Loss of Heterozygosity at 2q37 in Sporadic Wilms' Tumor: Putative Role for miR-562

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Abstract

Purpose: Wilms’ tumor is a childhood cancer of the kidney with an incidence of ~1 in 10,000. Cooccurrence of Wilms’ tumor with 2q37 deletion syndrome, an uncommon constitutional chromosome abnormality, has been reported previously in three children. Given these are independently rare clinical entities, we hypothesized that 2q37 harbors a tumor suppressor gene important in Wilms’ tumor pathogenesis.

Experimental Design: To test this, we performed loss of heterozygosity analysis in a panel of 226 sporadic Wilms’ tumor samples and mutation analysis of candidate genes.

Results: Loss of heterozygosity was present in at least 4% of cases. Two tumors harbored homozygous deletions at 2q37.1, supporting the presence of a tumor suppressor gene that follows a classic two-hit model. However, no other evidence of second mutations was found, suggesting that heterozygous deletion alone may be sufficient to promote tumorigenesis in concert with other genomic abnormalities. We show that miR-562, a microRNA within the candidate region, is expressed only in kidney and colon and regulates EYA1, a critical gene for renal development. miR-562 expression is reduced in Wilms’ tumor and may contribute to tumorigenesis by deregulating EYA1. Two other candidate regions were localized at 2q37.3 and 2qter, but available data from patients with constitutional deletions suggest that these probably do not confer a high risk for Wilms’ tumor.

Conclusions: Our data support the presence of a tumor suppressor gene at 2q37.1 and suggest that, in individuals with constitutional 2q37 deletions, any increased risk for developing Wilms’ tumor likely correlates with deletions encompassing 2q37.1. (Clin Cancer Res 2009;15(19):5985–92)

Wilms’ tumor (nephroblastoma) is the most common pediatric renal malignancy, affecting ~1 in 10,000 children (1). Most cases of Wilms’ tumor are sporadic and unilateral, but a minority (2%) have a family history (2). Wilms’ tumors appear to develop from nephrogenic rests, an abnormal structure in the kidney that is formed by a failure of the mesenchymal tissue to differentiate into nephrons (3). Additional genetic events are then required to transform these undifferentiated cells, thus causing uncontrolled growth that can lead to the formation of Wilms’ tumor.

Wilms’ tumor is also a feature in several syndromes, notably WAGR (Wilms’ tumor, aniridia, genitourinary abnormalities, and mental retardation), Simpson-Golabi-Behmel, and Beckwith-Wiedemann (4). Analysis of chromosome deletions in patients with WAGR led to the identification of the Wilms’ tumor suppressor gene, WT1, on chromosome 11p13 (5, 6). Homozygous mutations in WT1 are found in ~18% of Wilms’ tumors (7), whereas point mutations of WT1 in patients with Denys-Drash and Frasier syndromes underscore its importance in normal renal and urogenital development (8). Two other genes, WTX (Wilms’ tumor on the X) and CTNNB1, have also been
Translational Relevance

2q37 deletion syndrome is an uncommon constitutional chromosome abnormality. An association with Wilms’ tumor has been reported in three cases, suggesting the presence of a tumor suppressor gene. In a panel of 226 sporadic Wilms’ tumors, we identified loss of heterozygosity in at least 4% of tumors. Homozygous deletions in two independent tumors strongly implicate a 360-kb region containing the *DIS3L2* gene and microRNA *miR-562*. Previously, it has been unclear whether children with 2q37 deletions are at increased risk for developing Wilms’ tumor; ~100 cases have been described, only 3 of whom had this malignancy. However, the majority of cases without malignancy where the breakpoints have been molecularly defined do not encompass the critical 360-kb region we identified, suggesting a genotype-phenotype correlation. Overall, our results therefore suggest that any increased susceptibility to Wilms’ tumor in children with a constitutional 2q37 deletion likely correlates with deletions encompassing 2q37.1.

Implicated in the pathogenesis of Wilms’ tumor, *CTNNB1*, which codes for β-catenin, is mutated in ~15% of Wilms’ tumors but rarely occurs without concomitant mutation of *WT1* (7, 9), whereas somatic mutations of *WTX* are present in 11% to 29% of Wilms’ tumors and occur with and without WT1 mutation (7, 9, 10). Interestingly, germ-line mutations of *WTX* were recently shown to underlie osteopathia striata congenita with cranial sclerosis, a X-linked sclerosing bone dysplasia, but these patients had no predisposition to Wilms’ tumor or other malignancies, suggesting temporal or spatial constraints on the action of *WTX* during tumorgenesis (11).

Due to an improved combination of surgery, chemotherapy, and radiotherapy, there has been a dramatic improvement in Wilms’ tumor survival over the past 40 years, with the cure rate now approaching 90% (12). Despite this, the molecular pathogenesis of Wilms’ tumor and factors determining the subset that relapse remain largely unknown. Identification of other genes involved in the etiology of sporadic Wilms’ tumors therefore remains an important priority. Studies of loss of heterozygosity (LOH), loss of imprinting, and constitutional chromosomal defects have implicated several recurrent changes in Wilms’ tumor at chromosomes 11p15, 1p, 1q, 7p, 9q, 14q, 16q, and 22 (13–16).

2q37 deletion syndrome is a chromosomal disorder characterized by developmental delay, dysmorphic facies, skeletal abnormalities, and an increased risk of congenital heart defects (17–20). Although most cases have no associated malignancies, three children with constitutional 2q37 monosomy and Wilms’ tumor have been reported (21–24). Two of these were *de novo* deletions and the third case resulted from unbalanced segregation of a reciprocal translocation from an unaffected parent with a balanced karyotype. All three cases showed additional urogenital anomalies: hypospadias and a small penis in a male patient (21); gonadal dysgenesis, bifid uterus, and dysplasia of the contralateral kidney in one female (24); and a horseshoe kidney and bilateral ovarian dysgenesis in the female translocation case (23). Features of urogenital anomalies and horseshoe kidney have also been noted in cases of constitutional 2q37 deletions without Wilms’ tumor (19, 20, 25, 26), suggesting the presence of a gene at chromosome 2q37 that, like WT1, is important in both normal development and as a tumor suppressor gene.

We therefore hypothesized that chromosome 2q37 harbors a tumor suppressor gene, the deletion of which predisposes to Wilms’ tumor, and that this gene, or a closely linked gene, is important in renal/urogenital development. To test this, we conducted LOH and candidate gene analyses in a large panel of sporadic Wilms’ tumors.

Materials and Methods

**LOH analysis in sporadic Wilms’ tumors.** Wilms’ tumor samples and paired normal tissue or blood (where available) were accrued from centers in Europe and North America with appropriate ethics board approval and written informed consent. The initial panel used for LOH screening comprised 226 randomly selected tumors. Seventy-three of these were subjected to genome-wide screening and aggregate results for 2q have been reported previously (14). The remainder were specifically analyzed for LOH at 2q37 using a high-density microsatellite panel as described previously (19). Allele ratios were calculated as described, with ratios <0.45 classified as LOH and ratios of 0.45 to 0.66 as possible mosaic LOH or trisomy (14). Additional samples with known copy number loss were subsequently accrued to enrich the pool for candidate gene analysis (27). Copy number at 2q37 was determined by multiplex ligation–dependent probe amplification (28) using custom-designed oligonucleotide probes. Where sufficient DNA was available, precise breakpoints were defined by genome-wide single nucleotide polymorphism analysis using Illumina Hap300 arrays and Beadstudio software (Illumina). Mutation analysis and promoter methylation assays were done using standard methods as detailed in Supplementary Data.

**miR-562 expression analysis.** Total RNA from Wilms’ tumor and normal adjacent kidney tissue was extracted using Trizol (Invitrogen). RNA from other human organs was purchased commercially (Agilent Technologies). Cell lines used included the fetal kidney-derived HEK-293 and 293T lines, the breast cancer–derived MCF-7 cell line, and WTI-49 cells derived from a Wilms’ tumor. RNA from these lines was extracted using the mirNeasy mini kit (Qiagen). RNase protection assay of *miR-562* was done using 2 μg RNA with the mirVana miRNA detection kit (Ambion) according to the manufacturer’s protocol. Probes for microRNA detection were end-labeled with γ-32P by using the mirVana probe and marker kit (Ambion). For quantitative real-time PCR, two commercially available quantitative PCR assays for mature *miR-562* failed completely even on control RNA samples that showed high expression in our RNase protection assay. We therefore opted to amplify the primary *miR-562* transcript, designing primers within the precursor stem loop. Validation on the RNA panel used for RNase protection assays gave concordant results (data not shown). Total RNA was DNase I treated (Invitrogen) and reverse transcribed using SuperScript III (Invitrogen) and oligo(dT) primer. Samples were amplified on an Eppendorf Realplex MasterCycler (Eppendorf) with QuantiTect SYBR Green PCR master mix (Qiagen). The relative abundance of *miR-562* was determined by using a standard curve generated from 5-fold serial dilutions of fetal kidney cDNA and normalized to *GAPDH* mRNA. To analyze changes in microRNA expression, ratios of the geometric means between control (fetal kidney) and experimental (Wilms’ tumor and adjacent normal kidney) samples were calculated. Significance was determined by testing the difference of two means. One advantage of analyzing the primary *miR-562* transcript is that the same aliquots of cDNA could also be used for analysis
Results

LOH and homozygous deletions at 2q37. In the initial panel of 226 Wilms’ tumors, 9 (4%) showed LOH with clonal loss of one allele, indicating that this was an early event in tumorigenesis. Six of these were copy neutral LOH and three harbored deletions. A further ~6% showed ratios in the range 0.45 and 0.66 and may represent later mosaic LOH events or trisomy. A mosaic deletion at 2q36.3-q37.1 has recently been documented (16). We subsequently ascertained an additional three tumors with known deletions, making a total of 12 samples for detailed analysis (Table 1). Two had a WT1 mutation, one was somatic, and the other was heterozygous in blood DNA and reduced to homozygosity in the tumor. In most of these tumors, the region of LOH is extensive, encompassing the terminal 13 Mb of chromosome 2q. Crucially, however, two tumors (NWTS-99 and 06-0116) were identified with homozygous deletion at 2q37. In the initial panel of 226 Wilms’ tumors, 9 (4%) showed LOH with clonal loss of one allele, indicating that this was an early event in tumorigenesis. Six of these were copy neutral LOH and three harbored deletions. A further ~6% showed ratios in the range 0.45 and 0.66 and may represent later mosaic LOH events or trisomy. A mosaic deletion at 2q36.3-q37.1 has recently been documented (16). We subsequently ascertained an additional three tumors with known deletions, making a total of 12 samples for detailed analysis (Table 1). Two had a WT1 mutation, one was somatic, and the other was heterozygous in blood DNA and reduced to homozygosity in the tumor. In most of these tumors, the region of LOH is extensive, encompassing the terminal 13 Mb of chromosome 2q. Crucially, however, two tumors (NWTS-99 and 06-0116) were identified with homozygous deletion at 2q37.1 (Figs. 1 and 2). Additional cases showing interstitial LOH in this region define a minimal 360-kb interval bounded by the polymorphisms rs2679184 and rs13386477 (region A, Figs. 1 and 2). The only known gene within this region is DIS3L2, a homologue of the yeast mitotic control gene DIS3. Within 13 Mb of DIS3L2 is miR-562, a previously uncharacterized microRNA. Case NWTS-99 also showed a heterozygous deletion of ~1 Mb at 2q37.3 (region B), encompassing histone deacetylase 4 (HDAC4) and TWIST2 (Figs. 1 and 2). The t(2;15) translocation case (MDA-74T) was the only tumor available from a patient with a known constitutional 2q37 rearrangement. Only the terminal ~500 kb of 2q37.3 was deleted in this patient, in-
**Mutation analysis of candidate genes.** The presence of homozygous deletions in two tumors strongly suggested that any tumor suppressor gene at 2q37.1 follows the classic two-hit hypothesis. We therefore analyzed the subset of Wilms' tumor samples that showed LOH in region A for evidence of a second mutation, screening candidate genes within the homozygously deleted region: **DIS3L2, GIGYF2** (GRB10-interacting GYF protein 2), **NPPC** (natriuretic peptide precursor C), and **miR-562**. No additional genetic changes were identified. Bisulfite sequencing of the CpG island at the **DIS3L2** promoter was also done, but there was no evidence for abnormal methylation in these tumors (data not shown). Similarly, there was no evidence of a second mutation in **TWIST2** or **HDAC4** among the tumors with LOH in region B.

As no second mutations were identified in the Wilms' tumors exhibiting LOH, it is possible that hemizygous deletion or mutation might be sufficient to contribute to tumorigenesis. We therefore screened a panel of 96 Wilms' tumor samples with no LOH at 2q37, looking for heterozygous mutations of genes within regions A and B: **DIS3L2, miR-562, HDAC4**, and **TWIST2**. A 18-bp deletion of **miR-562** was identified in one tumor (Fig. 3A), the follow-up of which is detailed below. No pathogenic mutations were identified in **DIS3L2, HDAC4**, or **TWIST2**. We also screened for microdeletions in region A across the same panel using seven polymorphisms, ~60 kb apart (rs2679184, rs12988522, rs4973500, rs3100586, rs3116179, rs923333, and rs2633254). No additional microdeletions were detected.

**Mutation and expression analysis of miR-562.** To further characterize the 18-bp deletion of **miR-562**, we extended sequence analysis to a total of 176 Wilms' tumor samples and 210 controls. The heterozygote frequency was 3 of 176 Wilms' tumors (0.017) and 5 of 210 controls (0.024), suggesting that it is an uncommon polymorphism. **miR-562** expression has

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**Fig. 1.** 2q37 deletions identified in Wilms' tumors. **A,** ideogram of chromosome 2 enlarged to show regions of LOH at 2q37. Pale gray columns, copy neutral LOH; dark gray columns, heterozygous deletion; black columns, homozygous deletion (06-0116 and NWTS-99T); thin black lines, minimum candidate regions A, B, and C. For simplicity, six additional tumors that show LOH across the entire region have been omitted. **B,** enlargement of region A showing the position of **DIS3L2** and **miR-562**.
Characterized the expression pattern of miR-562 in colorectal cancer cells (29). We therefore characterized previously, except for a single report of expression in the mouse kidney, confirming genome sequence data. miR-562 is only present in primate genomes (data not shown), but expression was significantly decreased (P ≤ 0.005), indicating that it is a genuine target of miR-562 (Fig. 4). Consistent with this, EYA1 was highly expressed in Wilms' tumors but not in normal adjacent kidney tissue (Fig. 5), a result that is consistent with previous microarray expression analysis (30).

Discussion

The discovery of cytogenetic abnormalities in syndromes predisposing to Wilms' tumor, such as 11p deletions in WAGR and 11p trisomies and translocations in Beckwith-Wiedemann syndrome, has been proven critical for the identification of Wilms' tumor genes (31, 32). This combination of LOH data and rare constitutional chromosome abnormalities, used to pinpoint WT1, has also identified up to three loci on chromosome 7p that have a possible role in the etiology of Wilms' tumor (13, 33–35). 2q37 deletion syndrome is a rare constitutional chromosome abnormality, and although most cases have no associated malignancies, reports of Wilms' tumor in three cases (21–24) suggested the presence of a tumor suppressor gene.

Our analysis of a large panel of sporadic Wilms' tumors identified clonal LOH at 2q37 in 4% of cases and allelic imbalance in another 6%. Remarkably, two of these tumors harbor homozygous deletions, strongly supporting our hypothesis of a tumor suppressor gene present in this region and suggesting that it follows a classic Knudson two-hit model (36). Furthermore, genome-wide single nucleotide polymorphism array analysis of these two tumors showed few additional cytogenetic abnormalities (Table 1). In contrast, the tumors that showed only a heterozygous loss at 2q37 harbored multiple additional chromosomal abnormalities, such as 11p LOH and isochromosome-7q (Table 1). We propose that homozygous deletion of one or more key genes at 2q37.1 is sufficient to initiate Wilms' tumor development, whereas, in the absence of a second mutation, heterozygous loss can contribute to the pathogenesis in concert with other abnormalities elsewhere in the genome.

The significance of two additional regions of localized LOH (Fig. 1) is less clear-cut. Region B, encompassing HDAC4 and TWIST2, is defined by a 1-Mb deletion in sample NWTS-99. This same sample also harbors one of the homozygous deletions in region A, yet the intervening DNA shows normal copy number and no LOH. These deletions were all confirmed to be de novo in the tumor. One explanation is that they represent a more complex rearrangement, such as an inversion/deletion event that masquerades as contiguous deletions at the DNA microarray level. Dividing tumor cells are not available for the metaphase analysis needed to investigate this further, but it is possible that the region B deletion is a bystander and does not contribute to the pathogenesis of Wilms' tumor. Similarly, the significance of the ∼500-kb terminal deletion in the translocation case (region C) is somewhat unclear. It encompasses five genes, including ING5, a putative tumor suppressor gene that may modulate p53 function (37). The translocation is unbalanced and duplicates a 28-Mb region of distal 15q, a rearrangement that has also been implicated in the pathogenesis of Wilms' tumor (15, 38). Thus, although this is one of the three germ-line rearrangements that inspired the study, the partial trisomy 15q likely also contributed.
to the pathogenesis of Wilms' tumor in this patient and the 2q37 deletion alone may not have been causal. In support of this, among the constitutional 2q37 deletions that have been well characterized at the DNA level, almost all harbor terminal deletions that extend proximally to HDAC4/TWIST2 and are therefore deleted for both regions B and C, yet these patients do not have Wilms' tumor (19, 39–42). In contrast, most of the proximal breakpoints localize distal of region A; in our panel of 30 deletion patients without malignancy, only one has a deletion of region A, with a breakpoint between NPPC and DIS3L2.15 Additionally, both of the constitutional deletion cases with Wilms' tumor had breakpoints in 2q37.1 (21–24). Combined with our identification of homozygous somatic deletions in two tumors, these data strongly suggest that region A in 2q37.1 is the primary Wilms' tumor susceptibility locus on 2q.

Fig. 3. Characterization of miR-562. A, sequence analysis identified a heterozygous 18-bp deletion of miR-562 in 1.7% of Wilms' tumors and 2.4% of controls. The miR-562 hairpin is shown with the mature microRNA in bold text. Large arrows, terminal ends of miR-562 in the reference sequence; black box, 18-bp deletion. RNA folding analysis using the program Mfold (http://mfold.bioinfo.rpi.edu/) indicates that the 18-bp deletion will abolish hairpin formation. B, RNase protection assay detected miR-562 expression in human colon, fetal kidney, and several kidney-derived cell lines but not in other major organs. The miR-562 probe is 21 nucleotides in length. C, primary miR-562 expression in Wilms' tumor samples was determined by quantitative real-time PCR and normalized to GAPDH. NK, normal adjacent kidney from Wilms' tumor patients; 08-03XX samples are Wilms' tumors; *, a Wilms' tumor heterozygous for the miR-562 deletion polymorphism; #, Wilms' tumor samples with 2q copy neutral LOH. Bars, SE. Nine of the 12 tumor samples show at least a 2-fold decrease in expression compared with normal kidney.

15 M.A. Aldred, unpublished data.
or promoter methylation were identified in tumors with LOH of this region and no mutations or microdeletions were identified in our wider tumor panel. We therefore focused on miR-562, a microRNA that lies within intron 9 of DIS3L2. microRNAs are a group of noncoding ~22-nucleotide RNA molecules that post-transcriptionally regulate the expression of target mRNAs (45). These small RNAs are evolutionarily conserved and regulate processes as fundamental as cellular proliferation, differentiation, and apoptosis. It is increasingly recognized that dysregulation of microRNAs plays an important role in cancer (46, 47).

miR-562 showed a tissue-restricted expression pattern, strongest in fetal kidney. Real-time PCR analysis showed a significant reduction in Wilms’ tumors compared with normal kidney and suggested that tumors may stratify into two groups based on miR-562 expression level. Clinical data do not suggest a correlation with therapy response, histology, or survival between these two groups, but complete data were only available for 6 of the 12 cases where expression analysis was done, so no firm conclusions can be drawn. A polymorphic deletion of miR-562 was identified, which probably does not represent a major predisposing factor in the etiology of Wilms’ tumor but could potentially increase susceptibility to Wilms’ tumor in the presence of additional mutations. Decreased miR-562 expression was also observed in 8 of 11 tumors with no deletion. This suggests that miR-562 is frequently downregulated at the transcriptional level perhaps due to mutations of its promoter. In general, microRNAs residing in introns are coexpressed with their “parent” gene, presumably directed by that gene’s promoter (48), whereas miR-562 expression is apparently independent of the DIS3L2 promoter (data not shown). miR-562 is believed to be derived from a transposable element (49) and its expression may therefore be regulated by its own transposon-derived transcription machinery or by another locus. Defining the promoter for miR-562 will be important in further examining its regulation and its role in normal kidney development and Wilms’ tumor.

**Fig. 4.** miR-562 regulates EYA1 expression in vitro. A luciferase reporter construct containing the putative EYA1 3’-untranslated region binding site for miR-562 was transfected into 293T cells. Relative luciferase activity was measured after 48 h. Luciferase activity in the presence of three different concentrations of miR-562 was significantly reduced compared with empty vector (pMIR-REPORT), indicating transcriptional downregulation of EYA1 by miR-562. This was reversed by addition of anti-miR-562 competitor, confirming specificity of the response. Bars, SD from three independent experiments.

**Fig. 5.** EYA1 is overexpressed in Wilms’ tumor. Expression of EYA1 was determined by quantitative real-time PCR and normalized to GAPDH. NK, normal adjacent kidney from Wilms’ tumor patients; 08-03XX samples are Wilms’ tumors; *, a Wilms’ tumor heterozygous for the miR-562 deletion polymorphism; †, Wilms’ tumor samples with 2q copy neutral LOH. Bars, SE. EYA1 is significantly overexpressed in all tumors compared with normal kidney. However, there was no clear inverse correlation with miR-562 expression, suggesting that multiple factors contribute to the regulation of EYA1.

EYA1, a gene essential for cell survival and proliferation in early metanephenic development (50, 51), was validated as a target of miR-562. We confirmed that EYA1 was significantly overexpressed in Wilms’ tumors (30), suggesting that haploinsufficiency of miR-562 is likely one factor that contributes to increased EYA1 expression in Wilms’ tumors. Given that we did not see a strong inverse correlation between these two transcripts, it is clear that other genetic events also influence EYA1 expression. Notably, the gene is located on chromosome 8, the gain of which is observed in up to 30% of Wilms’ tumors (27). Downregulation of miR-562 in conjunction with gain of chromosome 8 would therefore be predicted to result in synergistic overexpression of EYA1.

In summary, we have shown LOH at 2q37 in at least 4% of sporadic Wilms’ tumors. Identification of two tumors with homozygous deletions strongly suggests the presence of a Wilms’ tumor suppressor gene at 2q37.1. Expression of miR-562, a microRNA within this region, is significantly reduced in Wilms’ tumors even in the absence of LOH or other detectable abnormality of the microRNA sequence. We showed that EYA1, which is overexpressed in Wilms’ tumors, is a target of miR-562, suggesting that haploinsufficiency of miR-562 contributes to the etiology of Wilms’ tumor by promoting deregulation of EYA1. Further study of the role of miR-562 in normal renal development and Wilms’ tumor is hampered by the fact it is primate-specific and no orthologue is present in model organisms such as mouse or zebrafish. Clinically though, our data may be helpful in clarifying the risk of Wilms’ tumor in children diagnosed with a constitutional 2q37 deletion. Our results from sporadic Wilms’ tumors are broadly concordant with published data on constitutional breakpoints: deletion patients who developed Wilms’ tumor had breakpoints in 2q37.1, whereas the majority of patients with no malignancy have smaller deletions encompassing only 2q37.2-4.37. Some caution is still required, because we identified two regions of uncertain significance at 2q37.3 in sporadic Wilms’ tumors, but
overall our data suggest that any increased risk for developing Wilms' tumor likely correlates with deletions encompassing 2q37.1.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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