Penetrance of Mutations in the Familial Wilms Tumor Gene FWT1

Nazneen Rahman, Laura Arbour, Richard Houlston, Catherine Bonaiti-Pellé, Fatima Abidi, Julie Tranchemontagne, Debbie Ford, Steven Narod, Kathy Pritchard-Jones, William D. Foulkes, Charles Schwartz, Michael R. Stratton

Wilms tumor is an embryonal kidney cancer that affects one in 10,000 children. Epidemiologic studies have shown that 1%–3% of cases of Wilms tumor are familial and that a predisposition to Wilms tumor is probably caused by rare germline mutations acting in a dominant fashion (1). The risks of Wilms tumor conferred by mutations in these genes are poorly characterized, with estimates of their penetrance ranging from 18% to 63% (2–4). These estimates represent an average of the risks of all genes that predispose an individual to Wilms tumor and, therefore, are influenced by population-dependent variation in the prevalence of mutations in different genes.

Constitutional mutations in the WT1 gene on chromosome 11p13 predispose an individual to Wilms tumor and are associated with genitourinary abnormalities. Germline WT1 mutations have been reported in only four families (three with two cases of Wilms tumor and one with three cases of Wilms tumor) and do not appear to be a common cause of familial predisposition to the disease [reviewed in (5)]. Several genetic syndromes (e.g., the Beckwith–Wiedemann syndrome) have been associated with a predisposition to Wilms tumor, but such syndromes only rarely result in familial cases of the disease [reviewed in (5)].

We previously localized a familial Wilms tumor predisposition gene, designated FWT1, to chromosome 17q12–q21 by genetic linkage analysis of a French–Canadian pedigree, MON 480 (6). Subsequently, the existence of the locus was confirmed by extension of this family (logarithm of odds [LOD] score = 5.7) and by strong evidence of linkage (LOD score = 2.7) in an unrelated family, K1104, from Utah (5). Unlike mutations in WT1, mutations in FWT1 are not commonly associated with developmental abnormalities and do not appear to predispose an individual to early-onset Wilms tumor (5). Moreover, on the basis of currently available information, FWT1 does not appear to function as a tumor suppressor gene (7). In this study, we have estimated the penetrance of FWT1 mutations and have thus provided the first gene-specific estimate of the risks conferred by a Wilms tumor susceptibility gene.

The penetrance of FWT1 was estimated by use of the two families (MON 480 and K1104) in which Wilms tumor is clearly linked to the gene. None of the other 17 Wilms tumor families in our series generate an LOD score greater than 0.4 when markers in the vicinity of FWT1 are used [(5); Rahman N: unpublished data]. Both FWT1-linked pedigrees were systematically extended so that samples from all individuals willing to participate, irrespective of their disease status, were collected. Genotyping of microsatellite markers D17S250, D17S806, and D17S1820 was used to determine the carrier status of 113 potential carriers of the FWT1 mutations segregating in the two families (67 individuals from MON 480 and 46 individuals from K1104). These markers are approximately ordered cen–D17S250–6.5 cM–D17S806–6 cM–D17S1820–tel (where cen = centromere, cM = centimorgan, and tel = telomere) and are located within the 14-cM interval containing FWT1 defined by recombinants.
in MON 480 (5). In four individuals, an obligate recombinant event within this interval precluded attribution of carrier status, and these individuals were not included in the penetration analyses. Because the incidence of Wilms tumor after the age of 20 years is extremely low, individuals older than this age who inherited the mutation were coded as unaffected mutation carriers. Five unaffected carriers were under the age of 20 years at the time of the analysis and were excluded.

The penetrance of FWT1 mutations was estimated with three different approaches. In the first method, by use of the program MFLINK, the LOD scores at $\theta = 0$ for the two families were maximized over a range of penetrance functions under a dominant model constraining parameters to the population prevalence of Wilms tumor (8,9). The maximum LOD score was obtained at a penetrance of 20% (95% confidence interval [CI] = 0.2%–50%). This method is equivalent to maximizing the likelihood conditional on all phenotypic data and is, therefore, free from the ascertainment bias caused by family selection on the basis of multiple affected individuals. However, because it is based on information from unaffected individuals carrying the disease haplotype, it results in wide CIs.

The second method of determining penetrance was classical segregation analysis with maximum likelihood estimation. Sibships with a gene carrier parent were analyzed by taking into account the way in which sibships had been ascertained (10). This method provides an alternative method of deriving an unbiased estimate of penetrance. Among the two pedigrees studied, there were 24 sibships that could be used for estimation of penetrance. The penetrance of FWT1 mutations by use of this method was 15% (95% CI = 6%–27%).

In the third method, age-specific Kaplan–Meier curves were generated for carriers by use of the program EGRET (Statistics and Epidemiology Research Corporation and Cytel Corporation). The penetrance estimate for FWT1 mutations generated by this method was 26% (95% CI = 17%–38%) (Fig. 1). Although this is a commonly used method for determining penetrance, it has the limitation that it is sensitive to ascertainment bias within pedigrees. This may account for the higher estimate of the penetrance of FWT1 mutations obtained, although it should be noted that the CIs for the penetrance values derived by each method overlap.

There is a preliminary suggestion that the penetrance of FWT1 mutations may differ according to the sex of the transmitting parent. Of 16 individuals with Wilms tumor from the two families, 12 inherited the predisposing mutation from their mother and all developed Wilms tumor at or below the age of 7 years. The four individuals who inherited the mutation from their father developed Wilms tumor after the age of 7 years (5). The mean age at diagnosis of the patients who inherited the FWT1 mutation maternally is 4.1 years, whereas the mean age at diagnosis of the four patients who inherited the FWT1 mutation paternally is 10.4 years (test for difference between distributions, $P = .004$; Mann–Whitney $U$ test, two-sided). The penetrance estimated by segregation analysis in sibships was higher when the carrier parent was the mother (23% [95% CI = 9%–42%]) than when the carrier parent was the father (5% [95% CI = 0%–21%]). Although the difference is not statistically significant ($\chi^2 = 2.71; P = .10$; homogeneity test by maximum likelihood ratio, two-sided), it is consistent with a parent-of-origin effect. Further data are required to evaluate this possibility.

In this study, a maximum of two FWT1 mutations has been evaluated. It is possible that the penetrance estimates derived from this analysis may not be applicable to other mutations. Given that the analysis has been based on families with multiple cases of Wilms tumor, the penetrance estimates may be higher than the Wilms tumor risk of FWT1 mutations overall. However, it is also conceivable that the derived penetrance values represent underestimates. If the risks conferred by other FWT1 mutations are higher than estimated in this study, more carriers would develop Wilms tumor but may have died before having offspring. High-risk mutations would, therefore, be expected to result in smaller clusters of closely related affected individuals. Such families would exhibit weak evidence of linkage to FWT1 but, because of the heterogeneity of Wilms tumor predisposition, cannot confidently be included in the analyses. It should also be noted that the same mutations may be associated with different risks in the general population. Despite these limitations, the penetrance values currently represent the best estimate of the risk in carriers of mutations in a Wilms tumor susceptibility gene and could usefully form the basis of clinical risk assessment in Wilms tumor families.

Whatsoever method is used, the risk of Wilms tumor conferred by FWT1 mutations is only modest (15%–26%). Within each of the FWT1-linked pedigrees, there were only two first-degree affected relatives out of a total of 16 affected individuals (5). This low penetrance may have resulted in underascertainment of familial clustering of Wilms tumor in previous studies, since pedigree information is often restricted to first-degree relatives. Moreover, the low estimated penetrance of FWT1 mutations suggests that an appreciable proportion of patients with presumed sporadic Wilms tumor may carry germline mutations in this gene.

![Fig. 1. Estimate of the penetrance of FWT1 mutations from Kaplan–Meier analysis. Numbers of patients at risk at times 3, 6, 9, and 12 years were 4, 10, 13, and 16, respectively. Penetrance of FWT1 for these ages beginning at age 3 years is 0.063 (95% confidence interval [CI] = 0.024–0.160), 0.159 (95% CI = 0.089–0.275), 0.222 (95% CI = 0.138–0.346), and 0.256 (95% CI = 0.166–0.384), respectively.](image-url)
REFERENCES


NOTES

Approval by the local institutional review board and full informed consent from the patient or guardian were obtained as appropriate.

Supported by the Medical Research Council (U.K.), the Cancer Research Campaign, the South Carolina Department of Disabilities and Special Needs, the Canadian Genetic Diseases Network, the Canadian Breast Cancer Foundation, the Fonds de la Recherche en Santé du Québec, and the Cancer Research Society of Canada (Inc.).

We thank Nancy Hamel for her technical assistance.

Manuscript received September 14, 1999; revised January 28, 2000; accepted February 4, 2000.