et al., 2002). No mutations in p38α have been reported in primary tumors; the presence of three other p38 MAPK genes could compensate for any partial loss of function of p38α.

The successful creation of a tumor requires that the apoptotic and antiproliferative effects of p38 MAPK must be suppressed. Dolado et al. propose that one mechanism employed by tumor cells to overcome the tumor-suppressive function of p38 MAPK is to uncouple the production of ROS from p38 MAPK activation. The increased expression of GSTm proteins (Gstm1 and GSTm2) observed in tumor cells may serve this function. Dolado et al. show that reduced expression of GSTm2 in MCF7 breast cancer cells increased p38 MAPK activity and apoptosis, whereas forced overexpression of GSTm2 further potentiated the transformed phenotype. Since GSTm proteins can inhibit the ASK1/p38 pathway, these data are compelling. However, it is unclear if the overexpression of GSTm proteins in these cancer cells is a cause of or a result of transformation or if the increased levels reflect responses to tumor treatment or passage in tissue culture. Nevertheless, proteins that serve as sensors for ROS levels (e.g., GSTm1/2) and other proteins that attenuate the p38 MAPK pathway (e.g., WIP1) represent candidate drug targets for the design of new therapies for cancer.

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Ten Genes for Inherited Breast Cancer

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DOI 10.1016/j.ccr.2007.01.010

Inherited breast cancer is associated with germline mutations in ten different genes in pathways critical to genomic integrity. *BRCA1* and *BRCA2* mutations confer very high risks of breast and ovarian cancer. *p53* and *PTEN* mutations lead to very high breast cancer risks associated with rare cancer syndromes. Mutations in *CHEK2*, *ATM*, *NBS1*, *RAD50*, *BRIP1*, and *PALB2* are associated with doubling of breast cancer risks. In addition, biallelic mutations in *BRCA2*, *BRIP1*, and *PALB2* cause Fanconi anemia. The convergence of these genes in a shared role reveals underlying biology of these illnesses and suggests still other breast cancer genes.

Fanconi anemia (FA) is a recessive syndrome characterized by chromosomal instability, congenital malformations, progressive bone marrow failure, and hypersensitivity to DNA crosslinking agents (Taniguchi and D'Andrea, 2006). The genes responsible for 11 of the 12 FA complementation groups (A, B, C, D1, D2, E, F, G, I, J, L, and M) have been identified. Eight FA proteins form a complex that activates FANCD2 via monoubiquitination (Figure 1). Monoubiquitinated FANCD2 then translocates to damage-induced nuclear foci containing BRCA1, BRCA2, and RAD51, allowing recognition and repair of DNA interstrand crosslinks. Biallelic mutations in *BRCA2* cause a rare and highly cancer-prone form of FA (FA-D1) (Howlett et al., 2002), and biallelic mutations in the DNA helicase *BRIP1* cause FA-J (Litman et al., 2005). BRCA2 and BRIP1 function downstream of the FANCD2 activation step.

Biallelic mutations in *PALB2*, the "partner and localizer of BRCA2," are responsible for a new FA complementation group, FA-N (Xia et al., 2006a; Reid et al., 2006). PALB2 was originally identified in a screen for proteins present in complexes containing BRCA2 (Xia et al., 2006b). PALB2 binds to the extreme N terminus of BRCA2 and stabilizes BRCA2 in key nuclear structures, allowing it to function in DNA repair and at the S phase checkpoint. Decrease of

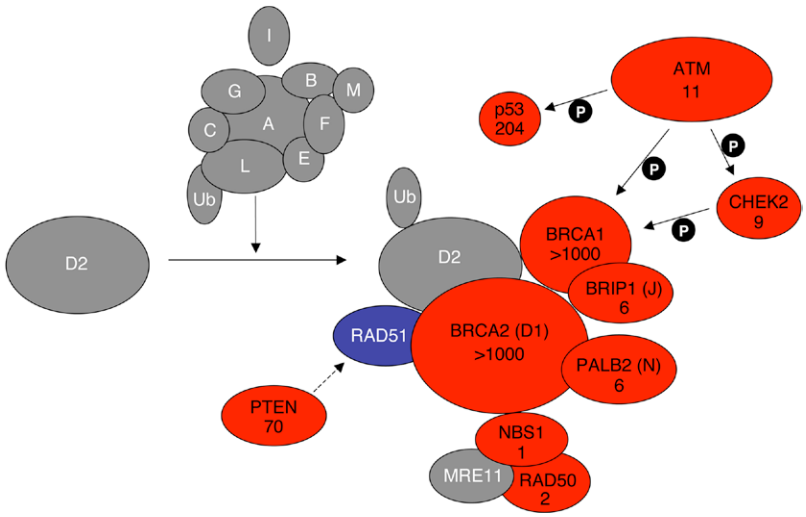

Figure 1. Interactions of Proteins Associated with Inherited Breast Cancer and with Fanconi Anemia

A complex of eight Fanconi proteins (A, B, C, E, F, G, L, and M) activates FANCD2 via monoubiquitination, allowing FANCD2 to translocate to damage-induced nuclear foci that contain BRCA1, BRCA2, and RAD51. DNA damage activates ATM and CHEK2, which in turn activate BRCA1 by phosphorylation. PTEN binds to the Rad51 promoter and may regulate its transcription (Shen et al., 2007). Proteins indicated in red carry germline mutations that predispose to breast cancer. The numbers indicate different breast-cancer-associated mutations identified thus far in each gene. A germline variant in the promoter of Rad51 (blue) may modify breast cancer risk in BRCA2 mutation carriers (Levy-Lahad et al., 2001).

PALB2 expression in HeLa cells by siRNAs leads to mitomycin C sensitivity, which causes interstrand crosslinking and eventually double-strand breaks. Mitomycin C sensitivity is a hallmark of Fanconi anemia.

Reid and colleagues identified biallelic protein-truncating mutations in *PALB2* in 7 of 82 individuals with FA not due to known genes (Reid et al., 2006). In a lymphoblastoid line from one patient with two such mutations, transfection of wild-type PALB2 reversed sensitivity to mitomycin C. All seven individuals with FA-N developed cancer as children; six of the seven patients died before age 4.

Xia and colleagues evaluated one FA patient with normal monoubiquitination of FANCD2 and wild-type sequences of *BRCA2* and *BRIP1* (Xia et al., 2006a). This patient carried a premature truncation in exon 4 of *PALB2* inherited from the mother and a complete deletion of *PALB2* inherited from the father. A subline of the patient's lymphoblasts developed MMC resistance, that is, became a phenotypic revertant. Genomic analysis of this line revealed an Alu-mediated deletion of exon 4 that contains the premature truncation, creating an in-frame mRNA with exon 3 spliced to exon 5.

The cellular and cancer phenotypes of patients with biallelic *BRCA2* mutations and of patients with biallelic *PALB2* mutations are quite similar. Heterozygosity for mutations in *BRCA2* are associated with very high risk of breast cancer. Is it possible that heterozygosity for mutations in *PALB2* also increase risk of breast cancer?

Rahman and colleagues sequenced the 13 coding exons of *PALB2* in DNA from 923 familial breast cancer patients with wild-type sequences at *BRCA1* and *BRCA2* (Rahman et al., 2006). Five different truncating mutations of *PALB2* were identified in ten patients (1% of the series; two of the five mutations were also observed in the FA-N families described above). No truncating mutations of *PALB2* appeared in 1084 control individuals. The relative risk of breast cancer associated with *PALB2* was estimated at 2.3 (3.0 for women younger than 50 years and 1.9 for women older than 50 years).

Erkko and colleagues sequenced *PALB2* in DNA from 113 families from northern Finland with breast and ovarian cancer, identifying a premature truncation in three families (Erkko et al., 2007). Further genotyping revealed the allele in 18 of 1918 (0.9%) breast cancer cases not selected for family history from the northern Finland population and 6 of 2501 (0.2%) controls, consistent with a 2- to 4-fold increased risk to mutation carriers.

PALB2 is a new addition to the growing list of genes associated with approximately 2-fold increased risk of breast cancer. *CHEK2* was the first gene of this type described. Truncating allele 1100delC of *CHEK2* was identified through a combined linkage and candidate gene approach in a single severely affected breast cancer family (Meijers-Heijboer et al., 2002). This allele has a frequency of 0.002–0.005 in northern Europe populations and confers an approximately 2-fold increased risk of breast cancer. Other *CHEK2* mutations have been subsequently associated with similarly increased risk of breast cancer (Walsh et al., 2006). In *NBS1*, a rare protein-truncating allele first identified in Polish breast cancer patients is associated with approximately 2-fold increased risk. Rare mutations of *BRIP1* (FA-J) were also identified in breast cancer families (Seal et al., 2006). Heterozygous carriers of ATM mutations have long been suspected of having increased risk of breast cancer. Recent comprehensive sequencing of ATM in 434 familial breast cancer patients revealed seven protein-truncating alleles, two splice mutations, and two missense alleles (one of which appeared in two families) experimentally verified to affect ATM function. In contrast, only two ATM sequence variants were found in 521 controls (Renwick et al., 2006). Finally, a protein-truncating allele of *RAD50* identified in northern Finland conferred an approximate 4-fold increased risk of breast cancer (Heikkinen et al., 2006). In each of these genes, more mutations are likely to be found: more populations will be analyzed, genomic rearrangements will be evaluated, and a larger subset of missense alterations will be validated by functional assays.

These ten genes share two important features in their impact on breast cancer. (1) A single deleterious mutation in any one of them is sufficient to

significantly increase breast cancer risk. (2) There are many deleterious mutations, and each mutation is individually rare. That is, for none of these genes (individually or in combination) does increased risk of breast cancer result from additive effects of multiple common alleles, each of small influence. Inherited breast cancer is highly genetically heterogeneous with respect to both loci and alleles involved. All evidence to date is that the model that best reflects this heterogeneity is not a "common disease-common allele" model, but instead a "common disease-multiple rare alleles" model.

The ten known genes for inherited breast cancer function in a pathway whose role is to preserve genomic integrity. Roughly 50% of familial breast cancer remains unresolved by any of these genes. Clearly other genes in this pathway are worthy of in-depth genomic analysis in unresolved families. Furthermore, in thus far unrecognized members of this pathway, mutations may also be associated with inherited breast cancer.

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Wilms Tumor Genetics: A New, UnX-pected Twist to the Story

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DOI 10.1016/j.ccr.2007.01.011

The study of the genetics of Wilms tumor has led to several highly unexpected and precedent-establishing discoveries. Ironically, however, the identification of "WT genes" has been painfully slow, and gene mutations have been identified in only ~25% of tumors. The discovery of an X chromosome gene, *WTX*, that is mutated somatically in ~30% of Wilms tumors is notable both for helping to explain the genetic etiology of a substantial proportion of tumors and also for underscoring the role that X chromosome genes can play in cancer genetics.

Wilms tumor (WT) is a childhood embryonal cancer of the kidney. Unlike most tumors, Wilms tumors generally exhibit few, if any, chromosomal abnormalities, and therefore WT was originally thought to represent a simple model for studying the genetic etiology of cancer. WT genetics, however, has turned out to be anything but simple; the road to identifying and understanding "WT genes" has been littered with false leads and dashed