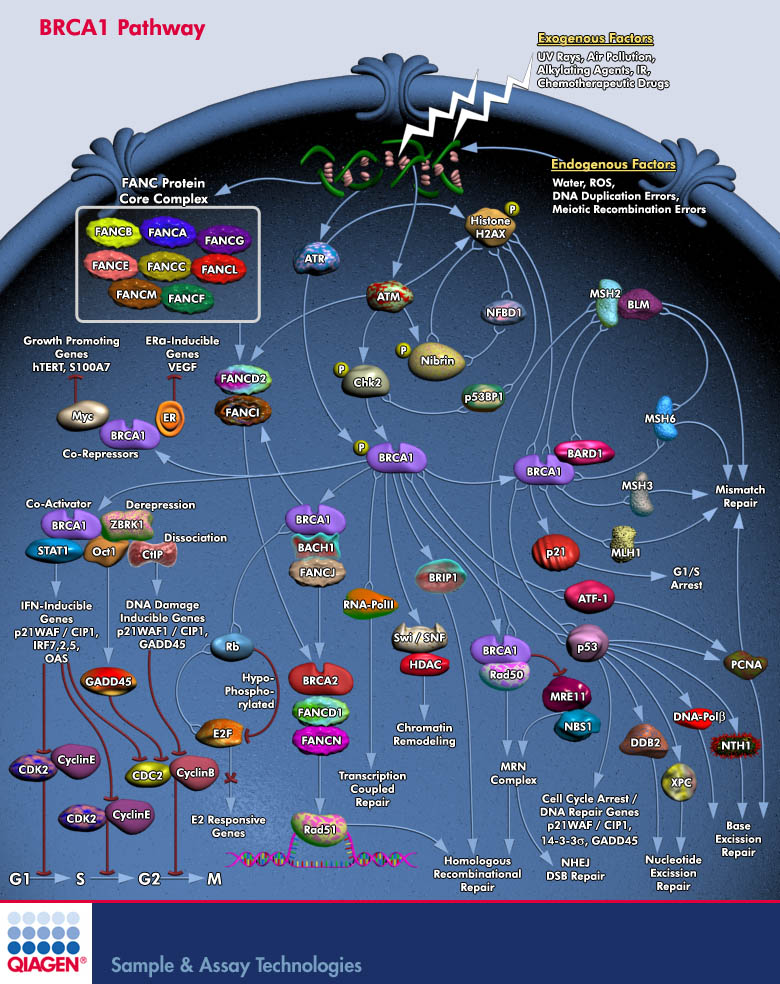
BRCA1 Pathway



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BRCA1 Pathway

The maintenance of genome integrity is essential to all life, but is particularly important to long-lived multicellular organisms, which are susceptible to cancer. DNA damage can take the form of base modifications, strand breaks, interstrand cross-links and other lesions. These requirements imply that signaling networks not only sense the presence of DNA damage, but also receive specific input such as the chemical nature of the damage, the timing of the cell cycle, the type of cell and the location of damage on the DNA. BASC (BRCA1-Associated Genome Surveillance Complex), a super complex of [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) (Breast Cancer Susceptibility Protein-1), is key to recognizing and repairing DNA damage. This complex includes tumor suppressors and DNA damage repair proteins [MSH2](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000251), [MSH6](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000179), [MLH1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000249), [ATM](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000051) (Ataxia-Telangiectasia), [BLM](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000057) (Bloom syndrome), and the [Rad50](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_005732)-[MRE11](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_005590) (Meiotic Recombination-11)-[NBS1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_002485) (Nijmegen Breakage Syndrome) protein complex. In addition, RFC (DNA Replication Factor-C), a protein complex that facilitates the loading of [PCNA](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_002592) onto DNA, is also part of BASC (Ref.1 and 2). Eleven or more genetically distinct groups of FA have been described ([FANCA](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000135) , [FANCB](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001018113), [FANCC](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000136), [FANCD1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000059), [FANCD2](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001018115), [FANCG](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_004629), [FANCE](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_021922), [FANCF](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_022725) and [FANCL](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001114636)), each caused by recessive mutations in a different gene. DNA damage activates the monoubiquitylation of [FANCD2](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001018115) (Fanconi Anemia subtype D2 protein), which is targeted to subnuclear foci, where it co-localizes with [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) and [Rad51](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001164269) (Ref.3 4, 5 and 6). Five of the proteins ([FANCA](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000135), [FANCC](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000136), [FANCE](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_021922), [FANCF](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_022725) and [FANCG](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_004629)) assemble in a multisubunit nuclear complex required for the activation of [FANCD2](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001018115) to a monoubiquitinated isoform (FANCD2-Ub), either in response to DNA damage or during S-Phase of the Cell Cycle, thereby targeting [FANCD2](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001018115) to DNA repair nuclear foci containing [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294), [BRCA2](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000059) and[Rad51](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001164269), which are important in maintaining genomic stability by promoting homologous recombination repair (Ref.7).[BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) is a nuclear phosphoprotein, which interacts with [Rad51](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001164269), a human homolog of [RecA](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001164269), and with the [Rad50](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_005732)-[MRE11](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_005590)-[NBS1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_002485) complex. In living cells, [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) exists mostly as a heterodimeric complex with [BARD1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000465) (BRCA1-Associated RING Domain-1). [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294)-[BARD1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000465) co-localizes with DNA replication and repair factors in response to DNA damage. [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294)-[BARD1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000465) heterodimers exhibit significant E3 Ub Ligase activity and the [BARD1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000465) RING finger domain greatly potentiates the Ligase activity of the [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) RING finger (Ref.8). The [ATM](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000051) and [ATR](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001184) (ATM and Rad3 related) kinases, both implicated in responses to genotoxic stress, are also involved for the radiation-induced phosphorylation of[BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) (Ref.9). Normally, [ATM](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000051) phosphorylates [Chk2](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001005735) (Chk1 Checkpoint Homolog), which in turn phosphorylates[BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294). The ring finger of [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) confers ubiquitin ligase activity that is markedly enhanced when complexed with another ring-containing protein, [BARD1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000465) (BRCA1 Associated Ring Domain-1), and is required for the function of this tumor suppressor protein in protecting genomic integrity (Ref.10). [ATR](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001184) and [ATM](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000051) kinase targets also include repair enzymes like[Rad51](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001164269), [Chk1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001114121) and [Chk2](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001005735). In response to ionizing radiation, [ATM](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000051) phosphorylates NBS1 leading to phosphorylation of[FANCD2](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001018115) and the establishment of an S-Phase checkpoint response, and in response to Mitomycin-C or Hydroxyurea, NBS1 assembles in nuclear foci with [MRE11](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_005590)-[Rad50](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_005732) and [FANCD2](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001018115). Like [ATM](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000051), the MRE11 complex is a crucial upstream regulator of checkpoint responses and DNA-repair responses in all eukaryotic cells. The MRE11 complex assembles with[BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) in nuclear foci following DNA damage and regulate homologous recombination repair (Ref.11). [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) induces[GADD45](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001924,NM_015675,NM_006705), a [p53](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000546)-regulated and stress-inducible gene that plays an important role in cellular response to DNA damage.[BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) activation of the [GADD45](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001924,NM_015675,NM_006705) promoter is mediated through the [OCT1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001198783) and CAAT motifs located at the [GADD45](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001924,NM_015675,NM_006705)promoter region (Ref.12). [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) can trigger a G1 arrest that is mediated by transcriptional activation of [p21Waf1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000389)/[Cip1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000389). In addition to its association with holoenzyme, [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) can bind to several different transcription factors, including [p53](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000546),[Myc](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_002467), [STAT1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007315), and [CtIP](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_002894) (CBP-Interacting Protein) (Ref.13). [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) acts in concert with [STAT1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007315) to differentially activate transcription of a subset of [IFN-Gamma](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000619) target genes and mediates growth inhibition by this cytokine. [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) also binds preferentially to the hypophosphorylated form of [Rb](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000321) (Retinoblastoma Protein) .DNA repair by homologous recombination is mediated by the [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294)-associated surveillance complex (comprised of [BLM](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000057), [MSH2](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000251)[MSH6](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_000179) and[MRE11](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_005590)[Rad50](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_005732)[NBS1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_002485)). [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) can form complexes with both [BACH1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001186) and [SWI/SNF](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001282874) to mediate chromatin remodeling and homologous recombination. HDACs regulate the access of the [SWI/SNF](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001282874)[BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) complex to DNA. Finally, [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294)interacts with [Chk1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001114121) and [PLK1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_005030) (Polo-Like Kinase-1) to regulate the G2/M and G1/S checkpoints, possibly via [GADD45](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_001924,NM_015675,NM_006705); thereby linking [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) to the regulation of apoptosis (Ref.14). [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) is a tumor suppressor gene implicated in the predisposition to early onset breast and ovarian cancer. Several functions have also been ascribed to [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) including double strand DNA break repair, participating in genome surveillance, transcription-coupled DNA repair, transcriptional regulation, chromatin remodeling, and ubiquitin ligation and cell cycle checkpoint arrests. In cells, loss of [BRCA1](https://www.qiagen.com/us/products/genes%20and%20pathways/pathway%20details.aspx?pathwayID=68&ID=NM_007294) function leads to spontaneous chromosome breakage and sensitivity to DNA damage (Ref.15).

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