SECOND EDITION
DNA Repair and Mutagenesis
For Rhonda, Jan, Jenny, Enid, Lisa, and Mary
About the Authors

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It has been a decade since the publication of the first edition of *DNA Repair and Mutagenesis*. It was noted in the preface then that “[I]n very recent times, progress in the DNA repair and mutagenesis fields has been particularly rapid. . . .” In fact, in recognition of the importance of mutagenesis as a fundamental aspect of DNA metabolism and the impressive gains made in our understanding of the intricate relationships between DNA repair and mutagenesis, the authors of the first edition elaborated the title *DNA Repair* used for the book published by W. H. Freeman in 1984.

The unabated progress of the DNA damage response field is reflected in further major changes in the present edition. The field has progressed to the point that a comprehensive treatment of the manifold responses to DNA damage (including sensing and signaling the presence of damage and other perturbations of DNA metabolism) now requires the efforts of an author group with expertise in multiple and diverse areas. Richard D. (Rick) Wood and Roger A. Schultz were invited to provide such expertise to bolster the team that wrote the first edition. Additionally, the inclusion of structural biologist Tom Ellenberger reflects our desire to incorporate the considerable recent contributions of protein structure to biology in general and the DNA repair field in particular. The six authors have labored to achieve a text that is seamlessly integrated.

The second edition of *DNA Repair and Mutagenesis* was initiated in late 1999. Our efforts to keep the final product manageable for the average reader notwithstanding, the size of the present work appropriately reflects the substantial growth of the field in the past decade. This edition is more a rewriting than a revision, and little of the text from the first edition remains. The first edition of *DNA Repair and Mutagenesis* comprised 14 chapters and contained about 400 illustrations. The present edition consists of 30 chapters divided into five major sections, and the text is adorned with more than 700 illustrations, including more than 80 structural representations. Additionally, more than ten thousand primary literature references are provided in full, reflecting the massive increase in the scientific literature through 2004.

We have strived to present readers with a comprehensive survey of the field, stressing basic principles wherever feasible but mainly describing the extensive progress achieved to date and highlighting the many problems remaining to be solved. We trust that our desire to represent the dynamic state of this active field of research will not hinder the primary educational purpose of this book, a basic text for advanced undergraduate and graduate students and a reference source for all students of DNA metabolism.

As was the case in the first edition, we have continued to present the field in a historical context, with the intent of sensitizing and inspiring students (and others) to the realities of how research progress unfolds and how ideas develop and attain maturity—or not. We have refrained
wherever possible from unadulterated dogma and from presenting the field of biological responses to DNA damage as anywhere near total clarification. While we are aware of presenting viewpoints that are sometimes controversial and even conflicting, we trust that readers, especially students, are not unduly confused or frustrated by our reluctance to always provide the final word, as it were. Rather, it is our hope that such controversies and complexities will inspire further studies.

The names of genes and their polypeptide products sometimes change with good reason as more is known about them and the families they belong to. Additionally, the value and utility of long-standing terminology are often challenged by new information. A textbook provides a valuable opportunity to address such revisions, and we have done so in some areas. However, we have consciously retained much original nomenclature in deference to historic recognition and popular usage.

No work of this sort can come to fruition without special assistance at every level. We owe an enormous debt of gratitude to many individuals for the help they have provided at every level of this labor. We have enjoyed scientific dialogues with an outstanding cadre of professional colleagues who have given unstintingly of their time, energy, and knowledge to review and discuss every chapter with us. In this respect, we owe particular thanks to Rafael Alvarez-Gonzalez, Carl Anderson, Daniel Bogenhagen, Rhona Borts, Vilhelm Bohr, Anne Casper, Stuart Clarkson, James Cleaver, Nils Confer, Richard Cunningham, Bruce Demple, Friederike Eckardt-Schupp, Andre Eker, Paula Fischhaber, Ann Ganesan, Myron Goodman, Thomas Glover, Philip Hanawalt, Ian Hickson, Peggy Hsieh, Sue Jinks-Robertson, Caroline Kisker, Beate Köberle, Nicole Kosarek, Y. W. Kow, Kenneth Kraemer, Susan LeDoux, Alan Lehmann, Michael Lieber, Tomas Lindahl, Sue Lovett, Carolina Marchetto, Lisa McDaniel, M. Stephen Meyn, Paul Modrich, Harvey Mohrenweiser, Robb Moses, Laura Niedernhofer, Shwetal Patel, Tony Pegg, Dean Rupp, Aziz Sancar, Gwen Sancar, Barbara Sedgwick, the late Erling Seeberg, Mutsuo Sekiguchi, Michael Smerdon, Kendric Smith, Robert Sobol, David Stern, James Stivers, John Tainer, Gail Thomlinson, Takeshi Todo, Bennett van Houten, Harry van Steeg, Greg Verdine, Zhigang Wang, Bernard Weiss, Dale Wigley, Sam Wilson, Birgitte Wittschien, John Wittschien, Roger Woodgate, and Akira Yasui. Final responsibility naturally rests with us, and we apologize for any inaccuracies and omissions that remain in this publication. Readers are encouraged to inform us of these if and when they are discovered.

We particularly wish to acknowledge the outstanding artistic talent and the dedication and commitment of Marty Burgin, who also worked as illustrator for the first edition. This book is as much hers as ours. We are also extremely grateful to Patrick Lane, whose technological wizardry solved tricky problems in the rendering of crystal structures in shades of just two colors. We thank Jeff Holtmeier of ASM Press for providing his strong personal commitment and that of his staff throughout the production of this work. The magnificent job of editing of the manuscript by Yvonne Strong merits special mention. Thanks are also due to Susan Birch, Production Manager at ASM Press, and to Cathy Balogh and Susan Schmidler.

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Over the course of many meetings, most of which took place over weekends, as well as innumerable phone calls and e-mails, each of us came to know and respect our fellow authors from unique perspectives. We are unanimous in our view that the camaraderie and friendships forged through these meetings have enormously enriched our lives, not to mention our taste in fine beverages and the musical pursuits of some of us—such as they are!

Errol C. Friedberg
Graham C. Walker
Wolffram Siede
Richard D. Wood
Roger A. Schultz
Tom Ellenberger
December 2004
Abbreviations

This text employs many standard (and some not so standard) abbreviations. In an effort to reduce confusion for the reader, abbreviations are spelled out in full when first employed in each chapter. Additionally, the following list includes the abbreviations most frequently used.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAF</td>
<td>Acetylamino-fluorine</td>
</tr>
<tr>
<td>ALL</td>
<td>Acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>AML</td>
<td>Acute myeloid leukemia</td>
</tr>
<tr>
<td>AT</td>
<td>Ataxia telangiectasia</td>
</tr>
<tr>
<td>BER</td>
<td>Base excision repair</td>
</tr>
<tr>
<td>BIR</td>
<td>Break-induced replication</td>
</tr>
<tr>
<td>BPDE</td>
<td>Benzo[a]pyrene-diol-epoxide</td>
</tr>
<tr>
<td>BrdU</td>
<td>5-Bromodeoxyuridine</td>
</tr>
<tr>
<td>BrU</td>
<td>5-Bromouracil</td>
</tr>
<tr>
<td>BS</td>
<td>Bloom syndrome</td>
</tr>
<tr>
<td>CHO</td>
<td>Chinese hamster ovary</td>
</tr>
<tr>
<td>CPD</td>
<td>Cyclobutane pyrimidine dimer(s)</td>
</tr>
<tr>
<td>CS</td>
<td>Cockayne syndrome</td>
</tr>
<tr>
<td>dNTP</td>
<td>Deoxyribonucleoside triphosphate(s)</td>
</tr>
<tr>
<td>DSB</td>
<td>Double-strand break(s)</td>
</tr>
<tr>
<td>dsDNA</td>
<td>Double-stranded DNA</td>
</tr>
<tr>
<td>EMS</td>
<td>Ethyl methanesulfonate</td>
</tr>
<tr>
<td>ESS</td>
<td>Enzyme-sensitive site(s)</td>
</tr>
<tr>
<td>FA</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>FdU</td>
<td>5-Fluorodeoxyuridine</td>
</tr>
<tr>
<td>GFP</td>
<td>Green fluorescent protein</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray</td>
</tr>
<tr>
<td>HNPCCC</td>
<td>Hereditary nonpolyposis colon cancer</td>
</tr>
<tr>
<td>HR</td>
<td>Homologous recombination</td>
</tr>
<tr>
<td>HU</td>
<td>Hydroxyurea</td>
</tr>
<tr>
<td>ICL</td>
<td>Interstrand cross-link(s)</td>
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<tr>
<td>IR</td>
<td>Ionizing radiation</td>
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<tr>
<td>MEF</td>
<td>Mouse embryonic fibroblast(s)</td>
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<tr>
<td>MMC</td>
<td>Mitomycin C</td>
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<tr>
<td>MMR</td>
<td>Mismatch repair</td>
</tr>
<tr>
<td>MMS</td>
<td>Methyl methanesulfonate</td>
</tr>
<tr>
<td>MNase</td>
<td>Micrococcal nuclease</td>
</tr>
<tr>
<td>MSI</td>
<td>Microsatellite instability</td>
</tr>
<tr>
<td>NER</td>
<td>Nucleotide excision repair</td>
</tr>
<tr>
<td>NHEJ</td>
<td>Nonhomologous end joining</td>
</tr>
<tr>
<td>4-NQO</td>
<td>4-Nitroquinoline 1-oxide</td>
</tr>
<tr>
<td>NTP</td>
<td>Nucleoside triphosphate(s)</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>ORF</td>
<td>Open reading frame(s)</td>
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<tr>
<td>Pol</td>
<td>Polymerase</td>
</tr>
<tr>
<td>(6-4)PP</td>
<td>(6-4) photoproduct(s)</td>
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<tr>
<td>RNAPII</td>
<td>RNA polymerase II</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
</tr>
<tr>
<td>RR</td>
<td>Risk ratio</td>
</tr>
<tr>
<td>RS</td>
<td>Roberts syndrome</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Reverse transcription-polymerase chain reaction</td>
</tr>
<tr>
<td>SCE</td>
<td>Sister chromatid exchange(s)</td>
</tr>
<tr>
<td>SNP</td>
<td>Single-nucleotide polymorphism(s)</td>
</tr>
<tr>
<td>SSA</td>
<td>Single-strand annealing</td>
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<td>SSB</td>
<td>Single-strand break(s)</td>
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<td>ssDNA</td>
<td>Single-stranded DNA</td>
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<td>Trichothiodystrophy</td>
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<td>Werner syndrome</td>
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<td>XP</td>
<td>Xeroderma pigmentosum</td>
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## Appendix

**Table 1** Nomenclature of DNA repair genes

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<tr>
<th>Pathway</th>
<th>E. coli</th>
<th>S. cerevisiae</th>
<th>S. pombe</th>
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<th>Activity</th>
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<td><strong>Base excision repair (BER)</strong> DNA glycosylases</td>
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<td>ung1&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>UNG</td>
<td>U or hydroxymethyl U</td>
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<td>U or T opposite G at CpG sequences</td>
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<td>MBD4 (MED1)</td>
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<td>mag&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>thp1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Thd1</td>
<td>TDG</td>
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<td>U, T, or ethenoC opposite G</td>
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<td>fpg&lt;sup&gt;c&lt;/sup&gt; (mutM&lt;sup&gt;c&lt;/sup&gt;)</td>
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<td>Ring-saturated or fragmented pyrimidines</td>
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<td>alkA&lt;sup&gt;c&lt;/sup&gt;, tagA&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>NEIL3</td>
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<td>swi8&lt;sup&gt;+&lt;/sup&gt;</td>
<td>spell (spellchecker1)</td>
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<td>ercc3sp&lt;sup&gt;+&lt;/sup&gt;</td>
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<td>XPB (ERCC3)</td>
<td>3&lt;sup&gt;’&lt;/sup&gt;–to–5&lt;sup&gt;’&lt;/sup&gt; DNA helicase TFIH subunit</td>
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<td>SSL2 (RAD25)</td>
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<td>3&lt;sup&gt;’&lt;/sup&gt;–to–5&lt;sup&gt;’&lt;/sup&gt; DNA helicase TFIH subunit</td>
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<td>rad13&lt;sup&gt;+&lt;/sup&gt;, mus201</td>
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<td>Branch migration of Holliday junctions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ruvC</td>
<td>(mus81-eme1)</td>
<td>—</td>
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<td>Nuclease to cleave Holliday junctions</td>
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(continued)
### Table 1  Nomenclature of DNA repair genes (continued)

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<tr>
<th>Pathway</th>
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<tr>
<td><strong>Nonhomologous end joining (NHEJ)</strong></td>
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<td>E. coli</td>
<td>S. cerevisiae</td>
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<tr>
<td>YKU70 (HDF1)</td>
<td>pku70&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>YKU80 (HDF2)</td>
<td>pku80&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
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</tr>
<tr>
<td><strong>Modulation of nucleotide pools</strong></td>
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</tr>
<tr>
<td>MutT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td>Dut&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
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<tr>
<td><strong>DNA polymerases (catalytic subunits)</strong></td>
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<tr>
<td>polB&lt;sup&gt;a&lt;/sup&gt; (dinA, pol II)</td>
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<tr>
<td></td>
<td>MIP1</td>
</tr>
<tr>
<td></td>
<td>CDC2 (POL3)</td>
</tr>
<tr>
<td></td>
<td>POL2</td>
</tr>
<tr>
<td></td>
<td>REV3</td>
</tr>
<tr>
<td></td>
<td>REV7</td>
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<td>REV1</td>
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<td>—</td>
</tr>
<tr>
<td></td>
<td>RAD30</td>
</tr>
<tr>
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<tr>
<td><strong>dinB&lt;sup&gt;a&lt;/sup&gt; (Pol IV)</strong></td>
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<tr>
<td></td>
<td>POL4</td>
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<td>POL5</td>
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<td><strong>DNA polymerase accessory factors</strong></td>
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<td>dnaN&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>dnaX&lt;sup&gt;a&lt;/sup&gt; (γ-δ) complex</td>
<td>CDC44</td>
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<tr>
<td><strong>Processing nucleases</strong></td>
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<tr>
<td>mus81&lt;sup&gt;+&lt;/sup&gt;</td>
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<td>eme1&lt;sup&gt;+&lt;/sup&gt;</td>
<td>MMS4</td>
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<tr>
<td>rad2&lt;sup&gt;a&lt;/sup&gt; (5’ to 3’ exo)</td>
<td>RAD27 (RTH1)</td>
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<td>TREX1 (Dnase III)</td>
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<td></td>
<td>TREX2</td>
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<tr>
<td>eso1&lt;sup&gt;+&lt;/sup&gt;, Exo1&lt;sup&gt;+&lt;/sup&gt;</td>
<td>EXO1</td>
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<sup>a</sup> Table continued on next page
Table 1 (continued)

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<th>Activity</th>
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<td>Recombination endonuclease</td>
<td>SPO11</td>
<td>—</td>
<td>meiW-68</td>
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<tr>
<td>Incision 3′ of hypoxanthine and uracil</td>
<td>nfi^+ (EndoV^+</td>
<td>—</td>
<td>SPAC1F12.06c</td>
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<td>ENDOV (FLJ35220)</td>
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<tr>
<td>E2 ubiquitin-conjugating enzyme</td>
<td>RAD6</td>
<td>Ubc6</td>
<td>UBE2A (RAD6A)</td>
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<td>UBE2B (RAD6B)</td>
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<tr>
<td>E2 ubiquitin-conjugating enzyme</td>
<td>RAD18</td>
<td>rhp18^+</td>
<td>RAD18</td>
<td>—</td>
<td>RING domain E3 ubiquitin ligase</td>
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<td>RING domain E3 ubiquitin ligase</td>
<td>HPR5 (SNR1, RADH)</td>
<td>sir2^+</td>
<td>RAD5 (SNM2, REV2)</td>
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<td>DNA helicase</td>
<td>MMS2</td>
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<td>UBE2V2 (MMS2)</td>
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<td>DNA helicase</td>
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<td>E2 ubiquitin-conjugating complex</td>
<td>UBC13</td>
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<td>UBE2N (UBC13, BTG1)</td>
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<td>E2 ubiquitin-conjugating complex</td>
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<td>Bloom syndrome helicase</td>
<td>recQ^+</td>
<td>SGS1</td>
<td>npl1^+ (hus1^+, rad12^+)</td>
<td>mus309</td>
<td>BLM</td>
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<td>Werner syndrome helicase / 3′-exonuclease</td>
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<td>CG7670 (exo only)</td>
<td>WRN</td>
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<td>Rothmund-Thomson syndrome</td>
<td>RecQ4</td>
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<td>RECQL4</td>
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<td>Ataxia telangiectasia</td>
<td>TEL1</td>
<td>tefu tel1^+</td>
<td>CG6535</td>
<td>ATM</td>
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<td>Ataxia-oculomotor apraxia syndrome (aprataxin; interaction with XRCC1, XRCC4)</td>
<td>HNT3</td>
<td>SPCC18.09c</td>
<td>CG3316</td>
<td>APTX</td>
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<td>Fanconi anemia gene</td>
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<td>—</td>
<td>FANCA</td>
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<td>Fanconi anemia gene</td>
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<td>—</td>
<td>—</td>
<td>FANCB</td>
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<td>Fanconi anemia gene</td>
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<td>Fanconi anemia gene</td>
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<td>FANCE</td>
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<td>Fanconi anemia gene</td>
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<td>FANCF</td>
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<td>Fanconi anemia gene</td>
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<td>—</td>
<td>—</td>
<td>FANCG (XRCC9)</td>
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<tr>
<td>Ubiquitin ligase for monoubiquitination of FANCD2</td>
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<td>—</td>
<td>—</td>
<td>CG12812</td>
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<td>Dna cross-link repair nuclease</td>
<td>PSO2 (SNM1)</td>
<td>mus322</td>
<td>DCLRE1A (PSO2, SNM1)</td>
<td>—</td>
<td>DNA cross-link repair nuclease</td>
<td></td>
</tr>
<tr>
<td>Related to SNM1</td>
<td>—</td>
<td>—</td>
<td>SNM1B (DCLRE1B)</td>
<td>—</td>
<td>Related to SNM1</td>
<td></td>
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<tr>
<td>Converts some DNA breaks to ligatable ends</td>
<td>—</td>
<td>—</td>
<td>PNKP (PNK)</td>
<td>—</td>
<td>Converts some DNA breaks to ligatable ends</td>
<td></td>
</tr>
<tr>
<td>Similar to helicase domain of Mus308</td>
<td>—</td>
<td>—</td>
<td>mus301 (spin-C)</td>
<td>HEL308</td>
<td></td>
<td></td>
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<tr>
<td>Histone, phosphorylated after DNA damage</td>
<td>H2A</td>
<td>hta1^+, hta2^+</td>
<td>His2av</td>
<td>H2AFX (H2AX)</td>
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<tr>
<td>Transcription factor and DNA binding</td>
<td>—</td>
<td>—</td>
<td>p53</td>
<td>p53 (TP53)</td>
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<td></td>
</tr>
<tr>
<td>ATM- and PI3K-like essential kinase</td>
<td>MEC1</td>
<td>rad3^+</td>
<td>mei-41</td>
<td>ATR</td>
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</table>

(continued)
Table 1  Nomenclature of DNA repair genes\(^a\) (continued)

<table>
<thead>
<tr>
<th>Pathway</th>
<th>E. coli</th>
<th>S. cerevisiae</th>
<th>S. pombe</th>
<th>Drosophila</th>
<th>Human</th>
<th>Activity</th>
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</thead>
<tbody>
<tr>
<td>LCD1 (DDC2)</td>
<td>rad26(^a)</td>
<td>mus304</td>
<td>ATRIP</td>
<td>ATR interacting</td>
<td></td>
<td></td>
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<tr>
<td>RAD17</td>
<td>rad1(^a)</td>
<td>rad1</td>
<td>RAD1</td>
<td>PCNA-like DNA damage sensor (9-1-1 complex)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDC1</td>
<td>rad9(^a)</td>
<td>rad9</td>
<td>RAD9</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MEC3</td>
<td>hus1(^a)</td>
<td>Hus1-like</td>
<td>HUS1</td>
<td></td>
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<tr>
<td>RAD24</td>
<td>rad17(^a)</td>
<td>Rad17</td>
<td>RAD17</td>
<td>RFC1-like DNA damage sensor</td>
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<tr>
<td>RAD9</td>
<td>crb2(^a) (rhp9(^a))</td>
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<td>Checkpoint function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHK1</td>
<td>chk1(^a) (rad27(^a))</td>
<td>grp (grapes)</td>
<td>CHEK1 (CHK1)</td>
<td>Effector kinase</td>
<td></td>
<td></td>
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<tr>
<td>RAD53</td>
<td>cds1(^a)</td>
<td>lok (loki)</td>
<td>CHK2 (CHEK2)</td>
<td>Effector kinase</td>
<td></td>
<td></td>
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</tbody>
</table>

\(^a\)Entries in Table 1 are organized according to DNA repair pathway, emphasizing functional orthologs. In many cases, but not all, these are also sequence or structural homologs. Caution is recommended in this respect, and the text should be consulted for details, together with public DNA sequence databases. For example, the major DNA glycosylase for removal of 7,8-dihydro-8-oxoquinine (8-oxoG) from DNA is encoded by fpg in Escherichia coli and OGG1 in human cells, but the two gene products are not related by amino acid sequence and do not fall into the same structural family. The symbol “\(^a\)” indicates that no ortholog is detected.

Some DNA repair genes play roles in more than one pathway but are listed here only once for simplicity. HUGO-approved gene names (http://www.gene.ucl.ac.uk/nomenclature) are presented in nearly all cases, with a few of the commonly used synonyms provided in parentheses. The name used most commonly in this book is usually presented first here. See also the table “Human DNA Repair Genes” (http://www.cgal.icnet.uk/DNA_Repair_Genes.html). For Drosophila, official gene names from http://flybase.bio.indiana.edu are used. For Schizosaccharomyces pombe, official gene names from http://www.genedb.org/genedb/pombe/index.jsp are used. For Saccharomyces cerevisiae, official gene names from http://www.yeastgenome.org/ are used. For E. coli, official gene names from http://www.ncbi.nlm.nih.gov/ are used.

\(^a\)Dashes indicate that no gene exists. Blank spaces indicate that the status is unknown.
### Table 2  Human hereditary diseases and defective cellular responses to DNA damage

**A. Human hereditary diseases with defective cellular responses to DNA damage**

<table>
<thead>
<tr>
<th>Human disease</th>
<th>Gene(s)</th>
<th>Principal defective response</th>
<th>Principal clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xeroderma pigmentosum (XP)</td>
<td>XPA–XPG; XPV</td>
<td>Nucleotide excision repair (NER); translesion DNA synthesis</td>
<td>Dermatitis, freckling, skin cancer, sometimes neurological defects</td>
</tr>
<tr>
<td>Cockayne syndrome (CS)</td>
<td>CSA, CSB</td>
<td>Transcription-coupled NER</td>
<td>Post-natal developmental defects, neurological defects</td>
</tr>
<tr>
<td>Combined XP/CS complex</td>
<td>XPB, XPD, XPG</td>
<td>NER and basal transcription by RNA polymerase II</td>
<td>Features of both XP and CS</td>
</tr>
<tr>
<td>Trichothiodystrophy (TTD)</td>
<td>XPB, XPD, TTDA</td>
<td>NER and basal transcription by RNA polymerase II</td>
<td>Photosensitivity, brittle hair, post-natal developmental defects, neurological defects</td>
</tr>
<tr>
<td>Cerebro-oculo-lacio-skeletal (COFS) syndrome</td>
<td>CSB</td>
<td>Transcription-coupled NER</td>
<td>Post-natal developmental defects, neurological defects</td>
</tr>
<tr>
<td>UV-sensitive (UV') syndrome</td>
<td>CSB</td>
<td>Transcription-coupled NER</td>
<td>Photosensitivity</td>
</tr>
<tr>
<td>Ataxia telangiectasia (AT)</td>
<td>ATM</td>
<td>Repair of DNA strand breaks</td>
<td>Cerebellar ataxia, defective immune function, neurological problems, predisposition to hematolymphoid cancer</td>
</tr>
<tr>
<td>Nijmegen breakage syndrome</td>
<td>NBS1</td>
<td>Repair of DNA strand breaks</td>
<td>Developmental abnormalities, growth retardation, cancer predisposition</td>
</tr>
<tr>
<td>AT-like disorder (ATLD)</td>
<td>MRE11A</td>
<td>Repair of DNA strand breaks</td>
<td>Defective immune function, neurological problems, predisposition to hematolymphoid cancer</td>
</tr>
<tr>
<td>LIG4 syndrome</td>
<td>LIG4</td>
<td>Repair of DNA strand breaks</td>
<td>Defective immune function, neurological problems, predisposition to hematolymphoid cancer</td>
</tr>
<tr>
<td>Seckel syndrome</td>
<td>ATR</td>
<td>Chromosome stability in response to specific treatments</td>
<td>Developmental, immunological, and hematolymphoid abnormalities</td>
</tr>
<tr>
<td>Severe combined immunodeficiency (SCID)</td>
<td>RAG1, RAG2, SNM1C (Artemis)</td>
<td>V(D)J recombination</td>
<td>Severe immunodeficiency</td>
</tr>
<tr>
<td>Spinocerebellar ataxia with axonal neuropathy (SCAN1)</td>
<td>TDP1</td>
<td>Processing of topoisomerase-DNA intermediates</td>
<td>Neurodegeneration</td>
</tr>
<tr>
<td>Ataxia-ocular apraxia 1 (AOA1)</td>
<td>APTX (Aprataxin)</td>
<td>None known; possibly double-strand break repair</td>
<td>Neurodegeneration</td>
</tr>
<tr>
<td>Bloom syndrome (BS)</td>
<td>BLM</td>
<td>Resolution of stalled replication/transcription intermediates</td>
<td>Dwarfism, immunodeficiency, cancer predisposition</td>
</tr>
<tr>
<td>Werner syndrome (WS)</td>
<td>WRN</td>
<td>Resolution of stalled replication/transcription intermediates</td>
<td>Premature aging, cancer predisposition</td>
</tr>
<tr>
<td>Rothmund-Thomson syndrome (RTS)</td>
<td>RECQL4</td>
<td>Resolution of stalled replication/transcription intermediates</td>
<td>Skin, hair, and skeletal abnormalities, cancer</td>
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</table>

(continued)
### Table 2  Human hereditary diseases with defective cellular responses to DNA damage (continued)

#### A. Human hereditary diseases and defective cellular responses to DNA damage (continued)

<table>
<thead>
<tr>
<th>Human disease</th>
<th>Gene(s)</th>
<th>Principal defective response</th>
<th>Principal clinical features</th>
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</thead>
<tbody>
<tr>
<td>RAPADILINO syndrome (RS)</td>
<td>RECQL4</td>
<td>Resolution of stalled replication/transcription intermediates</td>
<td>Skeletal abnormalities</td>
</tr>
<tr>
<td>46BR syndrome</td>
<td>LIG1</td>
<td>Modest chromosome instability</td>
<td>Immunodeficiency, cancer</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colon cancer</td>
<td>MLH1, MSH2, MSH6, PMS1, PMS2, MLH3, EXO1</td>
<td>Mismatch repair</td>
<td>Colon and other cancers</td>
</tr>
<tr>
<td>Fanconi anemia (FA)</td>
<td>FANCA, FANCB, FANCC, FANCD1, BRCA2, FANCD2, FANCE, FANCF, FANCG, FANC1, FANCI, FANCl</td>
<td>Chromosomal stability, spontaneous and in response to cross-linking agents</td>
<td>Limb defects, anemia, cancer disposition</td>
</tr>
<tr>
<td>Hyper-IgM syndrome</td>
<td>UNG</td>
<td>Removal of uracil during class switch recombination</td>
<td>Immune deficiency</td>
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#### B. Human hereditary diseases implicated in defective cellular responses to DNA damage

<table>
<thead>
<tr>
<th>Human disease</th>
<th>Gene(s)</th>
<th>Principal defective response</th>
<th>Principal clinical features</th>
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</thead>
<tbody>
<tr>
<td>Retinoblastoma (RB)</td>
<td>RB1</td>
<td>Cell cycle response to DNA damage</td>
<td>Retinoblastoma and other cancers</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome (LFS)</td>
<td>p53, CHEK2</td>
<td>Cell cycle response to DNA damage</td>
<td>Broad spectrum of cancer</td>
</tr>
<tr>
<td>Hereditary breast cancer</td>
<td>BRCA1, BRCA2</td>
<td>Cell cycle response to DNA damage</td>
<td>Breast and ovarian cancer</td>
</tr>
<tr>
<td>Familial adenomatous polyposis (FAP)</td>
<td>APC</td>
<td>Cell proliferation and chromosomal stability</td>
<td>Gastrointestinal cancer and thyroid cancer</td>
</tr>
<tr>
<td>MYH-associated polyposis (MAP)</td>
<td>MYH</td>
<td>None noted, despite mutations in a base excision repair gene</td>
<td>Gastrointestinal cancer</td>
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<tr>
<td>Juvenile polyposis syndrome (JPS)</td>
<td>SMAD4, BMPRIA</td>
<td>Cell-signaling and &quot;landscaper&quot; functions</td>
<td>Juvenile polyps and gastrointestinal malignancy</td>
</tr>
<tr>
<td>Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome</td>
<td>PTEN</td>
<td>Cell cycle responses and apoptosis (but not in response to DNA damage)</td>
<td>Breast, thyroid, and endometrial cancer</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome (PJS)</td>
<td>STK11</td>
<td>Cell cycle responses and apoptosis</td>
<td>Hamartomas, gastrointestinal and non-gastrointestinal tumors</td>
</tr>
<tr>
<td>Basal cell nevus syndrome (BCNS)</td>
<td>PTCH2</td>
<td>Cell-signaling pathways</td>
<td>Malignant melanoma</td>
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<tr>
<td>Cutaneous malignant melanoma</td>
<td>CDKN2A, CDK4</td>
<td>Cell cycle responses and apoptosis</td>
<td>Malignant melanoma</td>
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</tbody>
</table>
### Table 2 (continued)

**B. Human hereditary diseases implicated in defective cellular responses to DNA damage**

<table>
<thead>
<tr>
<th>Human disease</th>
<th>Gene(s)</th>
<th>Principal defective response</th>
<th>Principal clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilm's tumor (WT)</td>
<td><strong>WT1</strong></td>
<td>Transcriptional regulation</td>
<td>Pediatric kidney tumors</td>
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<tr>
<td>Hereditary papillary renal cell carcinoma (HPRCC)</td>
<td><strong>MET</strong></td>
<td>Cell signaling</td>
<td>Papillary renal cell carcinoma</td>
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<tr>
<td>von Hippel-Lindau (VHL)</td>
<td><strong>VHL</strong></td>
<td>Multiple associated functions, possibly defective in cell cycle regulation</td>
<td>Renal cell and other cancers</td>
</tr>
<tr>
<td>TSC Tuberous sclerosis complex</td>
<td><strong>TSC1, TSC2</strong></td>
<td>Cytoskeleton maintenance</td>
<td>Multiple hamartomas, renal cell cancer</td>
</tr>
<tr>
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