.[7] We found that ~50% of our MSK probands had one or more relatives affected. This finding suggests that familial MSK is common, contrary to the general belief. In our families with one or more relatives affected, the individuals with MSK were of both genders and almost invariably in each successive generation, suggesting an autosomal dominant inheritance (Figure 1).