Published in final edited form as:

Cancer Res. 2008 April 15; 68(8): 2551–2556. doi:10.1158/0008-5472.CAN-07-2095.

The Quest for the *1p36* Tumor Suppressor

Anindya Bagchi and Alea A. Mills*

Cold Spring Harbor Laboratory One Bungtown Road Cold Spring Harbor, NY 11724

Abstract

Genomic analyses of late-stage human cancers have uncovered deletions encompassing *1p36*, thereby providing an extensive body of literature supporting the idea that a potent tumor suppressor resides in this interval. Although a number of genes have been proposed as *1p36* candidate tumor suppressors, convincing evidence that their encoded products protect from cancer has been scanty. A recent functional study identified *CHD5* as a novel tumor suppressor mapping to *1p36*. Here we discuss evidence supporting *CHD5*'s tumor suppressive role. Together, these findings suggest that strategies designed to enhance *CHD5* activity could provide novel approaches for treating a broad range of human malignancies.

Keywords

1p36; *CHD5*; chromosome engineering; p53; *Ink4/Arf*

Introduction

Deletions of the short arm of human chromosome 1 were first reported in neuroblastoma in 1977 (1), presaging a flurry of reports indicating that the region referred to as *1p36* is frequently deleted in a broad range of human cancers including those of neural-, epithelial-, and hematopoietic origin (2–22) (fig 1). These findings suggest that loss of a tumor suppressor mapping to this region is a critical event in tumorigenesis. Since such a diverse array of human cancers have been associated with deletion of *1p36*, loss or inactivation of this region might be a common initiating event for a number of malignancies. The search for the *1p36* tumor suppressor has led to some exciting candidates (fig 1). While some of these proposed tumor suppressors have tumor protective capabilities in specific cellular contexts, none can account for the wide range of tumor types that have been associated with the three decades of literature documenting *1p36* deletions. Hence, the search for the *1p36* tumor suppressor has continued.

Why has it been so difficult to identify the tumor suppressor in this region of the genome? One reason could be that more than one *1p36* tumor suppressor exists. Support for this idea is that although the prevalence of tumor-derived deletions attests to *1p36* loss as being an important event in cancer, these deletions do not always overlap and therefore fail to identify a single genomic interval (fig 1). Perhaps distinct tumor suppressors function tissue-specifically; this might be the reason that the various malignancies in which *1p36* deletions have been documented cannot be explained by any of the individual candidate tumor suppressors described to date. A feature of most late-stage tumors with *1p36* deletions is that the interval involved is typically extremely large, often encompassing the entire short arm; therefore, informative tumors that might reveal the location of the tumor suppressor and lead to its identity are rare. One idea is that *1p36* is inherently unstable. Another possibility is that several *1p36*

*To whom correspondence should be addressed: Alea A. Mills, Ph.D., (516) 367-6910, mills@cshl.edu.

tumor suppressors work together, and therefore that loss of a combination of these genes is a prerequisite for cancer. Since hereditary cancer predisposition syndromes do not exist for this genomic region, linkage-based methodologies that were so crucial for discovering tumor suppressors such as retinoblastoma are not helpful for identifying tumor suppressors in this interval. In short, *Ip36* has presented a major challenge for the cancer community.

Pinpointing the tumor suppressive region

The underlying assumption for the approach that we took was that there was a region of *Ip36* that when deleted, would predispose to cancer. Therefore, increased tumorigenicity would provide the functional readout needed to reveal the location of the tumor suppressor. Chromosome engineering, a Cre/*loxP*-based methodology (23) reviewed in (24), was used to systematically delete regions of the mouse genome corresponding to human *Ip36* (25). This seemed a logical approach since genes are conserved between mouse and man in this region of the genome, with genes present on human *Ip36* mapping to distal mouse chromosome 4 (fig 2). This strategy identified a tumor suppressive interval that when deleted caused enhanced proliferation, loss of contact inhibition, and spontaneous immortalization in cultured cells—hallmarks of increased tumorigenic potential. These cellular phenotypes culminated as cancer *in vivo*; mice heterozygous for this deletion developed spontaneous tumors, including many types associated with deletion of the corresponding region in humans. Further functional evidence that this region harbored a potent tumor suppressor was garnered when it was discovered that mice engineered to have an extra copy of this region had excessive tumor suppression. Three copies of this interval caused an increase in the tumor suppressive mechanisms of cellular senescence in cultured cells, and markedly enhanced apoptosis *in vivo*. This combined loss- and gain-of-function approach identified a potent tumor suppressive region corresponding to human *Ip36*.

Identifying the tumor suppressor in the interval

Although a tumor suppressive region of mouse chromosome 4 had been identified, this genomic interval was 4.3 megabases [Mb] and encompassed 52 genes (25). Therefore, the next phase of this work was to identify the tumor suppressor in the interval. It had been shown that cells with an extra copy of the region proliferated very poorly in culture, and that this proliferative defect was rescued by “correcting” dosage of the interval i.e. cells with an extra copy of the region on one chromosome and a deletion of the same interval on the other chromosome were effectively diploid for that region. Mice carrying both a deletion and a duplication of the 4.3 Mb interval were viable and fertile, and cells from these animals proliferated at rates comparable to those of wild type cells. Therefore, Occam’s razor—the principle that the simplest solution is usually the best one—posed the possibility that cells with an extra copy of the region proliferated poorly because they had increased expression of *a single gene* within the interval. This meant that the tumor suppressor could be identified by systematically reducing expression of candidate genes in cells with an extra copy of the interval. The assay was simply looking for *the* gene that restored proliferation when its dosage was reduced. Genes were prioritized based on gene ontology terms, and RNAi was then used to reduce expression of the top candidates in the region (25). Knockdown of all but one gene tested failed to rescue the proliferative defect. For example, knockdown of *p73*, *Dnajc11*, and *Camta1*, genes within the interval that had previously been proposed as *Ip36* tumor suppressor candidates, failed to enhance proliferation, thereby excluding these genes as being responsible for the tumor suppressive phenotypes observed. In contrast, two different hairpins against Chromodomain helicase DNA-binding protein 5 (*Chd5*) effectively restored proliferation to these poorly proliferating cells, and even enhanced proliferation of wild type cells. This identified *Chd5* as the tumor suppressor candidate in the region.

CHD5 is a proposed chromatin remodeller

Human CHD5 had previously been proposed to function as a chromatin remodeling protein based on its homology with members of the chromodomain superfamily of proteins (26). CHD5 is one of nine members of the CHD family, named because of its unique combination of Chromo (*chromatin organizing modulator*)-, Helicase-, and DNA binding domains. The CHD family can be further subdivided; CHD5 is similar to CHD3 and CHD4 in that it is endowed with *plant homeodomain* (PHD) motifs (27). Interestingly, CHD3 and CHD4 are components of the nucleosome remodelling complex, an assembly of proteins that remodels chromatin by sliding nucleosomes out of the way, thereby providing polymerase with the access needed to activate gene expression. Other than this homology between CHD5 and previously described chromatin remodeling proteins, very little functional data existed for this protein. How might this hypothesized chromatin remodeling protein function to prevent cancer?

Chd5 is a master regulator of a tumor suppressive network

1. The tumor suppressive region modulates p16^{Ink4a}/Rb- and p19^{Arf}/p53-mediated pathways—To explore the mechanism whereby Chd5 protects from tumorigenesis, models with loss- and gain of the region encompassing *Chd5* were first examined (25). The first clue was that the phenotypes of poor proliferation, enhanced cellular senescence and augmented apoptosis that were caused by just one extra copy of the 4.3 Mb interval were dependent upon p53. When p53 was reduced, either by RNAi-mediated knockdown in cultured cells or by germline deficiency *in vivo*, the phenotypes of exacerbated tumor suppression disappeared completely; cells proliferated normally or mice were viable and fertile. This demonstrated that the tumor suppressor in the region positively regulated p53.

An important advantage of the chromosome engineering approach is that the consequence of gain- and loss of the same genomic interval can be directly compared and contrasted (24). Therefore, the phenotypes resulting from incremental changes in dosage (0-, 1-, 2-, 3-, and 4 copies) can be analyzed—something that cannot be easily done using conventional mouse models. Since an extra copy of the region encompassing *Chd5* intensified p53 function, it was predicted that cells with the corresponding deletion would have compromised p53 (25). Cells with the deficiency expressed reduced p53 at the protein- (but not the transcript-) level, demonstrating that the tumor suppressor was regulating p53 post-transcriptionally. Despite this reduction in p53 expression, cells heterozygous for the deficiency were as efficient as wild type cells in their ability to induce p53 in response to DNA damage, indicating that DNA damage-induced pathways upstream of p53 were intact. This suggested that oncogene-induced pathways that mediate p53 function were compromised by deletion. Indeed, cells heterozygous for the 4.3 Mb region were susceptible to transformation by oncogenic Ras, further substantiating their p53-compromised status.

Having implicated p53 in the tumor suppressive effect, the mechanism whereby p53 was regulated was next explored (25). Since deficiency cells were sensitized to oncogenic transformation and oncogenic stimuli is known to function through p19^{Arf} (28), we asked whether p19^{Arf} was compromised when the tumor suppressive region was deleted. Indeed, compared to wild type cells, p19^{Arf} expression was reduced at both the transcript- and the protein level in cells with the deficiency, but was expressed more highly in cells with an extra copy of this interval. Furthermore, p19^{Arf} depletion significantly enhanced proliferation of cells with an extra copy of the region, and both the extent and time course of rescue by p19^{Arf} reduction was essentially identical to that caused by depletion of Chd5 itself. This clearly implicated a second tumor suppressor—p19^{Arf}—in the tumor suppressive phenotype.

p19^{Arf} is encoded by the *Ink4/Arf* locus, which also encodes a distinct tumor suppressor: p16^{Ink4a}. As was the case for p19^{Arf}, p16^{Ink4a} was compromised at both the transcript- and the

protein level in cells with the deletion but was expressed at higher levels in cells with an extra copy of this region (25). But in contrast with the ability of p19^{Arf} depletion to restore proliferation in cells with three copies of the interval, p16^{Ink4a} depletion caused only a modest increase in proliferation that was not statistically significant. This indicated that in the context of these cultured cells, the phenotype caused by an extra copy of the region was dependent on p19^{Arf}, whereas p16^{Ink4a} was dispensable. Since p19^{Arf} inhibits Mdm-2-mediated degradation of p53, the finding that p19^{Arf} expression correlated with dosage of the tumor suppressive interval provided a mechanistic explanation for how p53 was being modulated.

2. Chd5 depletion phenocopies deletion of the tumor suppressive interval—The chromosome engineering strategy provided a powerful approach for functionally mapping the tumor suppressive region. But because the rearrangement encompassed a large interval (hence allowing the interrogation of multiple loci simultaneously), it was important to determine which of the genes were responsible for the observed phenotype. In this study, it was essential to demonstrate that Chd5 depletion alone accounted for the phenotype characteristic of the 52-gene deletion (25). Importantly, for every assay performed, wild type primary cells in which Chd5 was knocked down closely phenocopied cells with an engineered heterozygous deficiency of the 4.3 Mb region encompassing *Chd5*. For example, Chd5-compromised cells had reduced expression of p16^{Ink4a}, p19^{Arf}, and p53, and expression levels correlated closely with those of cells heterozygous for the deficiency. The finding that both p16^{Ink4a} and p19^{Arf} were co-suppressed by heterozygous deficiency of the interval encompassing *Chd5* was consistent with the view that Chd5 is a chromatin remodeling protein that mediates expression of the *Ink4/Arf* locus.

The consequence of crippling the tumor suppressive network in cultured cells was enhanced proliferation and susceptibility to oncogenic transformation, with the phenotype of wild type cells in which Chd5 was specifically knocked down closely paralleling that of cells heterozygous for the engineered deficiency. Heterozygosity of the 4.3 Mb region predisposed to spontaneous tumors. To conclusively demonstrate that Chd5 deficiency was responsible for this tumor-prone phenotype, wild type cells in which Chd5 had been depleted were compared to cells with the deletion for their ability to form tumors in the context of activated Ras *in vivo*. This analysis revealed that cells in which Chd5 was specifically knocked down were as tumorigenic as cells with the heterozygous deficiency: tumors grew with the same kinetics and had indistinguishable histopathology. These findings provided genetic and molecular evidence that *Chd5* was the gene within the region that was responsible for tumor suppression.

Since *Chd5* could account for each of the tumor suppressive properties analyzed, it is likely that *Chd5* is the sole tumor suppressor within the 4.3 Mb interval. Although it cannot be excluded that other genes in the region affect aspects of tumorigenesis not assessed in this study (e. g. angiogenesis, metastasis, or as yet undiscovered mechanisms of tumor suppression), it is clear that Chd5 deficiency is an initiating event in tumorigenesis because 1) heterozygosity of the region encompassing *Chd5* predisposes to spontaneous tumors, and 2) specific depletion of Chd5 cooperates with activated oncogenes to enhance tumor growth in nude mice. Despite these lines of evidence, it will be imperative to assess spontaneous tumorigenesis in *Chd5* heterozygous null mice, as well as to determine whether gain of Chd5 function invokes the tumor suppressive mechanisms of senescence and apoptosis. These approaches will conclusively determine whether Chd5 is solely responsible for the phenotypes caused by loss and gain, respectively, of the 52-gene interval.

CHD5 is frequently deleted/mutated in human cancer

Identification of *Chd5* as a tumor suppressor in the mouse is in agreement with the rich body of literature describing *1p36* deletions in human cancer; many of these encompass *CHD5* (2–

22) (see fig 1). Our analyses revealed that *CHD5* was frequently deleted in human glioma (25), and more recent reports found that *CHD5* was deleted in leukemia/lymphoma (29) and neuroblastoma (30) (see fig 2). The Brodeur group used expression analyses to prioritize between candidate genes mapping to a 2.2 Mb minimally common region of deletion (mcr) that they identified in neuroblastoma, and concluded that *CHD5* was the strongest candidate in the interval (30). Maser and colleagues identified an mcr encompassing *Chd5* in a mouse model of chromosomally unstable lymphoma, and also demonstrated that *CHD5* is one of only three genes mapping to an mcr that they discovered in human T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) (29). Furthermore, mutation of *CHD5* was recently reported in human breast cancer (31) and neuroblastoma (30). Combined, these studies define an mcr that not only includes *CHD5*, but excludes nearby tumor suppressor candidates such as *p73*, *Icat*, and *Riz1* (see figs 1 & 2). Similarly, these analyses exclude *miR34*, a micro RNA that was recently reported as being regulated by p53 (reviewed in (32)). It should be emphasized that while this demonstrates that these loci are not responsible for the tumor suppressive phenotypes addressed in these particular studies (25,29–31), it does not eliminate the possibility that these genes contribute to carcinogenesis in other cellular contexts or cooperate with *CHD5* in a manner that has not been revealed to date. Together, these findings support *CHD5*'s tumor suppressive role, leading to a number of important questions.

Do multiple *1p36* tumor suppressors exist?

The observation that *1p36* deletions are typically very large has led to the speculation that more than one tumor suppressor resides in this region. Although there is substantial support for the tumor suppressive role of *CHD5*, these studies do not exclude the possibility that additional *1p36* tumor suppressors exist. It should be noted that the 5.7 Mb interval that functionally identified *CHD5* as a tumor suppressor comprises less than one quarter of the 24.9 Mb *1p36* region (see fig 2) (25). Therefore, additional tumor suppressors may map to the portions of *1p36* that were not studied. Indeed, mcr's in several hematopoietic malignancies do not encompass *CHD5* (see fig 1). Although this does not support *CHD5* deficiency as being a causal event in these cancers, the finding that mice heterozygous for the 4.3 Mb interval encompassing *Chd5* are prone to spontaneous lymphoma (25) and an independent report that *Chd5* and *CHD5* are deleted in lymphoid cancers of mouse and man, respectively (29), provide evidence that *CHD5* deficiency plays a key role in these hematopoietic malignancies. Generation of a series of chromosome engineered deletion/duplication mouse models that in sum span the entire region corresponding to human *1p36* could be used to functionally address the issue of whether or not additional *1p36* tumor suppressors exist. Another approach would be to more fully evaluate spontaneous tumorigenesis in *Chd5*-compromised mice, and to compare these tumors to those associated with *1p36* deletions in humans. Can loss of the region encompassing *Chd5* account for each of the tumor types that have been associated with *1p36* deletion? Mice heterozygous for the engineered deletion develop lymphoma and squamous cell carcinoma, two of the three major tumor types in which *1p36* deletions have been reported. While *CHD5* loss has been documented in human glioma (25) and neuroblastoma (30) neural-associated malignancies have not yet been reported in mice heterozygous for the deficiency. Whether neural tumors develop in *Chd5* compromised mouse models warrants further investigation. Approaches that directly assay for cooperation between *CHD5* and previously reported *1p36* candidate tumor suppressors may also be used to test the idea that multiple tumor suppressors reside in this region of the genome.

Is complete loss/inactivation of *CHD5* a prerequisite for tumorigenesis?

Although it is clear that heterozygous deletions encompassing *CHD5/Chd5* predispose to cancer, there is currently no evidence that the remaining wild type *Chd5* allele is lost or mutated in the tumors that develop. In the small number of tumors analyzed to date in mice with a deficiency encompassing *Chd5*, as well as in cells from these mice that spontaneously

immortalize, the *Chd5* allele is retained, suggesting that complete loss of *Chd5* is not a prerequisite for tumorigenesis (25). This idea is consistent with results of an independent study in human neuroblastoma (30). In addition, *CHD5* mutations in human breast cancer (31) and in neuroblastoma (30) are heterozygous, with the wild type *CHD5* allele being retained. *CHD5* status needs to be examined in additional types of human cancers to more fully appreciate the scope of *CHD5* loss in various malignancies and to assess whether retention of the wild type *CHD5* locus is cancer-specific. This endeavor could be guided by the spontaneous tumor spectrum of mice with compromised *Chd5*, especially given the recent report that modeling cancer in the mouse can accurately reflect genomic alterations in human cancer (29). *CHD5* expression should be examined at the protein level to determine whether the CpG-rich *CHD5* promoter is silenced by methylation. If it holds that *CHD5* function is partially retained, this would represent a paradigm shift in the current view of carcinogenesis. Perhaps this would provide an explanation for why studies relying on complete loss as a criterion for tumor suppressors did not identify *CHD5*.

How do tumor-derived mutations affect *CHD5* function?

Although mutation of one copy of *CHD5* accompanies tumorigenesis (30,31), it is not currently known whether these mutations are driver mutations, or whether they are passenger mutations that simply reflect the genomic instability of end-stage cancers. It is not immediately apparent how these tumor-derived mutations thwart *CHD5*'s tumor suppressive function, as the affected amino acids are not within any of the known functional domains. Do these mutations affect *Chd5*'s ability to epigenetically regulate expression of the *Ink4/Arf* locus? Although *Chd5* is proposed to function as a chromatin remodeling protein, there is currently no functional evidence that it directly binds to- or modulates *Ink4/Arf*. Assessing the motifs of *CHD5* required for tumor suppression and elucidating the biochemical properties of *CHD5* may provide a foundation for designing strategies for effectively modulating its tumor suppressive function.

What additional genomic lesions cooperate with *CHD5* deficiency?

Although heterozygosity of *CHD5* predisposes to cancer, additional cooperating events undoubtedly contribute to this process. *Chd5* facilitates both p16^{Ink4a}/Rb- and p19^{Arf}/p53-mediated pathways (25). Although p16^{Ink4a} is dispensable for regulating proliferation in the context of cultured cells, it is intriguing that the very first tumor observed in mice heterozygous for the deficiency was a squamous cell carcinoma of the skin—a tumor type that does not develop in p53-compromised mouse models. Therefore, it is likely that p16^{Ink4a}/Rb-mediated pathways impact the tumor suppressive effects of *Chd5 in vivo*. *Chd5*'s ability to modulate the *Ink4/Arf* locus was evident because *Chd5*-compromised cells were sensitized to oncogenic transformation. However, it is likely that *Chd5* regulates chromatin structure globally, as was elegantly demonstrated for Bmi-1 (33). Therefore, additional genes that are modulated by *Chd5* could be discovered using a combination of expression- and chromatin immunoprecipitation microarrays using cells/tissues with altered dosage of *Chd5*. We propose that a partial crippling of this tumor suppressive network culminates in cancer, and predict that combined heterozygosity of *Chd5* and other members of the tumor suppressive network that is modulated by *Chd5* leads to carcinogenesis. This hypothesis can be directly tested by assessing whether loss or inactivation of *Chd5* cooperates with a compromise in p16^{Ink4a}/Rb- and p19^{Arf}/Rb-mediated pathways, or in combination with compromised function of additional members of the *Chd5*-modulated network that are yet to be discovered. Additionally, in light of the observation that *Chd5* deficiency renders cells sensitive to oncogenic transformation and that *Ip36* deletions in neuroblastoma frequently have amplification of N-MYC, it will be important to assess whether *CHD5* deficiency cooperates with activated oncogenes in human cancer.

Closing

The above findings represent the initial stages of investigating the role of CHD5 in cancer. It will be important to assess the role of CHD5 in diverse types of human cancer and to more fully elucidate the mechanism by which the tumor suppressive effects are thwarted. In addition, biochemical studies designed to interrogate the mechanistic basis of CHD5's tumor suppressive role are needed. Finally, it will be important to determine whether this chromatin remodeling protein affects gene expression globally. These studies are likely to have a significant impact on our understanding of tumorigenesis that could ultimately pave the way for better cancer diagnostics and pharmaceuticals.

Acknowledgments

We thank Hannes Vogel, Markus Bredel, and Cristian Papazoglu for contributing to the work discussed in this review.

References

1. Brodeur GM, Sekhon G, Goldstein MN. Chromosomal aberrations in human neuroblastomas. *Cancer* 1977;40:2256–2263. [PubMed: 922665]
2. Moley JF, Brother MB, Fong CT, White PS, Baylin SB, Nelkin B, Wells SA, Brodeur GM. Consistent association of 1p loss of heterozygosity with pheochromocytomas from patients with multiple endocrine neoplasia type 2 syndromes. *Cancer Res* 1992;52:770–774. [PubMed: 1346584]
3. Mulligan LM, Gardner E, Smith BA, Mathew CG, Ponder BA. Genetic events in tumour initiation and progression in multiple endocrine neoplasia type 2. *Genes Chromosomes Cancer* 1993;6:166–177. [PubMed: 7682102]
4. Bieche I, Champeme MH, Matifas F, Cropp CS, Callahan R, Lidereau R. Two distinct regions involved in 1p deletion in human primary breast cancer. *Cancer Research* 1993;53:1990–1994. [PubMed: 8097672]
5. White PS, Maris JM, Beltinger C, Sulman E, Marshall HN, Fujimori M, Kaufman BA, Biegel JA, Allen C, Hilliard C, et al. *Proc Natl Acad Sci U S A* 1995;92:5520–5524. [PubMed: 7777541]
6. Mori N, Morosetti R, Spira S, Lee S, Ben-Yehuda D, Schiller G, Landolfi R, Mizoguchi H, Koeffler HP. Chromosome band 1p36 contains a putative tumor suppressor gene important in the evolution of chronic myelocytic leukemia. *Blood* 1998;92:3405–3409. [PubMed: 9787180]
7. Bieche I, Khodja A, Lidereau R. Deletion mapping of chromosomal region 1p32-pter in primary breast cancer. *Genes Chromosomes Cancer* 1999;24:255–263. [PubMed: 10451706]
8. Kleer CG, Bryant BR, Giordano TJ, Sobel M, Merino MJ. Genetic Changes in Chromosomes 1p and 17p in Thyroid Cancer Progression. *Endocr Pathol* 2000;11:137–143. [PubMed: 12114819]
9. Caron H, Spieker N, Godfried M, Veenstra M, van Sluis P, de Kraker J, Voute P, Versteeg R. Chromosome bands 1p35–36 contain two distinct neuroblastoma tumor suppressor loci, one of which is imprinted. *Genes Chromosomes Cancer* 2001;30:168–174. [PubMed: 11135433]
10. Godfried MB, Veenstra M, Valent A, Sluis P, Voute PA, Versteeg R, Caron HN. Lack of interstitial chromosome 1p deletions in clinically-detected neuroblastoma. *Eur J Cancer* 2002;38:1513–1519. [PubMed: 12110498]
11. Edstrom Elder E, Nord B, Carling T, Juhlin C, Backdahl M, Hoog A, Larsson C. Loss of heterozygosity on the short arm of chromosome 1 in pheochromocytoma and abdominal paraganglioma. *World J Surg* 2002;26:965–971. [PubMed: 12045857]
12. Melendez B, Cuadros M, Robledo M, Rivas C, Fernandez-Piqueras J, Martinez-Delgado B, Benitez J. Coincidental LOH regions in mouse and humans: evidence for novel tumor suppressor loci at 9q22–q34 in non-Hodgkin's lymphomas. *Leuk Res* 2003;27:627–633. [PubMed: 12681362]
13. Mori N, Morosetti R, Mizoguchi H, Koeffler HP. Progression of myelodysplastic syndrome: allelic loss on chromosomal arm 1p. *Br J Haematol* 2003;122:226–230. [PubMed: 12846890]
14. Poetsch M, Dittberner T, Woenckhaus C. Microsatellite analysis at 1p36.3 in malignant melanoma of the skin: fine mapping in search of a possible tumour suppressor gene region. *Melanoma Res* 2003;13:29–33. [PubMed: 12569282]

15. Dong Z, Pang JS, Ng MH, Poon WS, Zhou L, Ng HK. Identification of two contiguous minimally deleted regions on chromosome 1p36.31–p36.32 in oligodendroglial tumours. *Br J Cancer* 2004;91:1105–1111. [PubMed: 15475940]
16. Felsberg J, Erkwow A, Sabel MC, Kirsch L, Fimmers R, Blaschke B, Schlegel U, Schramm J, Wiestler OD, Reifenberger G. Oligodendroglial tumors: refinement of candidate regions on chromosome arm 1p and correlation of 1p/19q status with survival. *Brain Pathol* 2004;14:121–130. [PubMed: 15193024]
17. Zhou CZ, Qiu GQ, Zhang F, He L, Peng ZH. Loss of heterozygosity on chromosome 1 in sporadic colorectal carcinoma. *World J Gastroenterol* 2004;10:1431–1435. [PubMed: 15133848]
18. Barbashina V, Salazar P, Holland EC, Rosenblum MK, Ladanyi M. Allelic losses at 1p36 and 19q13 in gliomas: correlation with histologic classification, definition of a 150-kb minimal deleted region on 1p36, and evaluation of CAMTA1 as a candidate tumor suppressor gene. *Clin Cancer Res* 2005;11:1119–1128. [PubMed: 15709179]
19. White PS, Thompson PM, Gotoh T, Okawa ER, Igarashi J, Kok M, Winter C, Gregory SG, Hogarty MD, Maris JM, Brodeur GM. Definition and characterization of a region of 1p36.3 consistently deleted in neuroblastoma. *Oncogene* 2005;24:2684–2694. [PubMed: 15829979]
20. Cheung TH, Lo KW, Yim SF, Poon CS, Cheung AY, Chung TK, Wong YF. Clinicopathologic significance of loss of heterozygosity on chromosome 1 in cervical cancer. *Gynecol Oncol* 2005;96:510–515. [PubMed: 15661244]
21. Piaskowski S, Rieske P, Szybka M, Wozniak K, Bednarek A, Pluciennik E, Jaskolski D, Sikorska B, Liberski PP. GADD45A and EPB41 as tumor suppressor genes in meningioma pathogenesis. *Cancer Genet Cytogenet* 2005;162:63–67. [PubMed: 16157202]
22. Aarts M, Dannenberg H, deLeeuw RJ, van Nederveen FH, Verhofstad AA, Lenders JW, Dinjens WN, Speel EJ, Lam WL, de Krijger RR. Microarray-based CGH of sporadic and syndrome-related pheochromocytomas using a 0.1–0.2 Mb bacterial artificial chromosome array spanning chromosome arm 1p. *Genes Chromosomes Cancer* 2006;45:83–93. [PubMed: 16215979]
23. Ramirez-Solis R, Liu P, Bradley A. Chromosome engineering in mice. *Nature* 1995;378:720–724. [PubMed: 7501018]
24. Mills, AAaBA. From mouse to man: generating megabase chromosome rearrangements. *Trends in Genetics* 2001;17:331–339. [PubMed: 11377795]
25. Bagchi A, Papazoglu C, Wu Y, Capurso D, Brodt M, Francis D, Bredel M, Vogel H, Mills AA. CHD5 Is a Tumor Suppressor at Human 1p36. *Cell* 2007;128:459–475. [PubMed: 17289567]
26. Thompson PM, Gotoh T, Kok M, White PS, Brodeur GM. CHD5, a new member of the chromodomain gene family, is preferentially expressed in the nervous system. *Oncogene* 2003;22:1002–1011. [PubMed: 12592387]
27. Marfella CG, Imbalzano AN. The Chd family of chromatin remodelers. *Mutat Res* 2007;618:30–40. [PubMed: 17350655]
28. Lowe SW, Sherr CJ. Tumor suppression by Ink4a-Arf: progress and puzzles. *Curr Opin Genet Dev* 2003;13:77–83. [PubMed: 12573439]
29. Maser RS, Choudhury B, Campbell PJ, Feng B, Wong KK, Protopopov A, O'Neil J, Gutierrez A, Ivanova E, Perna I, Lin E, Mani V, Jiang S, McNamara K, Zaghlul S, Edkins S, Stevens C, Brennan C, Martin ES, Wiedemeyer R, Kabbarah O, Nogueira C, Histen G, Aster J, Mansour M, Duke V, Feroni L, Fielding AK, Goldstone AH, Rowe JM, Wang YA, Look AT, Stratton MR, Chin L, Futreal PA, DePinho RA. Chromosomally unstable mouse tumours have genomic alterations similar to diverse human cancers. *Nature* 2007;447:966–971. [PubMed: 17515920]
30. Okawa ER, Gotoh T, Manne J, Igarashi J, Fujita T, Silverman KA, Xhao H, Mosse YP, White PS, Brodeur GM. Expression and sequence analysis of candidates for the 1p36.31 tumor suppressor gene deleted in neuroblastomas. *Oncogene*. 2007
31. Sjoblom T, Jones S, Wood LD, Parsons DW, Lin J, Barber TD, Mandelker D, Leary RJ, Ptak J, Silliman N, Szabo S, Buckhaults P, Farrell C, Meeh P, Markowitz SD, Willis J, Dawson D, Willson JK, Gazdar AF, Hartigan J, Wu L, Liu C, Parmigiani G, Park BH, Bachman KE, Papadopoulos N, Vogelstein B, Kinzler KW, Velculescu VE. The consensus coding sequences of human breast and colorectal cancers. *Science* 2006;314:268–274. [PubMed: 16959974]

32. He L, He X, Lowe SW, Hannon GJ. microRNAs join the p53 network--another piece in the tumour-suppression puzzle. *Nat Rev Cancer* 2007;7:819–822. [PubMed: 17914404]
33. Bracken AP, Dietrich N, Pasini D, Hansen KH, Helin K. Genome-wide mapping of Polycomb target genes unravels their roles in cell fate transitions. *Genes Dev* 2006;20:1123–1136. [PubMed: 16618801]

Figure 1. *1p36* is deleted in a variety of human cancers
The distal portion of the short arm of human chromosome 1 is shown, with the 24.9 Mb *1p36* region depicted by a gray rectangle. A subset of deletions that have been reported in a variety of epithelial- (green), neural associated- (blue), and lymphoid (red) malignancies are shown to scale. A number of *1p36* tumor suppressors have been proposed. Many of the deletions encompass *CHD5* (dotted line), whereas others are clearly in distinct regions of *1p36*.

Figure 2. A number of independent studies support a tumor suppressive role for CHD5

Genes mapping to *1p36* (upper panel) are contained within a conserved linkage group on distal mouse chromosome 4 (lower panel). Mouse models with gain- and loss of a 4.3 Mb region of mouse chromosome 4 identify a potent tumor suppressive region corresponding to a 5.7 Mb region of human *1p36*; this overlaps with a 5.4 Mb mcr in human glioma (green) (25). A more recent study identifies a 2.1 Mb mcr in neuroblastoma (red) (30). An independent study identifies a 3.9 Mb mcr in a genomically unstable mouse model of lymphoma, and also identifies a 0.34 Mb mcr in human T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) (blue) (29). Combined, these studies identify a 2.5 Mb and a 0.34 Mb mcr in mouse and humans that encompass *Chd5* and *CHD5*, respectively (arrows). Note that neither *p73* nor *miR34* map within the mcr. In addition, *CHD5* is mutated in both glioma (red asterisk) (30) and breast cancer (orange asterisks) (31). Each asterisk depicts a distinct mutation.