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Genetic Interactions between the *Wilms' Tumor 1* Gene and the *p53* Gene[1]

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ABSTRACT

In recent years, a number of proteins have been identified that can modify the activities of the Wilms' Tumor 1 (WT1) proteins. One of these modifiers is the p53 protein. To investigate a genetic interaction between the *p53* gene and the *wt1* gene, we have crossed their respective knockout mice. The absence of p53 appears to have no gross effect on the phenotype of *wt1*-null mice. Both *wt1*-null and double-null embryos develop pericardial bleeding and die *in utero*. In adult *p53*-null mice, *wt1*-heterozygosity (*wt1*het) predisposes to an earlier onset of lymphomagenesis and the development of kidney abnormalities resembling oncocytoma in humans. *wt1*-heterozygosity alone predisposes to the development of glomerular sclerosis.

INTRODUCTION

The *WT1*[3] gene contains 10 exons and specifies a 3-kb mRNA that can encode for 24 different isoforms as a result of alternative splicing, RNA editing, and the presence of three alternative translational initiation sites (1). WT1 has been detected in many tissues (2), and disruptions of its biological function may lead the development of tumors, *e.g.*, Wilms' tumor.

In recent years, a number of proteins have been identified that can modify the biological activities of WT1, one of which is the p53 protein. At present, it is unclear whether P53 and WT1 physically interact (3, 4), but several lines of evidence suggest that P53 and WT1 do affect each other's biological activities. P53 can alter the transcriptional activity of WT1 (4) and is found to be mutated in anaplastic Wilms' tumors, a more malignant form of Wilms' tumor (5). In turn, WT1 can stabilize P53, affect the transcriptional activity of P53 and rescue cells from P53-induced apoptosis (4, 6).

To investigate a genetic interaction between *wt1* and *p53*, we have crossed *p53*-knockout mice (7) with *wt1*-knockout mice (8). *wt1* expression has been detected in a number of tumor types that also develop in *p53*-null mice (9, 10, 11), including lung adenocarcinomas (12), mammary carcinomas (13), embryonal carcinomas (14), Leydig cell tumors (15), and lymphomas (16). The status of *wt1* may, therefore, have an effect on the development of these tumors in *p53*-null mice. We also hypothesized that the cross might predispose to the development of Wilms' tumor because some Li-Fraumeni patients develop this type of tumor (17).

Conversely, the status of p53 may also have an effect on the phenotype of the *wt1*-null mice. For example, blastema cells in the *wt1*-null mouse undergo apoptosis (8). Because of the role of p53 in certain apoptotic pathways, these cells may not go into apoptosis in the absence of p53.

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[3] The abbreviations used are: WT1, Wilms' tumor 1; *wt1*het, Wilms' tumor 1 heterozygote; *p53*het, *p53* heterozygote; RT-PCR, reverse transcription-PCR.

MATERIALS AND METHODS

Generation of p53- and wt1-deficient Mice. Both the *wt1*-knockout and the *p53*-knockout mice were of mixed genetic backgrounds (CBA, SWR, 129/Ola, C57/BL6, BalB/c). To minimize possible effects of genetic variation (10, 18, 19), male *wt1*het/*p53*-null mice were crossed with female *p53*-null mice. In this way, each litter contributed equally to the genetic pool of both the *wt1*het/*p53*-null cohort and the *p53*-null cohort. To be able to compare the *p53*het cohort with the *wt1*het/*p53*het cohort we used the same principle. This time male *wt1*het mice were crossed with female *p53*-null mice. Similarly, male *wt1*het-mice were crossed with female wild-type mice to be able to compare the *wt1*het cohort with the wild-type cohort.

The mice were screened at least three times a week for overt pathological signs. Sick mice were killed by cervical dislocation and underwent autopsy. All of the major organs and any tumor identified were sampled, fixed in 10% formalin, and processed to wax. Sections, 4 μm thick, were cut and mounted on glass slides and, after dewaxing, were stained with H&E (20). In addition, tumor material was snap-frozen in liquid nitrogen and stored at -80^{o} for immunophenotyping and RNA extraction.

wt1-null embryos were obtained by crossing *wt1*het/*p53*het mice with one another and by crossing *wt1*het mice with one another. Double-null embryos were obtained by crossing *wt1*het/*p53*-null mice with one another. The embryos were fixed in 10% formalin and processed for histopathology, as described above.

Immunophenotyping. This was done as described previously (21). Cells were stained using monoclonal antibodies (EACC, Porton Down, UK) and were washed and then incubated with antimouse immunoglobulin labeled with FITC (Serotec United Kingdom Ltd.). Analysis was carried out by selecting a viable cell bitmap using forward and right-angle light scatter. Cells (10^5) within the bitmap were counted, and the results expressed as the percentage of positive cells.

Analysis of RNA Transcripts (RT-PCR). RNA was isolated from thymic lymphomas using an RNA extraction kit from Advanced Biotechnologies, Inc. (Columbia, MD). Single-strand cDNA was made from 1 μg of total RNA, and amplification reactions were set up with one- twentieth of the cDNA. WT1 mRNA expression was analyzed with two primer sets, as follows: primer set 1: L966, 5′-ACA-GGT-GTG-CTG-TCT-TGG-AA-3′ (Exon 8), and L967, 5′-CCA-CAC-CAG-GAC-TCA-TAC-AG-3′ (Exon 10); primer set 2: J421, 5′-CCA-CAC-CAG-GAC-TCA-TAC-AG-3′ (Exon 9), and J420, 5′-TGC-ATG-TTG-TGA-TGG-CGG-AC-3′ (Exon 10). GAPDH mRNA expression was analyzed with primer set 108, 5′-ACC-ACA-GTC-CAT-GCC-ATC-AC-3′, and 109, 5′-TCC-ACC-ACC-CTG-TTG-CTG-TA-3′.

Conditions of amplifications were 25 cycles (primer set L966/L967 and primer set 108/109) or 30 cycles (primer set J420/J421) of amplification starting with a denaturing step of 2.5 min at 94°C and ending with an 8-min final extension at 72°C. The cycles were initiated by denaturing the first-strand cDNA at 94°C for 30 s, annealing for 45 s at 56°C, and extending for 1 min. at 72°C.

RESULTS

Generation of p53- and wt1-deficient Mice. Male newborn mice of the different crosses were recovered at the expected Mendelian frequency (Fig. 1*A*). In agreement with previous findings (22, 23), we found that in the absence of *p53*, there was a significant reduction in the number of females (χ^2 test, $P = 0.005$) with a proportion of female embryos developing exencephaly (Fig. 1*B*).

No newborn *wt1*-null mice or double-null (*wt1*-null/*p53*-null) mice were obtained. Histopathological analysis showed that the absence of

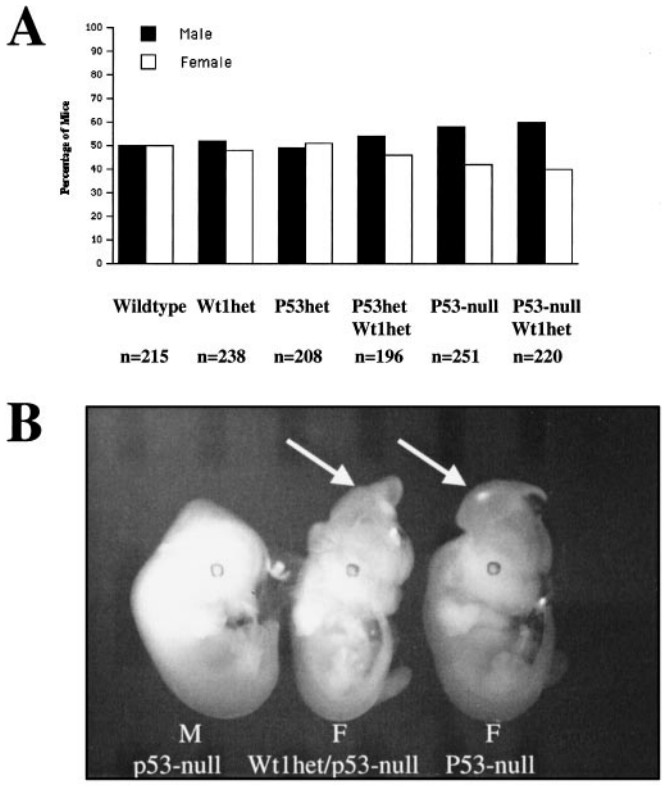

Fig. 1. In the absence of *p53*, some female embryos develop exencephaly. *A*, ratio between newborn males and females of the different genotypes. In the absence of *p53*, there is a significant reduction in the number of females ($P = 0.005$). *B*, morphology of E13.5 embryos with exencephaly (*arrows*) and without. ×4.

p53 had no gross effect on the phenotype of *wt1*-null mice. Both *wt1*-null and double-null embryos developed pericardial bleeding and died *in utero*. However, in contrast to *wt1*-null embryos, double-null embryos did not survive beyond 11.5 days (Table 1, Fig. 2). Extensive morphological analysis of these embryos, however, did not reveal any mechanism associated with this earlier mortality.

The ureteric bud was absent in both the *wt1*-null and the double-null embryos (Fig. 2*E*). In contrast to our hypothesis that the status of p53 may affect the apoptosis of the blastema cells, we found no differences between the blastemas of E11.5-day-old wt1-null embryos and double-null embryos (Fig. 2*F*).

***wt1*het/p53-null Mice Develop Disease Earlier Than p53-null Mice.** We found that the disease-free survival of female *p53*-null mice was reduced in comparison with that of male *p53*-null mice (Anderson Darling Test/χ^2 test, $P = 0.012$). We, therefore, plotted the disease-free survival curves of the males and females separately (Fig. 3). The *wt1*het/*p53*-null mice succumbed earlier than the *p53*-null mice ($P = 0.02$; Fig. 3, *A* and *B*). More than 90% of both the *p53*-null and the *wt1*het/*p53*-null mice developed lymphomas, predominantly involving the thymus (Table 2). In addition, ~15% of each cohort developed sarcomas, mainly hemangiosarcomas and osteosarcomas. These percentages were the same for both male and female mice.

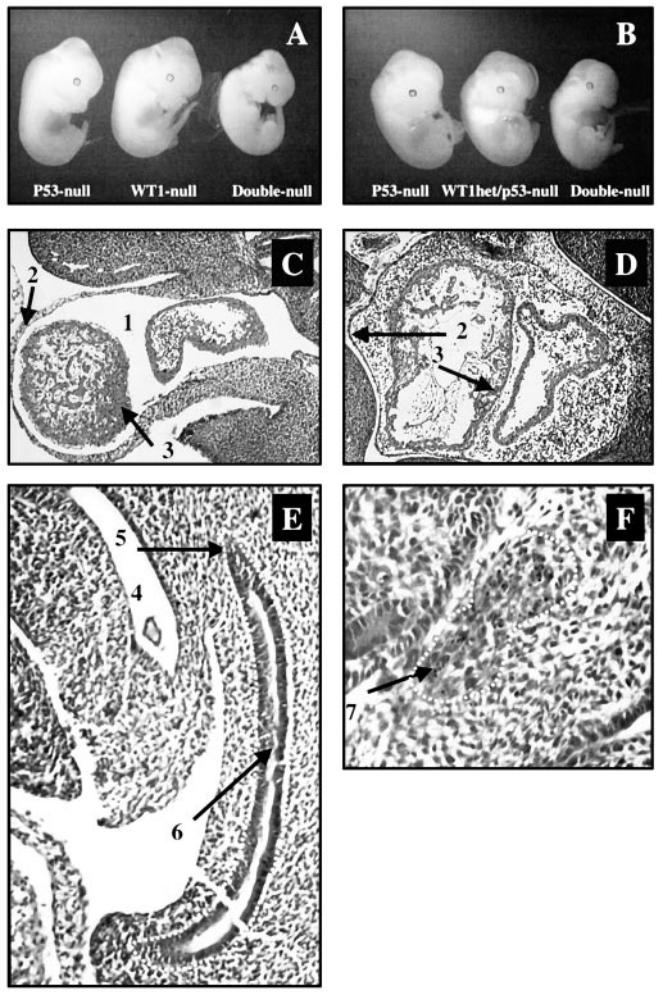

Fig. 2. Morphological and histological analysis of *p53*-null and double-null embryos. *A*, morphology of a *p53*-null, a *wt1*-null, and a double-null embryo (E13.5). *B*, morphology of a *p53*-null, a *wt1*-het/p53-null and a double-null embryo (E13.5). *C*, cross-section of the heart of a *p53*-null embryo (E11.5). *D*, cross-section of the heart of a double-null embryo (E11.5). In the double-null embryo, the heart ventricle has dilated and its ventricle wall is thin. Pericardial bleeding can be observed. *E*, cross-section of a double null embryo (E11.5) showing the wolffian duct. *F*, cross-section of a double null embryo (E11.5) showing the blastema. The sections were stained with H&E, as described in the "Materials and Methods" section: *1*, pericardial space; *2*, pericardium; *3*, ventricle wall; *4*, cloaca; *5*, mesonephric (Wolffian) duct before entry into cloaca; *6*, Wolffian duct; *7*, blastema. ×20.

Table 1 *Embryogenesis*

Developmental	*P53*-null	*wt1*het/*p53*-null	*wt1*-null	*wt1*-null/*p53*-null
E9.5	Normal ($n = 1$)	Normal ($n = 3$) Neural tube open ($n = 2$F)[a]		Normal ($n = 1$)
E10.5	Normal ($n = 8$)	Normal ($n = 4$) Neural tube open ($n = 1$F)	Normal ($n = 2$)	Normal ($n = 7$)
E11.5	Normal ($n = 14$)	Normal ($n = 20$)	Normal ($n = 1$) Pericardial bleeding ($n = 1$)	Pericardial bleeding ($n = 5$) Dead ($n = 2$)
E12.5	Normal ($n = 25$)	Normal ($n = 48$) Exencephaly ($n = 2$F)	Normal ($n = 3$) Pericardial bleeding ($n = 1$)	Dead ($n = 5$)
E13.5	Normal ($n = 2$) Exencephaly ($n = 1$F)	Normal ($n = 16$) Exencephaly ($n = 1$F)	Pericardial bleeding ($n = 1$)	Dead ($n = 9$)
E14.5	Normal ($n = 4$)	Normal ($n = 4$)		
E15.5	Normal ($n = 10$)	Normal ($n = 17$)		

[a] F, female embryo.

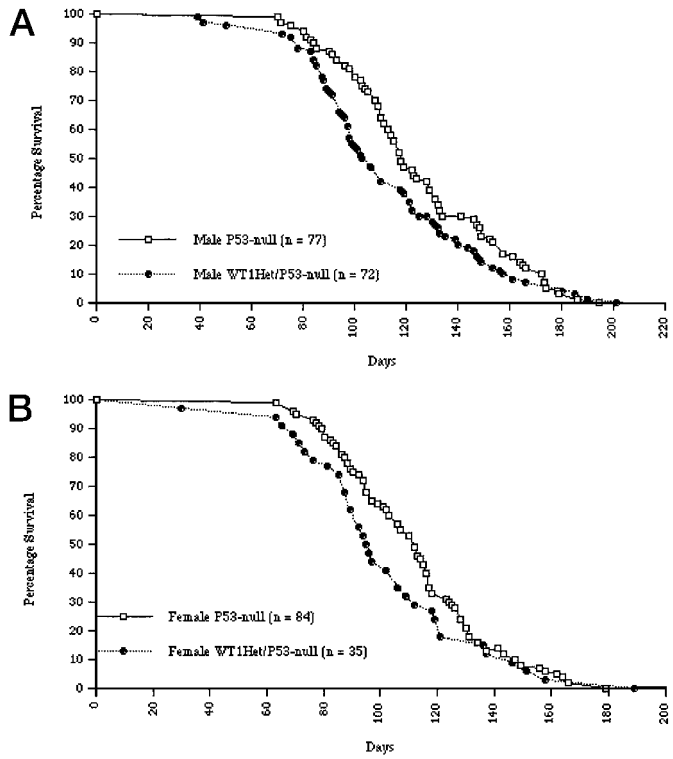

Fig. 3. Survival curves of *Wt1*het/*p53*-null and *p53*-null mice. *A*, male *wt1*het/*p53*-null mice *versus* male *p53*-null mice. *B*, female *wt1*het/*p53*-null mice *versus* female *p53*-null mice.

Table 2 *Tumors and phenotypes of the deceased mice*

Tumor	*P53*-null (n = 137)	*wt1*het/ *P53*-null (n = 89)	*p53*het (n = 10)	*p53*het/ *wt1*het (n = 16)	*wt1*het (n = 10)
Lymphoma	91%	91%	70%	75%	20%
Sarcoma	15%	12%	20%	19%	
Adenocarcinoma			10%	6%	
Preneoplastic tubuli		20%			
Glomerular sclerosis		3%		13%	80%

***wt1*het/p53-null Mice Develop Oncocytoma and Glomerular Sclerosis.** In addition to the observed lymphomas and sarcomas, the *wt1*het/*p53*-null mice also developed kidney abnormalities (Fig. 4). Twenty % developed epithelial neoplasms that resemble oncocytomas in humans (24). Three % developed glomerular sclerosis (Table 2). Regarding the development of oncocytomas, preneoplastic lesions and small neoplasms could be distinguished. The preneoplastic lesions were characterized by columnar tubule cells with densely eosinophilic cytoplasm and with nuclei of regular size and shape (Fig. 4*B*). In the case of the small neoplasms (Fig. 4*C*), the epithelial cells of the dilated tubule were irregular in size and shape, and there was some nuclear pleomorphism. No kidney abnormalities could be detected in the *p53*-null mice.

***wt1*het/p53-null Mice Have an Earlier Onset of Lymphoma Development.** The presence of oncocytomas could not explain the difference in disease-free survival between the *wt1*het/*p53*-null mice and the *p53*-null mice. Only 20% of the *wt1*het/*p53*-null mice developed these lesions, and only very small areas of the kidneys were affected. We hypothesized that accelerated lymphomagenesis could explain the reduced survival of the *wt1*het/*p53*-null mice. In agreement with this hypothesis, we found that male *wt1*het/*p53*-null mice of four randomly selected litters, became ill before their male *p53*-null littermates (Table 3; Sign test, $P = 0.06$). The *wt1*het/*p53*-null mice in these litters had developed overt lymphoma, whereas no lymphoma could be detected in the *p53*-null mice.

WT1 Is Expressed in Thymic Lymphomas. To test whether the loss of *wt1* expression could explain the differences in the onset of lymphoma development, we performed RT-PCR on thymic lymphoma samples derived from the *p53*-null and *wt1*het/*p53*-null mice. To avoid saturation of the PCR, the number of PCR cycles were varied (20, 25, 30, and 35 cycles; Fig. 5). Twelve samples of each cohort were analyzed in this way. In both cohorts, WT1 could still be detected in 84% of the samples. We found no correlation between the relative expression levels of wt1, the onset of disease, and the diameter of the tumor.

***wt1*het Does Not Affect the Differentiation of Thymic Lymphoma Cells.** Because WT1 may play a role during hematopoiesis (25), we investigated the expression of a number of differentiation markers in nine *wt1*het/*p53*-null thymic lymphomas and 15 *p53*-null thymic lymphomas (Table 4). We found no correlation between the expression pattern of the markers and the genotype or age of the mice.

***wt1*het Predisposes to the Development of Oncocytomas Only in the Absence of p53.** We hypothesized that the effect of *WT1* might be more pronounced in mice with a less severe phenotype than *p53*-null mice. We, therefore, compared *p53*het mice with *wt1*het/*p53*het mice. No significant differences in disease-free survival were observed between the sexes, and the males and females were, therefore, included in the same cohort. Both cohorts developed the same, sex-independent tumor types (Table 2). In addition, 13% of the *wt1*het/*p53*het mice also developed severe glomerular sclerosis. The

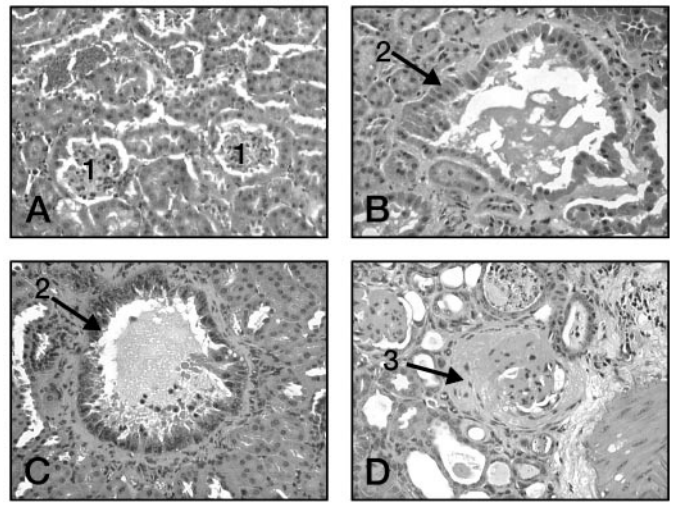

Fig. 4. Kidney sections of *p53*-null and *wt1*het/*p53*-null mice. *A*, normal *p53*-null kidney. *B*, *wt1*het/*p53*-null kidney showing preneoplastic tubule cells. *C*, *wt1*het/*p53*-null kidney section showing neoplastic tubule cells. *D*, *wt1*het/*p53*-null kidney section showing glomerular sclerosis. The sections were stained with H&E, as described in "Materials and Methods." *1*, glomerulus; *2*, preneoplastic and neoplastic tubule cells; *3*, extraglomerular matrix. ×20.

Table 3 *Onset of lymphoma and phenotypes of the deceased mice*

Litter	Mouse	Genotype	Born	Killed	Tumor (diameter)
1	WX 1791	*wt1*het/*p53*-null	8/29/00[a]	12/3/00	Thymic lymphoma (9 mm)
	WX 1792	*p53*-null	8/29/00	12/3/00	
2	WX 1743	*wt1*het/*p53*-null	8/28/00	12/5/00	Thymic lymphoma (7 mm)
	WX 1744	*p53*-null	8/28/00	12/5/00	
3	WX 1775	*wt1*het/*p53*-null	8/26/00	12/5/00	Gut lymphoma (20 mm)
	WX 1773	*p53*-null	8/26/00	12/5/00	
4	WX 1805	*wt1*het/*p53*-null	8/29/00	12/12/00	Thymic lymphoma (9 mm)
	WX 1806	*p53*-null	8/29/00	12/12/00	

[a] Month/Day/Year.

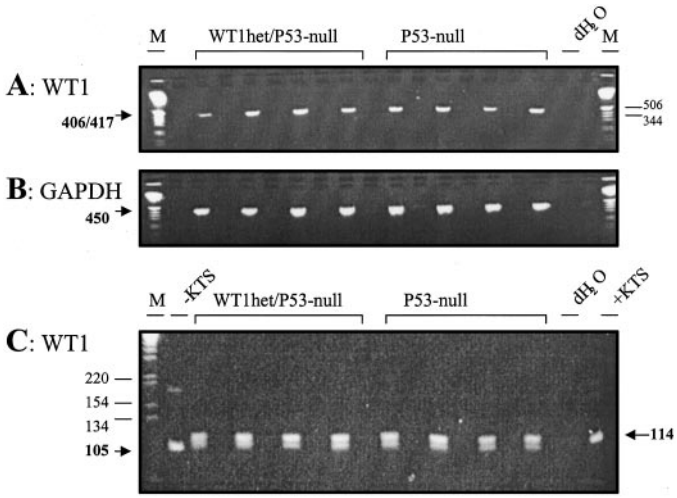

Fig. 5. RT-PCR expression analysis in thymic lymphomas. cDNA was amplified using the following primer sets: *A*: L966/L967 (WT1); *B*, 108/109 (GAPDH); *C*, J420/J421 (WT1). The PCR products were run on a 2% (*A* and *B*) or a 4% (*C*) agarose gel. The bands were visualized with ethidium bromide and were of the correct size. Using primer set J420/J421, one can distinguish between the wt1 splice variant containing nine nucleotides between zincfinger 9 and 10 (*band 114*) and lacking the nine nucleotides between zinc finger 9 and 10 (*band 105*). As a positive control, Wt1 cDNAs were included lacking the 9 nucleotides (*−KTS*) and containing the nine nucleotides (*+KTS*).

latter, together with the small increase in the number of lymphomas, may explain why the *wt1*het/*p53*het mice succumbed earlier than the *p53*het mice (Fig. 6*A*). Although the number of informative cases is small, no oncocytomas could be detected in the *wt1*het/*p53*het mice, which suggests that *wt1*het only predisposes to the development of these neoplasms in the complete absence of p53.

***wt1*het Predisposes to the Development of Glomerular Sclerosis.** To determine whether the observed glomerular sclerosis was the result of a genetic interaction between *p53* and *wt1*, we analyzed *wt1*het-mice and their wild-type littermates in a control experiment. To our surprise, we found that the *wt1*het-mice succumbed earlier than their wild-type littermates (Fig. 6*B*). Again, we found no significant differences in survival between the sexes, and the males and females were, therefore, included in the same cohorts. Eighteen % of the *wt1*het mice died within 250 days, compared with only 1% of their wild-type littermates. Despite intensive screening of the mice, the *wt1*het mice were found either moribund or dead in their cage, which indicated a rapid progression from the first symptoms of sickness to death. The cause of death could not be determined in about 1% of both wild-type and *wt1*het mice. Eighty % of the other deceased *wt1*het-mice suffered from severe glomerular sclerosis (Table 2). Interestingly, the remaining 20% of the *wt1*het mice developed lymphoma. Although the number of mice is small, this suggests that *wt1* heterozygosity alone may already predispose to the development of lymphoma.

DISCUSSION

In the present study, we have investigated the genetic interaction between *p53* and *wt1* by crossing their respective knockout mice. The absence of p53 appeared to have no gross effect on the development of the *wt1*-null embryos. Both *wt1*-null and double-null embryos died *in utero*, probably as a result of pericardial bleeding. However, in contrast to the analyzed *wt1*-null embryos, no double-null embryos survived beyond E11.5. Extensive morphological analysis of these embryos, however, did not reveal any mechanism associated with earlier mortality.

***wt1*het/*p53*-null Mice Have an Earlier Onset of Lymphoma Development.** The disease-free survival of *wt1*het/*p53*-null mice is markedly reduced compared with *p53*-null mice, probably because of the earlier onset of lymphoma development (Tables 2 and 3). The results indicate that WT1 may function as a tumor suppressor in lymphoma development. In agreement with such a role, *WT1* expression has been detected in the thymus (26) and in a number of T-lymphoid cell lines (27, 28) but was found to be very low or absent in most T-lymphoid tumors (16). In the present study, wt1 can still be detected with RT-PCR in 84% of the lymphomas with no clear differences in expression levels between the lymphoma samples of *wt1*het/*p53*-null and *p53*-null mice. Thus far, sequence analyses have revealed no wt1 mutations in the lymphomas of either cohort (data not shown).

It is clear that within the thymus, p53 is essential for the elimination, via apoptosis, of DNA-damaged cells (7, 29), and it appears that

Table 4 *Immunophenotyping of thymic lymphoma cells*

Sample	Genotype	Sex	Age[a]	MIgG[b]	CD45	CD4	Thy1	CD8	F4-80	CD2	CD24	IL2R
WX516	*p53*-null	M	83	1.2	98.9	68.9	98.3	99	10.6	95.7	99.2	23
WX426	*P53*-null	F	88	1.6	97.9	92.2	95.2	97.4	30.1	74.3	98.1	17.9
WX345	*P53*-null	M	92	3.4	97.7	81	90.5	96	7.9	71.7	97.2	9.5
WX530	*P53*-null	M	96	1.5	94.5	59.7	86.4	91.5	15.7	46.9	95.1	21.6
WX510	*P53*-null	M	98	2.3	98.9	98.8	68.7	80.4	14.4	90.3	98.6	22.4
WX475	*P53*-null	M	109	4.6	ND[b]	97.9	84.9	97.8	13.1	97.2	99.3	66.3
WX454	*P53*-null	M	131	1.1	98.1	97.1	97.1	97.9	5.2	77.3	98.1	2.8
WX329	*P53*-null	M	132	0.4	99.2	62.2	87.9	89.1	2.4	58.9	99.4	4.2
WX359	*P53*-null	M	134	2.7	98.5	87.4	83.3	96.6	4.8	89	98.4	33.9
WX337	*P53*-null	M	157	2.1	99.4	97	82.6	97.9	6.7	22.2	99.2	5.5
WX420	*P53*-null	M	186	3.3	57.9	41.5	50	50.9	29.7	43.6	61.5	41.1
WX338	*P53*-null	M	ND	2.1	97.7	96.8	34.6	82.3	3.4	63.5	98.4	4
WX427	*P53*-null	F	ND	5.2	98.5	98.5	90.2	90	27	85.2	98.7	45.6
WX363	*P53*-null	F	117	4	97.6	58.9	92.4	95.6	10.6	93.3	96.9	67.6
WX353	*P53*-null	F	130	1.9	99.3	97.1	93.8	69.8	15.6	99	73.9	4.6
WX505	*wt1*het/*p53*-null	M	84	1.2	96.7	81.2	95.1	96.6	8.3	88.9	96.6	28.5
WX447	*wt1*het/*p53*-null	M	87	6.9	99.6	68.4	61.8	86.7	5.5	52.6	98.4	4.8
WX402	*wt1*het/*p53*-null	M	91	2.2	99.1	62.2	96.4	98.7	8.6	95.8	99	88
WX497	*wt1*het/*p53*-null	M	100	4.2	98.1	89.3	90.2	96.6	13.8	88.7	98.8	18.3
WX406	*wt1*het/*p53*-null	M	128	6.8	98.6	97.7	66.3	94	8.6	85.6	99.3	24.2
WX474	*wt1*het/*p53*-null	M	128	2	98.9	98.3	97.4	59.7	12.4	ND	99.1	17.5
WX347	*wt1*het/*p53*-null	M	130	2.6	98.7	70.6	74	98.4	13.8	90.6	99	21.4
WX348	*wt1*het/*p53*-null	M	135	2.9	96	95.5	96	93.4	7	97.1	(3.3)	5
WX599	*wt1*het/*p53*-null	M	149	2.6	99.7	78.8	78.3	91	8.2	98.9	99.7	62.4

[a] Age in days.
[b] ND, not determined.

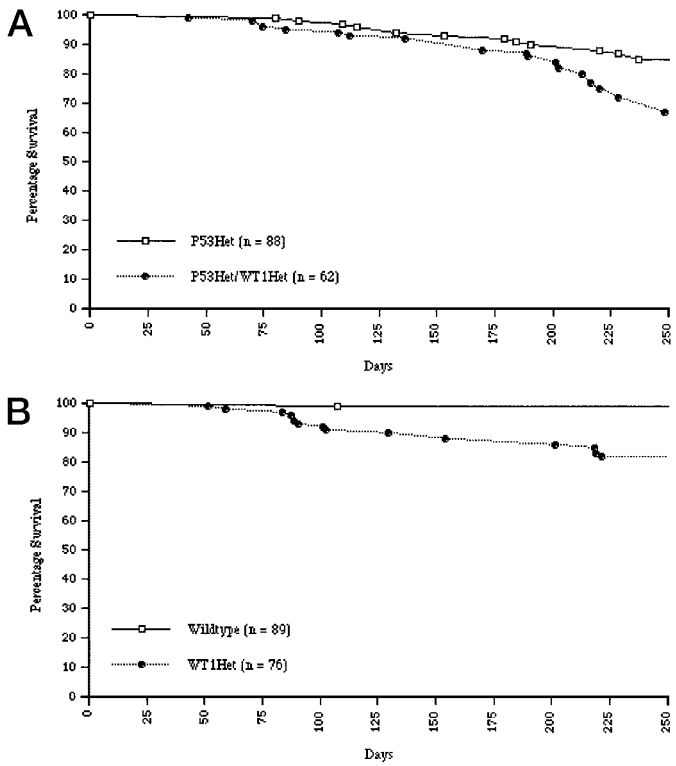

Fig. 6. Survival curves. *A*, *p53*het versus *wt*1het/*p53*het mice. *B*, *wt*1het versus wildtype mice.

loss of apoptotic pathways is critical to tumor formation within this cell type (30). We hypothesize that WT1 exerts its effect on lymphomagenesis by affecting the apoptotic pathway, but the exact mechanism remains to be elucidated. WT1 can induce apoptosis (31, 14) and can do so independently of the status of p53 (32). WT1 has been shown to regulate a number of genes that play an important role in the induction or inhibition of apoptosis (1). Interestingly, several of these genes, like *IGF-II*, *IGF-IR*, and *Bcl-2*, are also regulated by P53 (33–35).

Some *wt1*het mice also developed lymphoma, again supporting a role for WT1 as a tumor suppressor. Lymphoma development has been reported in a number of Wilms' tumor patients (36, 37) but it was hypothesized that these tumors develop as a result of the treatment against Wilms' tumor. Although the number of informative cases is small, our data suggest that *wt1* heterozygosity alone may already predispose to lymphoma development.

***wt1*het/*p53*-null Mice Develop Oncocytoma and Glomerular Sclerosis.** In the absence of *p53*, *wt1*-heterozygosity predisposes to the development of neoplastic lesions resembling oncocytoma, a form of epithelial neoplasm in humans. Because *WT1* is not expressed in adult tubule cells, we hypothesize that the neoplastic tubule cells are the result of disrupted normal development, when *WT1*-expressing mesenchyme cells differentiate into nonexpressing tubule cells (1). Oncocytoma is regarded as benign; and surgical resection, either by partial nephrectomy or by radical nephrectomy, is curative (24). Oncocytoma accounts for ~4% of renal tumors in adults, and most occur in patients over the age of 50 years with a male to female ratio of 2:1. They are often detected as incidental findings, although oncocytoma may present with hematuria or a palpable mass. Regarding the incidence of oncocytoma, we found no differences between male and female *wt1*het/*p53*-null mice, but several did develop hematuria as determined with urine test strips (Roche Combur 10; data not shown).

***wt1*het Mice Develop Glomerular Sclerosis.** To our surprise, we found that the *wt1*het mice died earlier than their wild-type littermates. Autopsy revealed that 80% of the *wt1*het mice suffered from severe glomerular sclerosis. The *wt1*het-mouse may serve as a good model to study the role of wt1 in the development of glomerular sclerosis.

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Genetic Interactions between the *Wilms' Tumor 1* Gene and the *p53* Gene

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