ANALYSIS

Transcriptional control of human p53-regulated genes

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Abstract | The p53 protein regulates the transcription of many different genes in response to a wide variety of stress signals. Following DNA damage, p53 regulates key processes, including DNA repair, cell-cycle arrest, senescence and apoptosis, in order to suppress cancer. This Analysis article provides an overview of the current knowledge of p53-regulated genes in these pathways and others, and the mechanisms of their regulation. In addition, we present the most comprehensive list so far of human p53-regulated genes and their experimentally validated, functional binding sites that confer p53 regulation.

Response element
A short sequence of DNA in or near a gene that can bind one or more transcription factors that can regulate the transcriptional activity of that gene.

Extracellular matrix
The complex, multi-molecular material that surrounds cells. It comprises a scaffold on which tissues are organized, provides cellular microenvironments and regulates various cellular functions.

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The p53 pathway responds to various cellular stress signals (the input) by activating p53 as a transcription factor (increasing its levels and protein modifications) and transcribing a programme of genes (the output) to accomplish a number of functions (FIG. 1). Together, these functions prevent errors in the duplication process of a cell that is under stress, and as such the p53 pathway increases the fidelity of cell division and prevents cancers from arising. The goals of this Analysis article are: first, to bring together as one source a list of p53-regulated genes and the criteria that permit this classification; second, to analyse the p53 response elements (REs) in DNA that bind the p53 protein and promote transcriptional control; third, to organize and explore the functions of the p53-regulated genes; and, finally, to review useful algorithms that can detect p53-regulated genes by their associated REs in DNA from various sources.

The purpose of this exercise is to amalgamate a large body of literature that has mostly been assembled one gene and one publication at a time. This has not permitted an appreciation of the cooperative and broad nature of the functions of many p53-regulated genes in altering the cell and the extracellular matrix, or the role of the p53 response in communicating with various organ systems of the body. There is good evidence that the nature of the stress signal and the cell type can both affect the modulation of the transcriptional pattern of p53-responsive genes that respond with a transcriptional programme[1,2]. Because we have imperfect information about cell and tissue types and the nature of the stress signal for every gene discussed here, we can provide only a broad overview of the transcriptional programme regulated by the p53 protein. Where detailed information is available about cell and tissue type, and the stress response, it will be discussed.

Criteria for p53-responsive genes

Four sets of experimental criteria have been used to identify a p53-regulated gene. The first is the presence of a p53 RE in the DNA close to or in the gene. The second is a demonstration that the gene is either upregulated or downregulated at the RNA and protein levels by the activated wild-type p53 protein (but not by the mutant protein). The third line of evidence is to clone the p53 RE from that gene, place it near a test gene, such as luciferase, and demonstrate that the p53 protein can regulate the test gene. The fourth approach is to use chromatin immunoprecipitation with a p53-specific antibody to demonstrate the presence of the p53 protein on the RE site in the DNA. In some cases, a gel-shift assay is also used to demonstrate that the p53 protein binds *in vitro* to the p53 RE sequence from that gene.

These criteria may be modified depending on the cell or tissue specificity of some p53-regulated genes or on the nature of the stress signal that the p53 pathway responds to. In this article we have included a list of p53-responsive genes that have met a minimum of three out of four of these criteria. On the basis of these criteria, Supplementary information S1 (table) and S2 (table) contain 129 genes and 160 p53 REs from both the human and viral genomes (several of the genes contain more than one p53 RE). Supplementary information S1 (table) provides the gene name, the full description of this name, its accession number, a description of the p53 RE and, if it has one, its spacer. Supplementary information S2 (table) provides the gene name, the location of the p53 RE, whether this RE functions as a transcriptional activator or a repressor, the distance from the transcriptional start site (TSS) of the p53 RE, the proposed functions of the gene product, and a reference to the publication that describes these properties of the p53-regulated gene. TABLE 1 lists

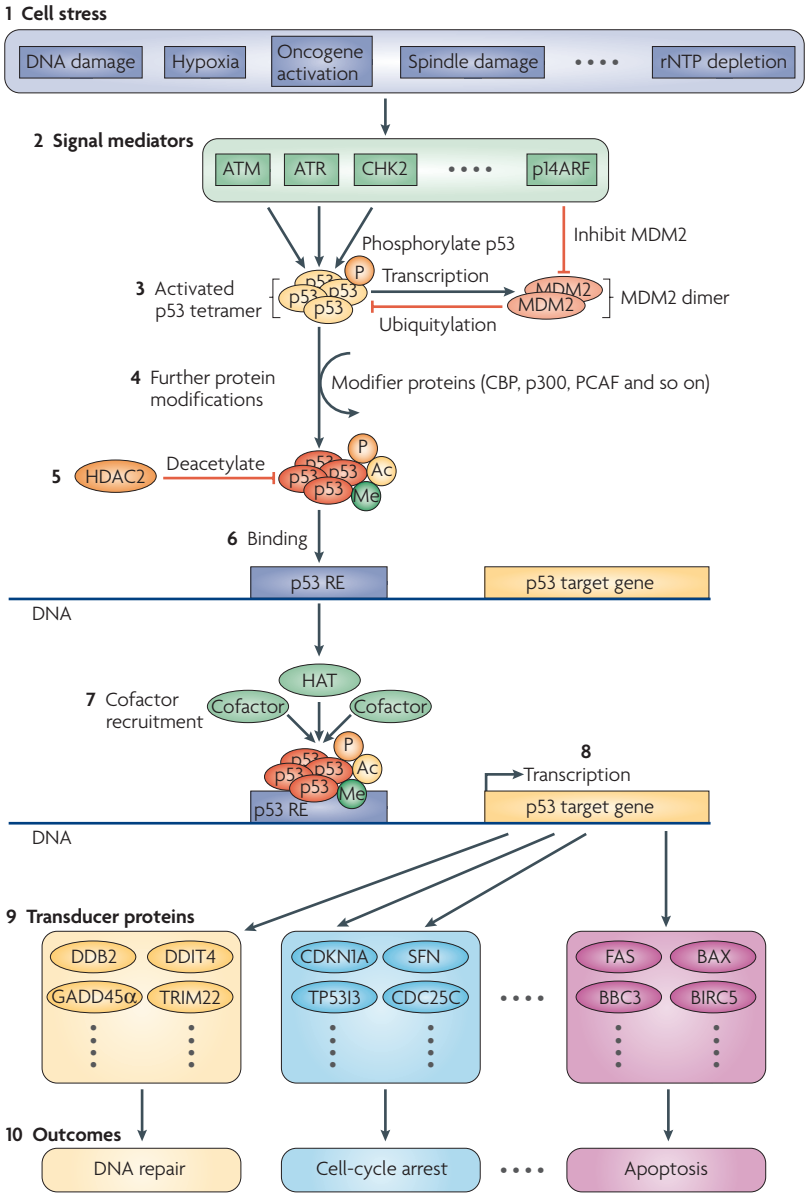

Figure 1 | **Mechanisms of p53 activation and regulation of downstream targets.** Step 1: Cells undergo stress, which can eventually lead to cancer. Step 2: Signal mediator proteins activate p53 by phosphorylating certain residues or inhibiting ubiquitylation by MDM2 (double minute-2). Step 3: Both processes increase the half-life of p53 by inhibiting ubiquitylation. The increased half-life, from minutes to hours, quickly leads to higher levels of p53. Step 4: Further p53 modifications by acetyltransferases (CBP, p300, PCAF) and methyltransferases (SET9) can further stabilize the p53 protein and increase site-specific DNA binding. Step 5: The deacetylase HDAC2 can inhibit p53 binding to DNA by deacetylating the protein. Step 6: The p53 tetramer binds to a p53 response element (RE) to regulate transcription of a nearby gene. Step 7: p53 also recruits cofactors such as histone acetyltransferases (HATs) and TATA-binding protein-associated factors (TAFs). Step 8: In this example, p53 mediates transactivation of its target gene, but p53 can also mediate transcriptional repression. Step 9: The p53 protein transactivates many genes, the protein products of which are involved in various pathways. Step 10: The most important pathways involved in tumour suppression that are activated by p53 lead to DNA repair, cell-cycle arrest, senescence and apoptosis. ATM, ataxia telangiectasia mutated; BAX, BCL2-associated X protein; BBC3, BCL2-binding component-3; BIRC5, survivin; CDKN1A, cyclin-dependent kinase inhibitor-1A; CHK2, checkpoint kinase-2; DDB2, damage-specific DNA-binding protein-2; DDIT4, DNA-damage-inducible transcript-4; FAS, TNF receptor subfamily, member 6; GADD45α, growth arrest and DNA-damage inducible α; p14ARF; SFN, stratifin; TP53I3, tumour protein p53-inducible protein-3; TRIM22, tripartite motif containing-22.

the 15 p53 cluster sites that are present in Supplementary information S1 (table) and S2 (table) and the number of half-sites found in each (p53 REs with more than two half-sites are referred to as cluster sites). We should note that the p53-target list found in Supplementary information S1 (table) and S2 (table) is probably not exhaustive, and is likely to grow as additional experimental evidence is acquired (see below).

The p53 consensus motif

Two different groups first identified a p53 consensus sequence in the DNA to which the p53 protein bound with high affinity and specificity[3,4]. The sequence was degenerate and was composed of 5′-RRRCWWGYYY-3′, where R is a purine, Y a pyrimidine, W is either A or T (adenine or thymine), G is guanine and C is cytosine[3,4]. The p53-binding site in the genomes of many organisms is composed of a half-site RRRCWWGYYY followed by a spacer, usually composed of 0–21 base pairs, which is then followed by a second half-site RRRCWWGYYY sequence (FIG. 2a). By labelling each quarter-site RRRCW as ⟶ and WGYYY as ⟵, the first discovered p53 consensus sequence can be graphically represented as ⟶⟵ spacer ⟶⟵. This configuration of the four quarter-sites is often referred to at the head-to-head (HH) orientation. The two other possible orientations of the quarter-sites are tail-to-tail (TT, ⟵⟶ spacer ⟵⟶) and head-to-tail (HT, ⟶⟶ spacer ⟶⟶). (TH is not used because the complementary strand would contain an HT-orientated site.)

In almost all natural p53-binding sites, the two half-sites share the same quarter-site orientations. Experiments have shown that the tetramer p53 protein can bind all three (HH, TT and HT) quarter-site orientations with equally high affinity[4]. However, only a few of the experimentally validated p53-binding sites in this analysis do not have the head-to-head (HH) orientation. Owing to allowed insertions and deletions relative to the consensus sequence, half-sites can vary in size between 8 and 12 base pairs, although most have 10. As mentioned above, some p53 REs have more than two half-sites, and as such are referred to as cluster sites. Various experiments have shown that the level of binding affinity and subsequent transactivation increases linearly with the number of adjacent half-sites[5–7]. Finally, some genes contain multiple p53-binding sites in different locations within the gene and promoter region, and each p53 RE can contribute to the p53 response. For example, a ⟶⟶⟶⟵⟶ cluster site is present in the promoter of *CDKN1A* (cyclin-dependent kinase inhibitor-1A, also known as *p21*) ~900 base pairs 3′ to a canonical ⟶⟵ spacer ⟶⟵ site, and both of these sites contribute to the induction of *CDKN1A* transcription after a p53 stress response[8–10].

Functions of p53-regulated genes

The mechanisms of p53-pathway activation and the cellular outcomes produced by p53-activated genes are presented in FIG. 1. Many proteins are involved in the p53 pathway in order to respond to stress signals and to produce the proper response.

Table 1 | **Cluster sites regulated by p53**

Gene name(s)	Short description	Number of half-sites
BTG2 (*TIS21*)	BTG family protein-2	3
CDKN1A (*p21*)	Cyclin-dependent kinase inhibitor-1A	2.5
DDB2	Damage-specific DNA-binding protein-2	4
GML	GPI-anchored molecule-like protein	3
HRAS (*c-Ha-Ras*)	Harvey rat sarcoma viral oncogene homologue	8
IGFBP3	Insulin-like growth factor binding protein-3	11
MDM2	Transformed 3T3-cell double minute 2	4
PCNA	Proliferating cell nuclear antigen	5
SH2D1A (*SAP*)	SH2 domain protein-1A, Duncan disease SH2 protein	4
TP53I3 (*PIG3*)	Tumour protein p53-inducible protein-3	7.5
TP73 (*p73*)	Tumour protein p73	3
TRPM2	Transient receptor potential cation channel M2	3
TYRP1 (*TRP1*)	Tyrosinase-related protein-1	6
VDR	Vitamin D (1,25-dihydroxyvitamin D3) receptor	3
HBV	Hepatitis B virus	3

The table lists genes that contain cluster-site response elements (REs) that have been shown experimentally to confer transcriptional regulation by p53. A cluster-site RE is defined as any RE that contains three or more half sites, each separated by no more than 15 base pairs.

Ubiquitin ligase
An enzyme that couples the small protein ubiquitin to Lys residues on a target protein, marking that protein for destruction by the 26S proteasome.

Polyubiquitylation
A process whereby a ubiquitin ligase protein attaches multiple ubiquitin molecules, one after the other, to a single Lys residue and thereby marks the protein for degradation by the 26S proteasome.

Senescence
An almost irreversible stage of permanent G1 cell-cycle arrest that is linked to morphological changes (flattening of the cells), metabolic changes and changes in gene expression (for example, β-galactosidase).

Autophagy
A pathway for the recycling of cellular contents, through which materials inside the cell are packaged into vesicles and are then targeted to the vacuole or lysosome for bulk turnover.

Endosome
A vesicle formed by invagination of the plasma membrane.

Stress signals decide the transcriptional programme. The p53 pathway responds to a wide variety of stress signals. These include several types of DNA damage: telomere shortening, hypoxia, mitotic spindle damage, heat or cold shock, unfolded proteins, improper ribosomal biogenesis, nutritional deprivation in a transformed cell, and even the activation of some oncogenes by mutation[11,12] (FIG. 1). These stress signals are detected by various proteins, the activities of which mediate the information about cellular damage (through protein modifications) to the p53 protein or to its negative regulator, MDM2 — a ubiquitin ligase that both blocks p53 transcriptional activity directly (sterically) and mediates the degradation of the p53 protein[13].

In many cells, the half-life of the p53 protein varies between 6 and 20 minutes. After a stress signal, MDM2 polyubiquitylates itself, which results in the degradation of MDM2 and an increase in the half-life of p53 from minutes to hours. Other mediators of the stress response act through protein modifications of p53. These rapid mechanisms of p53 modification and the greatly increased half-life of p53 do not depend on the slower mechanisms of transcription (of a damaged DNA template) or RNA transport. Thus, the response to stress is rapid, and it has been proposed (but not proven) that the nature of the stress signal determines the type of protein modification and, therefore, the transcriptional programme of the p53 protein.

This is one way to integrate cellular stress signals at a single cellular protein, whereby the activated p53 then binds to the p53 REs in the DNA and promotes a transcriptional programme that responds to that particular stress signal. There have been a number of experiments that suggest that, in addition to a transcriptional response to cellular damage, the p53 protein can act directly to trigger a response such as apoptosis[14]. Although this is an active area of research, detailed mechanisms describing how p53 acts on or in the mitochondria to promote apoptosis are still lacking.

Outcomes of transcriptional activation. There are three main outcomes after the activation of p53: apoptosis, senescence or cell-cycle arrest. The first two are terminal for the cell, whereas cell-cycle arrest permits repair processes to act and damage to be reversed, so that the cell survives. The choice between these three outcomes in a stressed cell depends on a number of other variables, which indicates that the p53 pathway is sensing the activities of other signal-transduction pathways. For example, glucose starvation of normal cells results in the AMP kinase-mediated phosphorylation by p53 on Ser15 but no further activation of p53-mediated transcription. By contrast, glucose starvation of a transformed cell results in p53-mediated apoptosis[2]. In some cell types in which p53 activation typically results in apoptosis, this can be reversed or reduced by treatment with interleukin-6 (REFS 15,16). The introduction of an activated *RAS* oncogene into a normal cell results in p53-mediated senescence[17]. As part of this senescent state, p53-mediated transcripts produce cytokines that attract inflammatory cells, which, in turn, eliminate the RAS-transformed cell from an organ[17]. So it is clear that elements of the p53 pathway are regulated by inputs from other signal-transduction pathways, resulting in different programmes of transcription by p53.

Although these three functional responses (apoptosis, senescence and cell-cycle arrest) are well appreciated, there are a number of other cellular processes that are altered by gene products regulated by the p53 protein. These include both positive and negative feedback loops in the p53 pathway[18], regulation of other signal-transduction pathways and autophagy[2,19], alterations in the extracellular matrix, alterations in the cytoskeleton of cells, activation of the endosome compartment of cells with increased exosomal and endosomal activity[20], and the regulation of protein translation[21–24], heat-shock proteins[25,26] and DNA-repair processes[7,27–29].

The above processes all occur within or around a cell at the molecular and cellular levels, but there are also physiological and systemic consequences of a p53 stress response. Exosomes produced by p53 activation of the endosomal compartment in an apoptotic cell after a p53 response to stress combine with dendritic cells in the body and can enhance the immunization process for antigens in the stressed cell[20]. Various p53-regulated genes that are expressed and act in the central nervous system can alter communication between neurons and, in some situations, result in neurodegeneration[30]. Regulation by p53 of the leukaemia inhibitory factor (*LIF*) gene in the uterus can directly regulate the efficiency of embryo implantation in mice[31]. Therefore, the p53-mediated transcriptional process can have systemic consequences in a host and communicate a stress signal throughout the body. These types of function are listed in Supplementary information S2 (table).

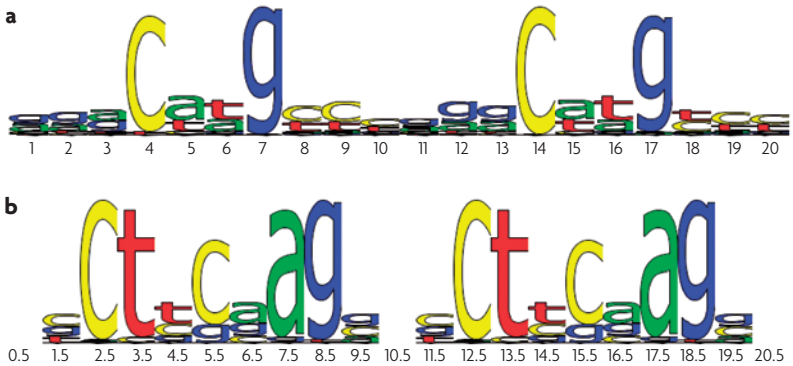

Figure 2 | **The p53-PHMM binding site motif. a** | The match-state sequence logo for the palindromic p53 motif: *1 2 3 4 5 6 7 8 9 10* $\tilde{10}$ $\tilde{9}$ $\tilde{8}$ $\tilde{7}$ $\tilde{6}$ $\tilde{5}$ $\tilde{4}$ $\tilde{3}$ $\tilde{2}$ $\tilde{1}$ (which correspond to nucleotide positions 1–20 in the figure). Model position $\tilde{a}$ has the complement nucleotide-emission distribution of *a*. The height of each letter is made proportional to its frequency at each position, and the letters are sorted in descending frequency order. The height of the entire stack at each position is then adjusted to signify the information content (in bits) of that position[103]. The match-state nucleotide positions 4, 7, 14 and 17 (model positions *4*, *7*, $\tilde{7}$ and $\tilde{4}$, respectively) are the most conserved and are the main points of contact with the p53 protein. **b** | The insert-state sequence logo for the combined-palindromic p53 motif: *1 2 3 4 5* $\tilde{5}$ $\tilde{4}$ $\tilde{3}$ $\tilde{2}$ $\tilde{1}$ *1 2 3 4 5* $\tilde{5}$ $\tilde{4}$ $\tilde{3}$ $\tilde{2}$ $\tilde{1}$. The inserted nucleotides occur in-between the match states; thus, insert position 1.5 is in-between position 1 and 2 in the match-state positions shown in part **a**. The specificity motif of the insert-state emissions is different from that of the match-state emissions. For example, there is a bias for T's to be inserted around the well-conserved C's (at nucleotide positions 4 and 14) and A's around the well-conserved G's (at nucleotide positions 7 and 17). Although insertion events in the motif are rare, the allowed nucleotide insertions at certain positions can be very specific. The match-state sequence logo, insert-state sequence logo and transition probabilities (not shown) make up the p53 profile hidden Markov model (PHMM).

Modes of p53 regulation

The p53 protein can either activate or repress the transcription of a gene. The main mode of transcriptional activation is through direct, sequence-specific DNA binding. However, a number of the genes listed in Supplementary information S2 (table) are transcriptionally repressed by p53. p53 uses both direct and indirect methods to repress gene transcription.

Activation through direct binding and recruitment. Almost all p53-activated genes have at least one putative DNA-binding site that moderately matches the consensus p53 response element. Through protein–protein interactions, p53 can bind to and then recruit general transcription proteins (TATA-binding protein-associated factors (TAFs)) to the promoter-enhancer region of p53-regulated genes to induce transcription[32,33]. Recent experiments have shown that p53 can also recruit the histone acetyltransferases (HATs) CBP, p300 and PCAF to the promoter-enhancer region of genes (through high-affinity protein–protein binding)[34,35]. These HATs acetylate Lys residues of histones in chromatin, increasing transcriptional activity.

Repression through direct and indirect means. In some genes, the binding of p53 to its RE results in direct repression of that gene. It is not clear what distinguishes an RE sequence from being a transcriptional-activator site versus a transcriptional-repressor site. At present, three generally accepted methods of direct p53-mediated repression are known: first, binding-site overlap (steric interference); second, p53 squelching of transcriptional activators; and third, p53-mediated recruitment of histone deacetylases (HDACs).

The p53-mediated repression by steric interference involves sequence-specific DNA binding by p53 that overlaps the binding site of another (more powerful) transactivating protein. Examples of genes repressed by the method of p53 steric interference include *AFP* (α-fetoprotein), *BCL2* (B-cell lymphoma-2) and *HBV* (hepatitis B virus). In these examples, the corresponding activators that are occluded by DNA-bound p53 are FOXA1 (forkhead box A1), POU4F1 (POU domain class 4 transcription factor-1) and both RFX1 (regulatory factor X1) and ABL1 (Abelson tyrosine kinase), respectively[36–38]. An entire family of cell-cycle regulatory genes now seem to share the same squelching mechanism, whereby p53 binds to and suppresses bound and unbound activators of the CCAAT box, namely heterotrimeric NF-Y (nuclear transcription factor-Y) and CEBP (CCAAT/enhancer binding protein). Examples of genes that share this mechanism are *cyclin A2*, *CDC25C*, *CDC2*, the heat-shock protein *HSP70* gene, the kinase-encoding *CHK2* and *CDK1* genes, fibronectin-1 (*FN1*), *BRCA1* (breast cancer-1, early onset) and *PTGS2* (prostaglandin-endoperoxide synthase-2, also known as *COX2*)[26,39–48].

The p53 squelching (inactivation) of other DNA-bound and DNA-unbound activators occurs through p53-mediated protein–protein interactions. Examples of p53 squelching of other transactivating genes are *cyclin B1*, *TERT* (telomerase reverse transcriptase), *IGF1R* (insulin-like growth factor receptor-1), *ALB* (albumin) and *MMP1* (matrix metallopeptidase-1). The corresponding DNA-bound proteins that are inactivated by direct p53 binding are transcription factors Sp1, Sp1, Sp1, CEBPβ and AP1 (activator protein-1), respectively[49–53]. Owing to the observation that p53 binds the transcription machinery proteins TBP (TATA-box-binding protein), TAF6 (TBP-associated factor-6, also known as TAFII70), TAF9 (also known as TAFII31) and others *in vitro*, it was initially believed that p53 repression was achieved through p53 binding and suppression of these TATA-box-bound basal factors *in vivo*[32,33,54,55]. Experimental evidence suggests that the preferred *in vivo* method of p53-mediated squelching is achieved by binding and inhibiting the transactivators of the CCAAT box[26,44,56]. However, it remains unclear whether or not these squelching mechanisms of repression are used *in vivo* under normal physiological conditions.

The p53-mediated recruitment of HDACs occurs through p53 binding to the repressor protein SIN3A, which, in turn, binds the histone deacetylase HDAC1 (REF. 57). After p53-mediated recruitment to the promoter-enhancer region of a gene, HDAC1 deacetylates Lys residues of histones in chromatin, thereby repressing gene transcription[57,58]. Examples of genes repressed through this p53-mediated mechanism include *MAP4* (microtubule-associated protein-4), *STMN1* (stathmin-1) and the heat-shock protein *HSP90AB1* gene (REFS 25,57).

Exosome
A membrane vesicle that is secreted into the extracellular milieu as a consequence of multivesicular-body fusion with the plasma membrane.

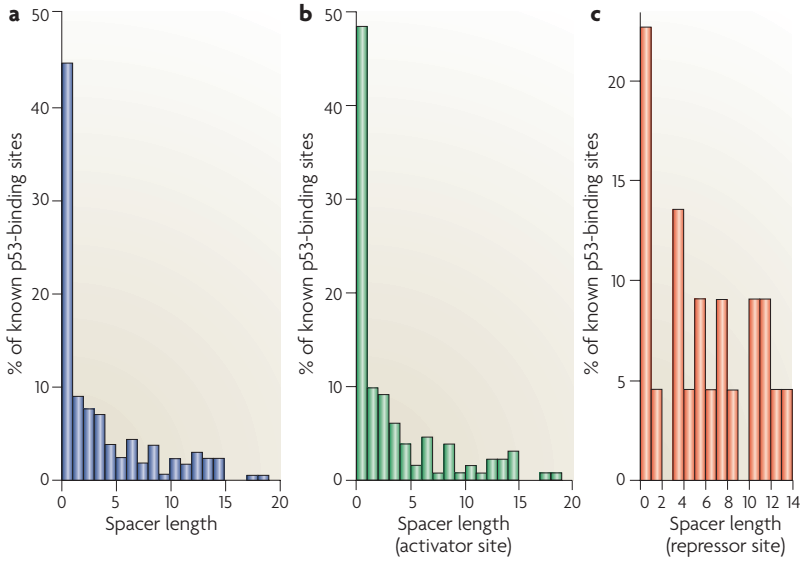

Figure 3 | **Histograms of spacer lengths by regulation types. a** | The histogram of all 160 spacer lengths of known, functional p53-binding sites reveals the following: first, almost 50% of the p53-binding sites have no spacer sequence (spacer length = 0 base pairs), and second, the distribution is relatively uniform for spacer lengths between 4 and 14 base pairs. This distribution does not match experimental results, which suggest a bimodal distribution with peaks at 0 and 10 base pairs, and which place the two half-sites on the same face of the DNA double helix[84,88]. **b,c** | Activation sites have a different distribution of spacer lengths compared with repressor sites. Most importantly, repressor sites do not show a great preference for 0-base-pair spacers.

There are two generally accepted modes of indirect p53-mediated repression. The first comes about by p53-mediated activation of *CDKN1A*, which, in turn, inhibits the cyclin D–CDK4 complex through direct binding. The consequence of this inhibition of cyclin D–CDK4 is the absence of hyperphosphorylation of the retinoblastoma (RB) protein from the G1 stage of the cell cycle[59]. Unphosphorylated RB represses the function of the E2F family of transcription factors through direct binding (forming an E2F–DP1–RB complex), thereby inhibiting the many downstream targets of E2F (including cyclin E, cyclin A, DNA polymerase and thymidine kinase) and halting the cell cycle in G1 phase. It seems that many genes are fully or partially repressed through p53-mediated induction of *CDKN1A* and ensuing repression of E2F by RB dephosphorylation[59]. Supplementary information S2 (table) shows only those genes that are directly repressed by p53 (and thus have an experimentally validated p53 RE). In the second mode of indirect p53-mediated repression, p53 binds to another transcription factor and, together, they repress a gene without a p53-specific RE.

Less established modes of p53 regulation. Investigators have also put forth other, sometimes controversial, models for mechanisms of p53-mediated repression and activation. One model proposes that the switch between p53-mediated activation and repression is determined by the length of the spacer[60]. The hypothesis is that p53 proteins bound to a 3-base-pair spacer-binding site are ineffective in recruiting the necessary additional activation proteins while simultaneously occluding them from adjacent or overlapping REs. Investigators were able to convert direct p53 repression of *BIRC5* (survivin) into direct p53 activation by deleting the 3-base-pair spacer present in the p53 RE[60]. In our analysis, we show that experimentally validated repressor sites do have longer spacers (FIG. 3). However, many activator sites also have spacers of three or more base pairs.

Another model proposes that the existence of an adjacent response element (designated 'EP'), which binds the proteins RFX1 and ABL1, is sufficient to transform an activating p53 RE into a repressing RE[38]. Interestingly, Ori *et al.* succeeded in transforming the direct p53 repression found in the enhancer of *HBV* into direct p53 activation by mutating the adjacent EP response element. They also succeeded in transforming the direct p53 activation of MDM2 into direct p53 repression by inserting an EP response element adjacent to the p53 RE.

Yet another model proposes that the orientation of the quarter-sites within the p53-binding element determines activation versus repression. Johnson *et al.* propose that head-to-head (HH) p53-binding sites produce p53 activation, whereas head-to-tail (HT) sites produce p53 repression[61]. Interestingly, they succeeded in converting the p53-repressed ABC transporter gene, *ABCB1*, into p53-activated *ABCB1* by replacing the HT p53 RE in the promoter with an HH p53 RE. No experiments were performed with tail-to-tail (TT) p53-binding sites. However, it should be noted that all other experimentally validated repressing p53 REs in this analysis have an HH configuration, and that the HT cluster site in the 5′ untranslated region (UTR) of *TP53I3* (tumour protein p53-inducible protein-3, also known as *PIG3*) confers p53 transactivation, rather than repression.

In the case of *HSP90AB1*, investigators discovered a biphasic p53 regulatory system in which the cofactor p300 mediated p53 activation, and the cofactors SIN3A and HDAC1 mediated p53 repression[25]. Another important cofactor for p53 regulation in some genes, including *CAV1* (caveolin-1), is E2F (REF. 62). Combining these observations leads to the following conclusions: first, properties of the p53 RE and adjacent cofactor REs confer the potential for direct p53 activation, repression, or both; and second, the induction of the right combination of p53 and cofactor proteins is required to regulate any potentially functional target site, when either activating or repressing.

Factors that affect p53 regulation

Experiments have shown that many factors can affect the mode and degree to which p53 regulates different target genes. These factors include cofactors, spacer lengths, quarter-site orientation, nucleosomes and post-translational modifications of p53.

The role of post-translational modifications of p53. An area of controversy is the role of post-translational modifications of p53 in determining the mode and efficacy of p53 transcriptional regulation. Experiments have shown that post-translational modifications of p53, such as phosphorylation, methylation and acetylation, alter the

Protein methylation
A type of post-translational modification, mediated by enzymes, whereby a hydrogen atom is replaced with a methyl group, typically on an Arg or Lys amino-acid residue in the protein sequence.

Protein acetylation
A type of post-translational modification, mediated by enzymes, whereby a hydrogen atom is replaced with an acetyl group.

stability and DNA-binding affinities of p53 (REFS 63–66). Investigators have shown that p53 needs post-translational modifications in the C-terminal domain to bind to naked DNA *in vitro*, but requires no modifications in the presence of chromatin to bind to p53 REs[9,67]. This also fits with experiments that showed that the deacetylated C-terminal domain inhibits binding to p53-binding sites in linear DNA and promotes binding to sites in nonlinear, circularized DNA[68]. The p53-binding sites in circularized DNA segments mimic *in vivo* conditions, whereby DNA is wrapped around histones. These experiments suggest that the C-terminal domain of the p53 protein confers DNA structure specificity (whereas the DNA-binding domain confers sequence specificity). In direct contradiction to these results, other researchers have shown that some of the experimentally validated p53-binding sites do not require any phosphorylation or acetylation of the p53 protein in order to confer high-affinity binding *in vitro* in the absence of chromatin[69].

Nevertheless, there are cases in which these post-translational modifications seem to have a major role. Investigators found that the induction of *p53AIP1* (p53-regulated apoptosis-inducing protein-1) depends on the phosphorylation of the Ser46 residue of p53 (REF. 70). Investigators also found that phosphorylation of the Ser15 and Ser392 residues conferred p53 activation of the adenomatosis polyposis coli (*APC*) gene, whereas non-phosphorylated p53 served as a repressor of *APC*[71].

The strongest evidence to support the idea that post-translational modifications of p53 are relevant to the p53 regulatory mechanism is the fact that HDAC inhibitors have been shown to simultaneously increase levels of acetylated p53 and induce apoptosis and senescence in cancerous and normal cells[58,72]. HDAC inhibitors are currently in clinical trials as cancer chemotherapeutics and initial results are promising[72]. Although post-translational modifications of p53 are certainly important, the ability to properly quantify which ones are relevant, under which conditions, has been elusive. Further experimentation is needed to shed light on this complex mechanism of regulation in the p53 pathway.

The flexible CATG effect. It has been shown experimentally that in the head-to-head (HH) orientation, p53 greatly prefers the repeated RRRCATGYYY motif [73,74]. On the basis of X-ray crystallography studies of the p53 DNA-binding core domain bound to a p53-RE DNA sequence, the most important bases for interactions with the p53 protein are the central RCWWGY, which come into close contact with the amino acids from the p53 core domain[75]. In conjunction with this, the most conserved positions after aligning all experimentally validated, functional p53-binding sites are the central CWWG nucleotides within each half-site, especially the C and G (FIG. 2). Therefore, changes in the nucleotides in these central positions should affect binding affinity the most. Indeed, binding-affinity measurements of 20 p53-binding sites revealed that 50% of the high-affinity sites contained the CATG sequence at the centre of both half-sites[69]. Investigators also found that replacing the central CATG with CTAG in both half-sites reduced transactivation 20-fold[76].

It is known that the CATG sequence element is unusually flexible and exhibits extreme bending and kinking in many DNA–protein complexes[77,78]. Therefore, it is widely assumed that the flexibility of the p53 RE also affects binding affinities. p53–DNA-binding affinity experiments have shown that p53 exhibits higher binding affinity for sites in cell-cycle control target genes than for sites in apoptosis target genes, and that these differences coincide with the prevalence of the highly flexible CATG in both groups[69].

p53 RE sites that are not functional. Investigators have repeatedly found that p53-mediated regulation of minimal promoters can be profoundly different from that of their respective full-length promoters. Examples include experiments that showed that p53 would no longer bind in the natural promoter[79], and experiments that showed that the p53 RE was no longer functional in the natural promoter, even though the presence of bound-p53 on the RE was confirmed[80,81]. These results indicate that the presence of cofactor sites and the p53-RE occlusion by nucleosomes or other proteins have an important role in p53 regulation. Examples of genes that contain p53-binding sites that have been shown not to be functional *in vivo* include: the intron 5 cluster site in the apoptosis-inducing factor *AIFM2*, the -328 site in *TP53I3*, and the promoter cluster site in human *BAX* (BCL2-associated X protein) [79–81]. In addition, experiments have shown that an adjacent Sp1 RE is necessary to confer p53-mediated activation of *BBC3* (BCL2-binding component-3, also known as *PUMA*) and *BAX*[82,83]. Clearly, binding of p53 to DNA is not sufficient for transcription.

The effects of distance and DNA looping. It is well known that the distance between a *cis*-element binding site and the transcription start site (TSS) can greatly affect the degree of regulation of a gene. In the case of p53, researchers showed that inserting an additional 200-base-pair segment between a p53 RE and the TATA box eliminated a 45-fold p53-mediated induction[84]. It is also known that eukaryotic cells contain transcription factor (TF)-binding proteins that bind together — 'sticky' TF proteins — and can mediate DNA looping. This process can bring distal TF-bound binding sites close to the TATA box, and can confer regulation. In the case of p53, investigators using electron microscopy techniques showed that p53 tetramers stack in register (on top of each other) when bound to a p53 RE, and thereby link distant p53-binding sites through DNA looping[85]. They also showed that, alone, distant p53-binding sites are poor inducers of transcription, but that in the presence of a site proximal to the TSS, induction by the distal site is increased 25-fold[85]. p53-tetramer stacking translocates distally bound p53 protein to the promoter and increases the concentration of local p53 near the TSS.

In the absence of a proximal p53 RE, other 'sticky' proteins may serve as a surrogate, provided that their REs are present close to the TSS and the distal p53 RE. An example of a proven sticky protein that mediates

DNA looping is the p53 cofactor Sp1. An example of Sp1-mediated DNA looping may be found in *MDM2*, where a functional single-nucleotide polymorphism (SNP), SNP309 T/G, within a cluster of Sp1-binding sites affects the level of regulation of nearby oestrogen and p53 REs, and has been associated with an early onset of breast cancer in pre-menopausal women[86]. In contradiction to this model, other investigators have hypothesized that distal sites may reduce transcription by attracting p53 proteins away from the TSS[87]. For example, in Polo-like kinase-2 (*PLK2*) the distant site is a repressor, whereas nearer sites are activators[87]. Further investigation will be necessary to determine exactly how and when distant p53 REs regulate gene expression.

The effects of spacers. Experiments have shown that the spacers that separate the half-sites can greatly affect the binding affinity for the p53 protein. For example, Tan *et al.* showed that mutating the spacer of a p53 RE from a GG to a T increased binding affinity 6.6-fold[7]. Two series of experiments that used minimal promoter assays found a bimodal induction distribution, whereby the two induction peaks occurred with spacer-lengths of 0 and 10 base pairs[84,88]. The authors hypothesized that optimum binding occurred with the half-sites aligned along the same face of the double helix (stereospecific alignment), either with the half-sites adjacent or separated by a helical turn (10 base pairs). Other researchers showed that, under certain experimental conditions, specific spacers with spacer lengths of size 4, 13 and 14 considerably decreased the RE's binding affinity for p53 as compared with having no spacer at all; however, a spacer length of 10 was not tested[89].

Unfortunately, only one spacer, as opposed to all possible spacers, of a certain length was tested for binding affinity in these experiments. Interestingly, our database of 160 functional p53-binding sites does not show a bimodal distribution of spacer lengths. It is possible that spacer lengths may affect binding affinity and regulatory function differently, in that high binding affinity does not necessarily confer regulatory function. Although it is obvious that different spacers affect the function of p53 REs differently, the ability to quantify these effects has been elusive.

Rescue by p63 and p73. Yet another proposed p53-mediated activation mechanism is the rescue of weak p53-binding sites by the p53 homologues p63 and p73. Investigators have found that in mouse fibroblasts both p63 and p73 are required for p53-dependent transactivation of *Noxa* and *Bax*[90].

To our knowledge, no experiments have been performed that elucidate how these seemingly disparate determinants of p53 regulation (spacer lengths, quarter-site orientation, cofactors, nucleosomes and post-translational modifications of p53) might relate to each other in determining functional p53 repression and/or activation. It is obvious that our understanding of the mechanism(s) that determine p53 repression versus activation is not complete, and requires further study.

LINE element
A long interspersed sequence that contains a promoter region, untranslated region and one or more open reading frames, and is generated by retrotransposition.

Experimental approaches and considerations

There are special considerations that need to be taken into account when attempting to experimentally validate putative p53-binding sites. Wei and his colleagues have used chromatin immunoprecipitation with p53-specific antibodies to collect all of the tight binding sites for p53 in the genome of a cancer cell line[91]. They then sequenced the DNA fragments selected for by p53 binding and identified the genes associated with p53. They went on to validate, using other criteria, that a subset of these genes did indeed have a p53 RE that was regulated by p53. This has been a useful approach for identifying candidates, but it is clear that binding to an RE is not necessarily equivalent to regulating a gene. In addition, this approach requires tight binding and longer residence times of p53 at a site that could just store p53 proteins on the DNA for rapid use (not diffusion-limited) at a regulated gene. This method could also be used to identify p53-like sites on retroviruses and LINE elements (repetitive elements in the genome), both of which are observed by p53 RE algorithms (see below)[92].

In addition to this approach, others have used RNA microarrays to explore the increases and decreases in the steady-state levels of RNAs in cells after the induction of p53 or exposure to a stress signal[1]. This too has been useful for identifying new p53-regulated genes, but they need to be shown to be directly regulated by p53, and not the consequence of a secondary event (such as the induction of a transcription factor by p53 that then acts on other genes). Moreover, any stress signal used to induce p53 (such as exposure to ultraviolet (UV) radiation) may well induce the transcription of a gene by a pathway not involving p53. For example, the *GADD45a* (growth arrest and DNA-damage-inducible-α) gene is induced by p53 (following exposure to UV radiation, as verified by chromatin immunoprecipitation) but is also induced by UV radiation in a p53-null or mutant cell (by another mechanism). For these reasons, an inducible *p53* gene or a temperature-sensitive *p53* gene in a cell are often better used to increase p53 levels and activity than a DNA-damaging agent. However, the protein products of an inducible *p53* gene in an unstressed cell might not have the same protein modifications (acetylation, for example) that are observed *in vivo* in a stress response. Those modifications (which include acetylation, phosphorylation, methylation, ubiquitylation and sumoylation) could well lead to the choice of a transcriptional programme resulting from that particular stress signal (UV radiation versus ionizing radiation, for example)[1]. Finally, the choice of cell lines used to follow p53-regulated genes in these experiments ignores the fact that there are cell-type and tissue-type specificities in the p53 response.

Computational methods of identification

Several algorithms have been devised to detect p53 REs in the DNA of all organisms and identify possible p53-responsive genes [92–98]. These computational algorithms have been used extensively to help the experimental process of finding functional p53-binding sites, transcriptional gene targets of p53 and functional SNPs in the p53 pathway. Although these algorithms have been

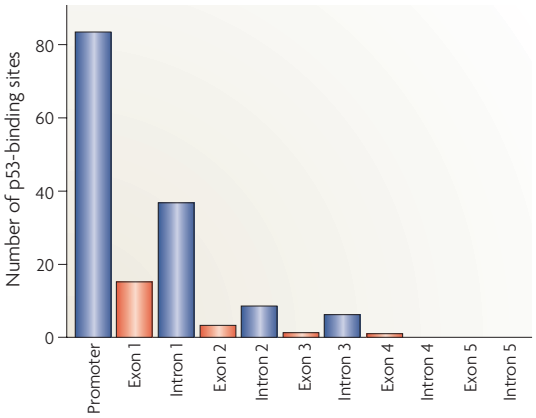

Figure 4 | **Histogram of p53-binding sites by gene region.** The histogram of 160 functional p53-binding sites (by gene region) reveals several things. First, there are slightly more p53 response elements (REs) upstream of the transcriptional start site (TSS) than downstream (83 of the 160 sites are completely within the promoter region, 3 straddle the TSS and 74 are downstream of the TSS). Second, there are significantly more p53 REs in non-coding regions (blue) than in coding regions (red). Third, there is an exponential decay of p53 REs as the distance from the TSS increases. Thirteen of the 15 exon-1 REs (87%) are in the 5′-untranslated region. Note that some p53 REs straddle both coding and non-coding regions and are counted twice.

extremely useful, they also have serious drawbacks. All the algorithms attempt to approximate the relative binding affinity of a putative p53-binding site by training a probabilistic model from a data set of experimentally validated, functional p53 REs (known as a 'training set'). Therefore, the strength and predictive power of any such model is completely dependent on the sampling size and quality of the training set.

In addition, experiments have repeatedly shown that relative binding affinity is not the only relevant factor when it comes to response elements (see above). Other important variables that affect the degree of function of a p53 RE include adjacent cofactor-binding sites, spacer length, distance from the TSS and nucleosome positioning. For these reasons, all the algorithms that approximate relative binding affinity alone have very high false-positive rates (for most TF-binding sites)[97]. In order to seriously boost predictive power, future algorithms will need to include at least some of the additional variables mentioned above.

The common position-specific score matrix. By far the most common computational method for predicting p53 REs (and other REs) is the position-specific score matrix (PSSM, or weight matrix), which attempts to estimate the binding affinity of a putative site[95]. Besides the drawbacks mentioned above, PSSMs have other serious limitations in their attempts to approximate relative binding affinity. The PSSM model contains the probabilities of each nucleotide at each position in the motif (or the logarithms of the probabilities) and is therefore static in length. So, PSSMs cannot model possible nucleotide insertions into, or possible deletions from, the consensus motif, because any nucleotide insertion or deletion throws off the PSSM reading frame. This is clearly a problem because the p53 RE is very degenerate and ~30% of the 160 functional p53-binding sites in Supplementary information S2 (table) have at least one nucleotide insertion or deletion relative to the consensus. Any PSSM approach would therefore misscore at least 30% of the binding sites in the data set. Examples of genes that contain these degenerate sites are: *BAI1* (brain-specific angiogenesis inhibitor-1), *CAV1*, *EEF1A1* (eukaryotic translation elongation factor-1 α1), *HSP90AB1*, *PCBP4* (poly(rC)-binding protein-4), *SH2D1A* (SH2 domain protein-1A), *TYRP1* (tyrosinase-related protein-1) and *LIF*.

The more powerful profile hidden Markov models. Profile hidden Markov models (PHMMs) provide a coherent theory for probabilistic profiling of degenerate binding sites that are subject to random insertions and deletions in the presence of natural selection[99,100]. The theory of selection postulates that critical nucleotides are conserved over evolutionary time, whereas noncritical nucleotides and tolerated insertions into a DNA-binding site are not conserved. It is exactly these conserved, critical nucleotides that serve as the blueprint for the match-state emissions (that is, the distributions of emitted nucleotides at each position in the p53 motif) of a PHMM of a binding site. The additional hidden insertion and deletion states give the model the ability to train for observed probabilistic insertions and deletions at different positions in the motif. In short, the training set of observed insertions and deletions serves to fine-tune the model to be properly sensitive to allowed deviations from the most prevalent consensus motif[101]. This inherent trained flexibility is the main strength of PHMMs. Their main drawback is that they require larger training sets to train extra parameters dependent on rare-occurrence insertions and deletions.

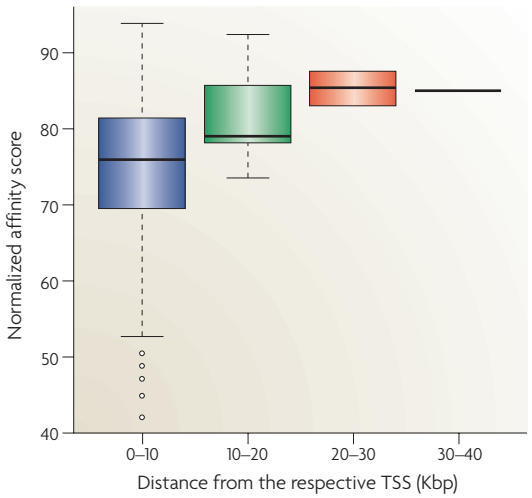

Figure 5 | **Box plots of normalized affinity scores by 10-kilobase-pair block distances from the transcriptional start site.** All low-affinity sites are within the first 10-kilobase pair (Kbp) block from the transcriptional start site (TSS). Median scores of the 10-Kbp blocks rise as a function of distance.

Profile hidden Markov model
(PHMM). A model that is designed to capture the statistical characteristics of biological sequence data (DNA, RNA or protein). All PHMMs typically have three hidden states (match, insertion and deletion) per nucleotide or amino-acid position.

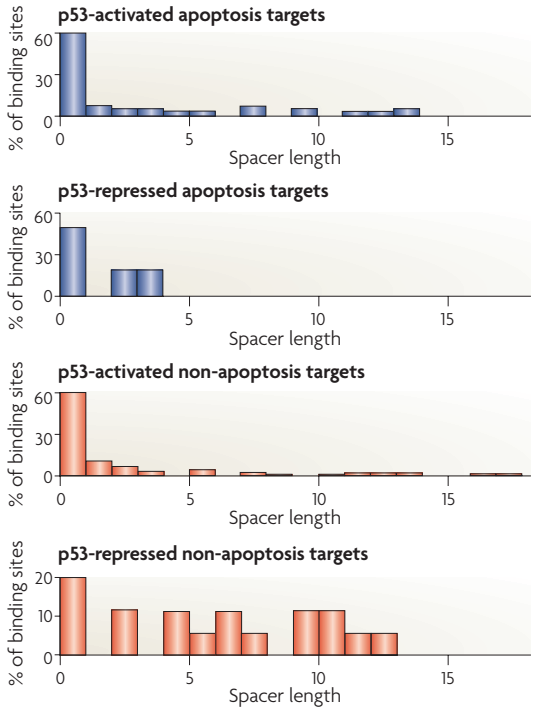

Figure 6 | **Histogram of spacer lengths by regulation type and gene-target function.** Non-apoptosis target sites (red) have a higher frequency of repressor sites compared with apoptosis target sites (blue). In addition, non-apoptosis target repressor sites have no preference for 0-base-pair-length spacers (bottom histogram). Thus, p53-repressor binding sites have significantly longer spacers on average.

PHMMs are hidden Markov models (HMMs) in which each position in the motif has three possible hidden states: match, insert and delete[99]. Each match and insert state has potentially different nucleotide-emission distributions. The delete state has no emissions and is therefore completely silent. PHMMs assume that each nucleotide position contributes independently to the overall binding free energy of the binding site[95,102]. The parameters that must be trained are the probabilities for the transitions to and from the match, insert and delete states (for each position), and the match- and insert-state emissions (for each position). The p53HMM algorithm, which can be used online, is a PHMM that has been trained on the data set of 160 functional p53 REs, and can be used to score putative p53-binding sites. In addition, the p53HMM algorithm has been optimized to increase predictive power by leveraging the redundancy of information found in the repeated, palindromic p53-binding motif.

Faithfulness within the p53 RE. Analysis of the 37 p53-binding sites identified by el Deiry *et al.*[3] and Funk *et al.*[4] showed that the left half-site seemed to be more faithful (that is, highly conserved) than the right half-site, which is graphically expressed as ⟶⟵ spacer ⟶⟵. It also seemed that the right quarter-sites (⟵) of the motif were more faithful than the left quarter-sites (⟶) within each half-site, graphically expressed as ⟶⟵ spacer ⟶⟵. However, these differences were not statistically significant[92]. Our findings with the current data set of 160 p53-binding sites show no significant differences in the faithfulness between the quarter-sites. Additional evidence that the half-sites share the same binding properties is given by the fact that the best computational predictor in this analysis assumes and leverages that the two half-sites share the same binding preferences.

Analysis and conclusions

This comprehensive analysis of the p53 REs, the genes they regulate and the properties they confer can add new information to our understanding of the p53 pathway and p53-mediated transcriptional control. First, the p53 RE in a gene (FIG. 4) is most commonly located in the 5′ promoter-enhancer region of the gene (~50%) or in intron 1 (~25%). More rarely it is located in introns 2 or 3 of a gene. Surprisingly, some functional p53 REs are in exon 1 or even exon 2. When this occurs, however, the p53 RE is predominately in the 5′ UTR or the intron–exon boundary. Furthermore, because ~50% of the experimentally validated p53 sites are downstream of the TSS, intronic and 5′-UTR regions are equally important to promoter-enhancer regions in conferring p53 regulation. The p53 RE is commonly located close to additional transcription factor RE sites.

Second, the distance of the p53 RE from the TSS helps to determine the threshold for accepting any putative p53 RE on the basis of the normalized affinity score of the p53 protein for the known p53 REs (FIG. 5). Functional, low-affinity p53 RE sites in the DNA only exist around the TSS. Therefore, computational methods can use a dynamic affinity threshold to reduce false-positives during p53-site searches.

Third, ~50% of the p53 RE sites have no spacer between the half-sites, and the distribution of spacer lengths is relatively uniform for spacer lengths between 4 and 15 base pairs (FIG. 3a). This distribution contradicts *in vitro* experiments that predict functional p53 RE sites on the basis of the half-sites being located on the same face of the DNA helix. Interestingly, the distribution of spacer lengths in the p53 RE is different for genes that are transcriptionally activated by p53 and those that are repressed by p53 (FIG. 3b,c). The spacer lengths in the p53 REs of repressed genes do not show a great preference for zero length or small spacers. This difference between spacer length and gene activation or repression is especially clear for those genes not involved in apoptosis (FIG. 6). p53-regulated non-apoptosis genes that are repressed by p53 have no preference for zero-length spacers.

The list of known p53-regulated genes collected in one place gives us a new feeling for the breadth of functions regulated in response to stress signals. After a p53-mediated response to stress, there are changes in the intracellular compartments, cytoskeleton, endosomal and exosomal functions, heat-shock induction and cellular-repair processes. There are also changes in the extracellular matrix, increased secretion of exosomes and proteins that affect angiogenesis, growth-factor functions and the immune response. The p53 response sets up a series of positive and negative feedback loops that regulate p53-mediated

functions as well as other signal-transduction pathways. In addition to these local effects of a p53 response, systemic signals are p53 regulated. Both exosomes and cytokines engage the immune response of the body. p53-mediated responses in the brain alter signal transmission in the central nervous system. Moreover, angiogenic signals and interactions with growth factors and their receptors can all have wider systemic impact. Clearly, the list of genes involved in a stress response mediated by p53 has a broad effect on the host as well as the host cell.

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DATABASES
UniProtKB: http://ca.expasy.org/sprot
BAX | *BBC3* | *CDKN1A* | *GADD45a* | HDAC1 | *HSP90AB1* | p53 | MDM2 | TAF6 | TAF9 | TBP | *TP53I3*

FURTHER INFORMATION
Todd Riley's homepage:
http://www.sns.ias.edu/~triley
p53HMM algorithm: http://tools.csb.ias.edu

SUPPLEMENTARY INFORMATION
See online article: S1 (table) | S2 (table)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

Supplementary information S1 (table) | Description of genes regulated by p53 (part I)*

#	Gene Name(s)	Short Description	Accession #	1st Half-site	Spacer	2nd Half-site	Refs
1	ABCB1, MDR1	ATP-binding cassette sub-family B member 1	AF016535	GGGCAGGAACA	gcgccggggcgt	GGGCTGAGCA	1
2	ACTA2	smooth muscle alpha-actin	NM_001613	AACCATGCCT		GCATCTGCCC	2
3	AIFM2, AMID	apoptosis-inducing factor, mitochondrion-assoc.	NM_032797	AGGCATGAGC	caccgtgcct	GGCCATGCCC	3
3	AIFM2, AMID	apoptosis-inducing factor, mitochondrion-assoc.	NM_032797	AGGTCTCGCTA	tgttgccc	AGGCTGGTCT	3
4	ANLN	anillin, actin binding protein	NM_018685	GAACTGGCTT	ttctga	GGGCCAGGCC	4
5	APAF1	apoptotic peptidase activating factor 1	NM_001160	AGACATGTCT	ggagaccctagga	CGACAAGCCC	5
6	APC	adenomatosis polyposis coli	NM_000038	GGGCATACCC	ccgaggggtacg	GGGCTAGGGCt	6
7	ARID3A, E2FBP1	AT rich interactive domain 3A (BRIGHT-like)	NM_005224	GGACACGCTG		GGACATGCCT	7
8	ATF3	activating transcription factor 3	NM_001674	AGTCATGCCG	ctggcttgggcaccatt	GGTCATGCCT	8
9	BAI1	brain-specific angiogenesis inhibitor 1	NM_001702	tGGCTGCCT		GGACATGTTC	9
10	BAX	BCL2-associated X protein	NM_004324	GGGCAGGCCC		GGGCTTGTCG	10
11	BBC3, PUMA	BCL2 binding component 3	NM_014417	CTGCAAGTCC		TGACTTGTCC	11
12	BCL2L14, BCL-G	BCL2-like 14 (apoptosis facilitator)	NM_030766	AGCCAAGGCT		GGTCTTGAAC	12
13	BCL6	B-cell CLL/lymphoma 6 (zinc finger protein 51)	NM_001706	AGACAGTGCTT	gggggtgattc	GGGCTAGTCT	13
14	BDKRB2, BK2	bradykinin receptor B2	NM_000623	GGAagTGCCC		AGGaggcTga	14
15	BID	BH3 interacting domain death agonist	NM_197966	GGGCATGATG		GTGCATGCCT	15
16	BIRC5, survivin	baculoviral IAP repeat-containing 5 (survivin)	NM_001168	GGGCGTGCGC	tcc	CGACATGCCC	16
17	BNIP3L	BCL2/adenovirus E1B interacting protein 3-like	NM_004331	AAGCTAGTCT	cagtg	GcGCATGCCT	17
18	BTG2, TIS21	BTG family, member 2	NM_006763	AGTCCGGGCA	g	AGCCCGAGCA	18
19	C12orf5	chromosome 12 open reading frame 5	NM_020375	AGACATGTCC	ac	AGACTTGTCT	19
20	C13orf15, RGC32	chromosome 13 open reading frame 15	NM_014059	AGGCgAGTTT	aag	cAGCTTGTCC	20
21	CASP1	caspase 1, apoptosis-related cysteine peptidase	NM_033292	AGACATGCAT		ATGCATGCAca	21
22	CASP10	caspase 10, apoptosis-related cys-peptidase	NM_032977	AAACTTGCTg	gttta	AAtCTTGgCT	22
23	CASP6	caspase 6, apoptosis-related cysteine peptidase	NM_001226	AGGCAAGGAG	tttg	AGACAAGTCT	23
24	CAV1	caveolin 1, caveolae protein, 22kDa	NM_001753	GCCCAAGCAC	cccagcgcg	GGAGAaACGTTC	24
25	CCNG1	cyclin G1	NM_004060	GcACAAGCCC		AGGCTAGTCC	25
26	CCNK	cyclin K	NM_003858	AAACTAGCTT	gc	AGACATGCTg	26
27	CD82, KAI1	CD82 molecule	NM_002231	AGGCAAGCT	ggggca	GctCAAGCCT	27
28	CDC25C	cell division cycle 25 homolog C (S. pombe)	NM_001790	GGGCAAGTCT	taccatttcca	GAGCAAGCaC	28
29	CDKN1A, p21	cyclin-dependent kinase inhibitor 1A (p21, Cip1)	NM_000389	AGACTGGGCA		TGTCTGGGCA	29
29	CDKN1A, p21	cyclin-dependent kinase inhibitor 1A (p21, Cip1)	NM_000389	GAAgAAGaCT		GGGCATGTCT	30
29	CDKN1A, p21	cyclin-dependent kinase inhibitor 1A (p21, Cip1)	NM_000389	GAACATGTCC		cAACATGTTg	30

30	Chmp4C	chromatin modifying protein 4C	NM_152284	AAACAAGCCC	agtagcagcagctgctcc	GAGCTTGCCC	31
31	COL18A1	collagen, type XVIII, alpha 1	NM_030582	TGACATGTGT		GAGCATGTAT	12
31	COL18A1	collagen, type XVIII, alpha 1	NM_030582	TGACATGTGT		GAGCATGTAT	12
32	CRYZ	crystallin, zeta (quinone reductase)	NM_001889	ctGCAAGTCC	att	AAACcTGTTT	4
33	CTSD, IRDD	cathepsin D	NM_001909	AAcCTTGgTT		tgcAAgAgGCTT	32
33	CTSD, IRDD	cathepsin D	NM_001909	AAGCTgGgCC		GGGCTgaCCC	32
34	CX3CL1, fractalkine	chemokine (C-X3-C motif) ligand 1	NM_002996	GGGCATGTTC	c	CAGCTTGTGG	33
35	DDB2	damage-specific DNA binding protein 2, 48kDa	NM_000107	GAACAAGCCC	t	GGGCATGTTT	34
36	DDIT4, REDD1	DNA-damage-inducible transcript 4	NM_019058	AAACAAGTCT		TTCCTTGATC	35
37	DDR1	discoidin domain receptor family, member 1	NM_013994	GAGCTGGTCC		AGGCTTATCT	36
38	DKK1	dickkopf homolog 1 (Xenopus laevis)	NM_012242	AGCCAAGCTT	ttaatg	AACCAAGTTC	37
39	DNMT1	DNA (cytosine-5-)-methyltransferase 1	NM_001379	GCGCATGCGT	gttccct	GGGCATGGCC	38
40	DUSP1, MKP1	dual specificity phosphatase 1	NM_004417	GGTCCTGCCC	a	GGCAAATGGG	39
41	DUSP5	dual specificity phosphatase 5	NM_004419	CAACAAGCCC	t	TGTCTAGTGC	40
42	EDN2	endothelin 2	NM_001956	CTGCAAGCCC		GGGCATGCCC	41
43	EEF1A1	eukaryotic translation elongation factor 1 alpha 1	NM_001402	GGGCAGACCC	ga	GAGCATGCCC	42
43	EEF1A1	eukaryotic translation elongation factor 1 alpha 1	NM_001402	GGACACGTAG	attc	GGGCAAGTCC	42
43	EEF1A1	eukaryotic translation elongation factor 1 alpha 1	NM_001402	AAACATGATT	ac	AGGGACATCT	42
44	EGFR	epidermal growth factor receptor	NM_005228	GAGCTAGACG	tcc	GGGCAGCCCC	43
45	EphA2	EPH receptor A2	NM_004431	CACCATGTTG	gcc	AGGCATGTCT	44
46	FANCC, FAC	Fanconi anemia, complementation group C	NM_000136	GGACATGTTT	aaatacttga	GAGCTATTTT	45
47	FAS, CD95	Fas (TNF receptor superfamily, member 6)	NM_000043	GGACAAGCCC		TGACAAGCCA	46
48	FDXR	ferredoxin reductase	NM_024417	GGGCAgGagC		GGGCTTGCCC	47
49	GADD45A	growth arrest and DNA-damage-inducible, alpha	NM_001924	GAACATGTCT		AAGCATGCTG	48
50	GDF15, MIC-1	growth differentiation factor 15	NM_004864	AGCCATGCCC		GGGCAAGAAC	49
50	GDF15, MIC-1	growth differentiation factor 15	NM_004864	CATCTTGCCC		AGACTTGTCT	50
51	GML	GPI anchored molecule like protein	NM_002066	AtGCTTGCCC		AGGCATGTCC	51
52	GPX1	glutathione peroxidase 1	NM_000581	GGGCCAGACC		AGACATGCCT	19
53	HBV	hepatitis B virus	get_this	TTGCATGTAT	acaagct	AAACAGGCTT	52
54	HD, Huntington	huntingtin (Huntington disease)	NM_002111	ATGCTTGTTC	tacagaa	GAGCATGTTA	53
54	HD, Huntington	huntingtin (Huntington disease)	NM_002111	CGCCATGTTG	gcc	AGGCTGGTCT	53
54	HD, Huntington	huntingtin (Huntington disease)	NM_002111	GGGCCTGCTT	ccagtt	AAGCTTGCTT	53
55	HGF, SF	hepatocyte growth factor	NM_000601	ACACATGTAT		TTTCCTGTTT	54
56	HIC1	hypermethylated in cancer 1	NM_006497	GGGCGCTGCCC		TGGCACAGCTC	55
57	HRAS, c-Ha-Ras	Harvey rat sarcoma viral oncogene homolog	NM_176795	large	cluster	site	56

58	HSP90AB1, hsp90beta	heat shock protein 90kDa alpha B 1	NM_007355	GGGACTGTCT	gggtatcgga	AAGCAAGCCT	57
59	HSPA8	heat shock 70kDa protein 8	NM_006597	GcACTAGTTC	tggacctc	GcGCgTGCTT	4
60	IBRDC2, p53RFP	IBR domain containing 2	NM_182757	AGACAGGTCC		TGACAAGCAG	58
61	IER3, IEX-1	immediate early response 3	NM_003897	GCCACATGCCT		CGACATGTGCC	59
62	IGFBP3	insulin-like growth factor binding protein 3	NM_000598	large	cluster	site	60
62	IGFBP3	insulin-like growth factor binding protein 3	NM_000598	GGGCAAGACC		TGCCAAGCCT	60
62	IGFBP3	insulin-like growth factor binding protein 3	NM_000598	AAACAAGCCA	c	CAACATGCTT	60
63	IRF5	interferon regulatory factor 5	NM_032643	AGGCATGCCa	ca	AGGCATGgTC	61
64	KRT8, CK8	keratin 8	NM_002273	ccGCcTGCCT	cc	ActCcTGCCT	62
65	LGALS3, galectin-3	lectin, galactoside-binding, soluble, 3	NM_002306	GGGCTTGCAA	gctg	GAGCCTTGTTT	63
66	LIF	leukemia inhibitory factor	NM_002309	GGACATGTCG		GGACAGCTC	64
67	LRDD, PIDD	leucine-rich repeats and death domain containing	NM_018494	AGGCcTGCCT	gcgtgctg	GGACATGTCT	65
68	MAD1L1, MAD1	MAD1 mitotic arrest deficient-like 1 (yeast)	NM_003550	GATTCAAGCTG		ATACTGAGT	66
69	mdm2	Mdm2, transformed 3T3 cell double minute 2	NM_002392	AGTTAAGTCC		TGACTTGTCT	67
69	mdm2	Mdm2, transformed 3T3 cell double minute 2	NM_002392	GGTCAAGTTC		AGACACGTTC	67
70	MET	met proto-oncogene	NM_000245	ggacggacag	cacgcgaggcagac	AGACAcGTgC	68
71	MLH1	mutL homolog 1, colon cancer	NM_000249	AGGCATGTAC	a	GCGCATGCCC	69
72	MMP2	matrix metallopeptidase 2	NM_004530	AGACAAGCCT		GAACTTGTCT	70
73	MSH2	mutS homolog 2	NM_000251	GAcCTAGgCg	c	AGGCATGCgC	71
73	MSH2	mutS homolog 2	NM_000251	AGGCTAGTTT	ttttttgttttc	AAGTTTCCTT	72
74	NDRG1	N-myc downstream regulated gene 1	NM_006096	CCACATGCAC	acgcacgagcgc	GCACATGAAC	73
75	NLRC4, Ipaf	NLR family, CARD domain containing 4	NM_021209	AGACATGTTC		CTGGTAGTTT	74
76	NOS3	nitric oxide synthase 3 (endothelial cell)	NM_000603	GAGCcTcCCa	gcc	GGGCTTGTTC	75
77	ODC1	ornithine decarboxylase 1	NM_002539	GGACcAGTTC	caggc	GGGCgAGaCC	4
77	ODC1	ornithine decarboxylase 2	NM_002539	GGGCTcGCCT	tggtacagac	GAGCggGCCC	4
78	P2RXL1	purinergic receptor P2X-like 1, orphan receptor	NM_005446	GAACAAGggC	at	GAGCTTGTCT	76
79	P53AIP1	p53-regulated apoptosis-inducing protein 1	NM_022112	TCTCTTGCCC		GGGCTTGTCG	77
80	PCBP4, MCG10	poly(rC) binding protein 4	NM_020418	GgtCTTGgCCC		AGACTTAGCaC	78
80	PCBP4, MCG10	poly(rC) binding protein 4	NM_020418	GAACTT	aagaccgaggctct	GGACAAGTT	78
81	PCNA	proliferating cell nuclear antigen	NM_002592	GAACAAGTCC		GGGCATaTgT	79
82	PERP	PERP, TP53 apoptosis effector	NM_022121	AGGCAAGCTC		CAGCTTGTTC	80
83	PLAGL1, ZAC	pleiomorphic adenoma gene-like 1	BC074814	CAACTAGACT		AGACTAGCTT	81
84	PLK2, SNK	polo-like kinase 2 (Drosophila)	NM_006622	AGACATGgTg	tgt	AAACTAGCTT	82
84	PLK2, SNK	polo-like kinase 2 (Drosophila)	NM_006622	GGtCATGaTT	cct	tAACTTGCCT	82
84	PLK2, SNK	polo-like kinase 2 (Drosophila)	NM_006622	AAACATGCCT		GGACTTGCCC	82

85	PLK3	polo-like kinase 3 (Drosophila)	NM_004073	TAACATGCCC	gggcaa	AAGCGAGCGC	19
86	PML	promyelocytic leukemia	NM_002675	GcGCTgGCCT	ggagccag	GGGCATGTCC	83
87	PMS2	PMS2 postmeiotic segregation increased 2	NM_000535	ATACTTGATT	tg	TTTCTTGTAA	69
88	PPM1J, MGC19531	protein phosphatase 1J (PP2C domain containing)	NM_005167	GAACATGCCT		GAGCAAGCCC	41
89	PRDM1, BLIMP1	PR domain containing 1, with ZNF domain	NM_182907	GTGCAAGTCT		GGACATGTTT	84
90	PRKAB1, AMPKbeta1	protein kinase, AMP-activated, beta 1	NM_006253	GTTCTTGCCG		CGGCTTGCCT	19
91	PTEN	phosphatase and tensin homolog	NM_000314	GAGCAAGCCC	caggcagctacact	GGGCATGCTC	85
92	PTK2, FAK	PTK2 protein tyrosine kinase 2	NM_153831	AAGCAAGCC		no 2nd site	86
93	PYCARD, ASC	PYD and CARD domain containing	NM_013258	GTGCAAGCCC	ag	AGACAAGCAG	87
94	RABGGTA	Rab geranylgeranyltransferase, alpha subunit	NM_004581	CCTCTTGTGG	aacgtgca	AAGCCTGTCC	19
95	RB1	retinoblastoma 1 (including osteosarcoma)	NM_000321	GGGCGTGCCC	cgac	GTGCgcGCgC	88
96	RFWD2, COP1	ring finger and WD repeat domain	NM_022457	AGACTTGCCT	gt	GAACAGTCAC	89
97	RPS27L	ribosomal protein S27-like	NM_015920	GGGCATGTAG		TGACTTGCCC	41
98	RRM2B, p53R2	ribonucleotide reductase M2 B	NM_015713	tGACATGCCC		AGGCATGTCT	90
99	S100A2	S100 calcium binding protein A2	NM_005978	GGGCATGTgT		GGGCAcGTTC	91
100	SCARA3, CSR1	scavenger receptor class A, member 3	NM_016240	GGGCAAGCCC		AGACAAGTTg	92
101	SCD	stearoyl-CoA desaturase (delta-9-desaturase)	NM_005063	GGGCcgGTCC	t	GGGCTAGgCT	4
102	SCN3B	sodium channel, voltage-gated, type III, beta	NM_018400	TGACTTGCTC		TGCCTTGCCT	93
102	SCN3B	sodium channel, voltage-gated, type III, beta	NM_018400	TGGCAAGGCT		GAGCTAGTTC	93
103	SERPINB5, maspin	serpin peptidase inhibitor, clade B, member 5	NM_002639	GAACATGTTg	g	AGGCcTtTTg	94
104	SERPINE1	serpin peptidase inhibitor, clade E, member 1	NM_000602	AcACATGCCT		cAGCAAGTCC	95
105	SESN1, PA26	sestrin 1	AF033120	GGACAAGTCT		CCACAAGTCa	96
106	SFN, 14-3-3sigma	stratifin	NM_006142	AGCATTAGCCC		AGACATGTCC	97
107	SH2D1A, SAP	SH2 domain protein 1A, Duncan's disease	NM_002351	GGCTGGCTC	agctgt	CAGCTTGCTT	98
107	SH2D1A, SAP	SH2 domain protein 1A, Duncan's disease	NM_002351	GGGCTGGCTC		GGCTGGCTC	98
107	SH2D1A, SAP	SH2 domain protein 1A, Duncan's disease	NM_002351	CAACACTGCAC	tagt	GGGCTGGCTC	98
108	SLC38A2	solute carrier family 38, member 2	NM_018976	AAcCATGCTg	ttacacgcacc	AGCTTGTCC	4
109	STEAP3, TSAP6	STEAP family member 3	NM_001008410	AGACAAGCAT	ag	GGACATGCTC	99
110	TAP1	transporter 1, ATP-binding cassette	NM_000593	GGGCTTGgCC	ctgccg	GGACTTGCCT	100
111	TGFA	transforming growth factor, alpha	NM_003236	GGGCAGGCCC		TGCCTAGTCT	101
112	TNFRSF10A, DR4	tumor necrosis factor receptor superfamily, 10a	NM_003844	GGGCATGTCC		GGGCAgGagg	102
113	TNFRSF10B, DR5	tumor necrosis factor receptor superfamily, 10b	NM_003842	GGGCATGTCC		GGGCAAGaCg	103
114	TNFRSF10C, DcR1	tumor necrosis factor receptor superfamily, 10c	NM_003841	GGGCATGTCC		GGGCAGGACG	104
115	TNFRSF10D, DcR2	tumor necrosis factor receptor superfamily, 10d	NM_003840	GGGCATGTCT		GGGCAGGACG	104
116	TP53, p53	tumor protein p53 (Li-Fraumeni syndrome)	NM_000546	TTACTTGCCC		TTACTTGTCA	105

117	TP53i3, Pig3	tumor protein p53 inducible protein 3	NM_004881	large	cluster	site	106
118	TP53INP1	tumor protein p53 inducible nuclear protein 1	NM_033285	GAACTTGggg		GAACATGTTT	107
119	TP63, TP73L	tumor protein p63, p73-like Delta N variant	AF075433	TAACTTGTTA	ttg	AAACATGCTC	108
120	TP73, p73	tumor protein p73	NM_005427	GtACTTGCCg	tccgggga	GAACTTGCag	109
120	TP73, p73	tumor protein p73	NM_005427	GAACTTGCag	agtaagctgga	GAGCTTGaaT	109
121	Tp73:Delta	tumor protein p73 Delta N variant	AY040827	GGGCAAGCT	gaggcctgcccc	GGACTTGGAT	110
122	TRIAP1, p53CSV	TP53 regulated inhibitor of apoptosis 1	NM_016399	CTTCATGTCC		GTGCATGCCT	111
123	TRIM22, Staf50	tripartite motif-containing 22	NM_006074	TGACATGTCT		AGGCATGTAG	112
124	TRPM2	transient receptor potential cation channel, M2	NM_003307	GGCCTTGCCT	tgctc	AGGCCTGCTT	4
124	TRPM2	transient receptor potential cation channel, M2	NM_003307	GAGCAGGTCT	gacctgcttccca	GGGCCTGCTT	4
124	TRPM2	transient receptor potential cation channel, M2	NM_003307	TGCCTTGCTC		AGGCCTGCTT	4
125	TSC2	tuberous sclerosis 2	NM_000548	TAACAAGCTC	g	GGGCTAGCCC	113
125	TSC2	tuberous sclerosis 2	NM_000548	AGGCTAGTCT	gaaactcctgggc	TGACGTGAC	113
125	TSC2	tuberous sclerosis 2	NM_000548	GGGCATGGTG		GCACATGCCT	113
126	TYRP1, TRP-1	tyrosinase-related protein 1	NM_000550	CGCCTAGTTT	gggt	GAGCAGATT	114
126	TYRP1, TRP-1	tyrosinase-related protein 1	NM_000550	GAGCAGATT	tgggattaattatc	AGGCAGCAA	114
126	TYRP1, TRP-1	tyrosinase-related protein 1	NM_000550	CCACATGCAC	t	TAACAGTTC	114
126	TYRP1, TRP-1	tyrosinase-related protein 1	NM_000550	AGACCAGCCC	cc	CGCCTAGTTT	114
126	TYRP1, TRP-1	tyrosinase-related protein 1	NM_000550	AGGCAGCAA	t	CCACATGCAC	114
127	UBD, FAT10	ubiquitin D	NM_006398	AGGCATGCTC		AGTGGCGTGG	115
128	VCAN, CSPG2	versican	NM_004385	AGACTTGCC	a	CAGACAAGTCC	116
129	VDR	vitamin D (1,25- dihydroxyvitamin D3) receptor	NM_000376	TAACTAGTTT		GAACAAGTTG	117
129	VDR	vitamin D (1,25- dihydroxyvitamin D3) receptor	NM_000376	AGGTTAGATG	tac	TAACTAGTTT	117

*This table provides the gene names, the accession numbers and the DNA response elements (REs) of experimentally validated p53-regulated genes. The REs typically consist of two half sites separated by a variable length spacer. Exceptional cases consist of only one apparent half site. The REs that consist of many (>4) half sites are annotated as 'large cluster sites', and as such, are too large to include in the space provided.

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Supplementary information S2 (table) | Description of genes regulated by p53 (part II)*

#	Gene Name(s)	Location	Type	bp from TSS	Function	PHMM Score	Refs
1	ABCB1, MDR1	Promoter	repressor	-89 to -57bp		63.34	1
2	ACTA2	Promoter	activator	-330 to -311bp	CytoS	67.61	2
3	AIFM2, AMID	Promoter	activator	-596 to -567bp	A	81.34	3
3	AIFM2, AMID	Promoter	activator	-682 to -654bp	A	66.15	3
4	ANLN	Promoter	repressor	-866 to -841bp	CytoS	73.89	4
5	APAF1	Promoter	activator	-603 to -571bp	A	90.33	5
6	APC	Promoter	both	-230 to -198bp	R-	74.23	6
7	ARID3A, E2FBP1	Intron 2	activator	4240 to 4259bp	C	83.53	7
8	ATF3	Promoter	activator	-388 to -352bp	T	80.67	8
9	BAI1	Intron 9	activator	17444 to 17462bp	ECM	79.09	9
10	BAX	Intron 1	activator	354 to 373bp	A	87.61	10
11	BBC3, PUMA	Promoter	activator	-145 to -126bp	A	79.34	11
12	BCL2L14, BCL-G	5'-UTR, Intron 1	activator	1612 to 1631bp	A	64.87	12
13	BCL6	5'-UTR, Intron 1	activator	696 to 728bp	-F	78.49	13
14	BDKRB2, BK2	Promoter	activator	-86 to -67bp	CytoR	45.12	14
15	BID	Intron 1	activator	17277 to 17296bp	A	80.44	15
16	BIRC5, survivin	5'-UTR, Exon 1	repressor	34 to 56bp	A	81.44	16
17	BNIP3L	Downstream (4476)	activator	34574 to 34598bp	A	85	17
18	BTG2, TIS21	Promoter	activator	-25 to -5bp	C, DNA-R	42.33	18
19	C12orf5	Intron 1	activator	411 to 432bp	?	93.39	19
20	C13orf15, RGC32	Intron 2	activator	1116 to 1138bp	C	76.75	20
21	CASP1	Promoter	activator	-99 to -79bp	CytoR	79.94	21
22	CASP10	Promoter	activator	-1082 to -1058bp		70.01	22
23	CASP6	Intron 3	activator	5974 to 5997bp	A	76.81	23
24	CAV1	Promoter, 5'-UTR, Exon 1	activator	-17 to 13bp	E,C	52.91	24
25	CCNG1	5'-UTR, Intron 1	activator	356 to 375bp	C	86.92	25
26	CCNK	5'-UTR, Intron 1	activator	2887 to 2908bp	C	81.53	26
27	CD82, KAI1	Promoter	activator	-886 to -862bp	ECM	77.17	27
28	CDC25C	Promoter	repressor	-155 to -125bp	C	87.3	28
29	CDKN1A, p21	Promoter	activator	-1373 to -1354bp	C, S	49	29
29	CDKN1A, p21	Promoter	activator	-1378 to -1359bp	C, S	70.59	30
29	CDKN1A, p21	Promoter	activator	-2260 to -2241bp	C, S	82.92	30
30	Chmp4C	Promoter	activator	-497 to -460bp	E	90.68	31

31	COL18A1	Promoter	activator	-2836 to -2817bp	ECM	77.62	12
31	COL18A1	Promoter	activator	-2360 to -2341bp	ECM	77.62	12
32	CRYZ	5'-UTR, Intron 1	repressor	7721 to 7743bp	?	74.99	4
33	CTSD, IRDD	Promoter	activator	-373 to -352bp	A	53.25	32
33	CTSD, IRDD	Promoter	activator	-144 to -125bp	A	66.26	32
34	CX3CL1, fractalkine	Promoter	activator	-279 to -259bp	CytoR	78.38	33
35	DDB2	5'-UTR, Exon 1	activator	18 to 38bp	DNA-R	92.09	34
36	DDIT4, REDD1	Promoter	activator	-302 to -283bp	DNA-R	66.03	35
37	DDR1	Promoter	activator	-1494 to -1475bp	GR, R+	74.81	36
38	DKK1	Promoter	activator	-2136 to -2111bp	A	75.34	37
39	DNMT1	5'-UTR, Exon 1	repressor	29 to 55bp	?	82.01	38
40	DUSP1, MKP1	Intron 2	activator	1235 to 1255bp	C, A	63.61	39
41	DUSP5	Promoter	activator	-1127 to -1107bp	C, CytoS	69.28	40
42	EDN2	Intron 3	activator	2197 to 2216bp	?	88.14	41
43	EEF1A1	Exon 4, CDS	activator	1869 to 1890bp	CytoS, A	81.43	42
43	EEF1A1	Exon 2, CDS	activator	1044 to 1067bp	CytoS, A	78.98	42
43	EEF1A1	Exon 3, CDS	activator	1670 to 1691bp	CytoS, A	61.94	42
44	EGFR	Promoter, 5'-UTR, Exon 1	activator	-19 to 3bp	C, R+	72.16	43
45	EphA2	Promoter	activator	-1541 to -1519bp	A	78.25	44
46	FANCC, FAC	Promoter	activator	-1286 to -1257bp	A, DNA-R	71.11	45
47	FAS, CD95	Intron 1	activator	779 to 798bp	A	84.08	46
48	FDXR	Promoter	activator	-43 to -24bp		80.48	47
49	GADD45A	Intron 3	activator	1576 to 1595bp	DNA-R	86.2	48
50	GDF15, MIC-1	5'-UTR, Exon 1, CDS	activator	12 to 31bp	A	79.68	49
50	GDF15, MIC-1	Promoter	activator	-866 to -847bp	A	80.39	50
51	GML	Promoter	activator	-18969 to -18950bp	C	90.16	51
52	GPX1	Promoter	activator	-182 to -163bp	DNA-R	83.67	19
53	HBV		repressor			69.91	52
54	HD, Huntington	Intron 2	activator	15233 to 15259bp	CNS	78.76	53
54	HD, Huntington	Promoter	activator	-1855 to -1833bp	CNS	72.93	53
54	HD, Huntington	Intron 3	activator	25968 to 25993bp	CNS	83.11	53
55	HGF, SF	Promoter	activator	-324 to -305bp	C, R+	59.08	54
56	HIC1	5'-UTR, Intron 1	activator	555 to 576bp	F	67.63	55
57	HRAS, c-Ha-Ras	5'-UTR, Intron 1	activator	735 to 851bp	C	79.63	56
58	HSP90AB1, hsp90beta	5'-UTR, Exon 1	repressor	16 to 45bp	HSP	80.95	57
59	HSPA8	5'-UTR, Intron 1	repressor	648 to 675bp	HSP	70.91	4

60	IBRDC2, p53RFP	Promoter	activator	-168 to -149bp	C	74.51	58
61	IER3, IEX-1	Promoter	repressor	-247 to -226bp	A	77.27	59
62	IGFBP3		activator				60
62	IGFBP3	Intron 2	activator	4090 to 4109bp	R-	77.64	60
62	IGFBP3	Intron 1	activator	3170 to 3190bp	R-	78.69	60
63	IRF5	Exon 2, CDS	activator	4007 to 4028bp	CytoR	84.55	61
64	KRT8, CK8	5'-UTR, Exon 1	activator	30 to 51bp	CytoS	63.36	62
65	LGALS3, galectin-3	Intron 2	repressor	8239 to 8263bp	A	74.97	63
66	LIF	Intron 1	activator	873 to 891bp	CytoR	80.9	64
67	LRDD, PIDD	5'-UTR, Exon 2	activator	804 to 831bp	A	90.45	65
68	MAD1L1, MAD1	Promoter	repressor	-316 to -297bp	C	47.36	66
69	mdm2	5'-UTR, Intron 1	activator	762 to 781bp	F-	70.03	67
69	mdm2	5'-UTR, Intron 1	activator	724 to 743bp	F-	77.32	67
70	MET	Promoter	activator	-232 to -199bp	C, R+	67.42	68
71	MLH1	Intron 1	activator	269 to 289bp	DNA-R	87.36	69
72	MMP2	Promoter	activator	-1645 to -1626bp	EMC	89.83	70
73	MSH2	Promoter	activator	-173 to -153bp	DNA-R	71.85	71
73	MSH2	Promoter	activator	-378 to -346bp	DNA-R	68.75	72
74	NDRG1	Promoter	activator	-373 to -342bp	A	65.88	73
75	NLRC4, Ipaf	Promoter	activator	-169 to -150bp	A	67.51	74
76	NOS3	5'-UTR, Intron 1	repressor	2575 to 2597bp	CytoR	72.37	75
77	ODC1	Promoter	repressor	-334 to -310bp	C	73.5	4
77	ODC1	5'-UTR, Intron 1	repressor	585 to 614bp	C	73.55	4
78	P2RXL1	Downstream (1631)	activator	15281 to 15302bp	CNS	78.99	76
79	P53AIP1	5'-UTR, Intron 1	activator	2002 to 2021bp	A	73.6	77
80	PCBP4, MCG10	Promoter	activator	-891 to -870bp	A	70.04	78
80	PCBP4, MCG10	Promoter	activator	-1852 to -1824bp	A	63.97	78
81	PCNA	5'-UTR, Intron 1	activator	6428 to 6447bp	C, DNA-R	77.17	79
82	PERP	Intron 1	activator	3361 to 3380bp	A	84	80
83	PLAGL1, ZAC	Promoter	activator	-861 to -842bp	C, F-	73.58	81
84	PLK2, SNK	Promoter	activator	-2258 to -2236bp	C	75.96	82
84	PLK2, SNK	Promoter	activator	-1303 to -1281bp	C	73.01	82
84	PLK2, SNK	Promoter	repressor	-2033 to -2014bp	C	93.13	82
85	PLK3	Promoter	activator	-439 to -414bp	C	73.15	19
86	PML	Intron 1	activator	643 to 670bp	T, S, A	85.42	83
87	PMS2	Intron 1	activator	2977 to 2998bp	DNA-R	50.66	69

88	PPM1J, MGC19531	Downstream (6082)	activator	11355 to 11374bp	?	92.48	41
89	PRDM1, BLIMP1	Promoter	activator	-356 to -337bp	CytoR	87.21	84
90	PRKAB1, AMPKbeta1	5'-UTR, Exon 1	activator	65 to 84bp	F-	74.37	19
91	PTEN	Promoter	activator	-117 to -84bp	A	93.98	85
92	PTK2, FAK	Promoter	repressor	-968 to -960bp	C, R	-18.5	86
93	PYCARD, ASC	Promoter	activator	-80 to -59bp	A	79.38	87
94	RABGGTA	5'-UTR, Exon 1	activator	226 to 253bp	?	66.72	19
95	RB1	5'-UTR, Exon 1	activator	59 to 82bp	C	73.47	88
96	RFWD2, COP1	Promoter	activator	-2198 to -2177bp	F-	75.83	89
97	RPS27L	Intron 1	activator	223 to 242bp	?	81.59	41
98	RRM2B, p53R2	Intron 1	activator	2259 to 2278bp	DNA-R	91.36	90
99	S100A2	Promoter	activator	-1850 to -1831bp	C	82.35	91
100	SCARA3, CSR1	Intron 2	unknown	17074 to 17093bp	DNA-R	87.81	92
101	SCD	Promoter	repressor	-199 to -179bp	ECM	78.12	4
102	SCN3B	Promoter	activator	-9137 to -9118bp	A	75.77	93
102	SCN3B	Intron 3	activator	13595 to 13614bp	A	77.54	93
103	SERPINB5, maspin	Promoter	activator	-224 to -204bp	ECM	64.63	94
104	SERPINE1	Promoter	activator	-226 to -207bp	ECM	82.89	95
105	SESN1, PA26	Intron 1	activator	511 to 530bp	C, S	77.67	96
106	SFN, 14-3-3sigma	Promoter	activator	-1812 to -1792bp	C	77.49	97
107	SH2D1A, SAP	Promoter	activator	-1884 to -1860bp	C, CytoR	70.91	98
107	SH2D1A, SAP	Promoter	activator	-1894 to -1876bp	C, CytoR	72.95	98
107	SH2D1A, SAP	Promoter	activator	-1909 to -1885bp	C, CytoR	66.65	98
108	SLC38A2	Downstream (532)	repressor	15079 to 15108bp	?	75.78	4
109	STEAP3, TSAP6	5'-UTR, Intron 1	activator	21225 to 21246bp	ECM, E	87.66	99
110	TAP1	Exon 1, CDS	activator	643 to 668bp	R	89.35	100
111	TGFA	Promoter	activator	-84 to -65bp	C, R	77.98	101
112	TNFRSF10A, DR4	Intron 1	activator	479 to 498bp	A	77.36	102
113	TNFRSF10B, DR5	Intron 1	activator	538 to 557bp	A	86.85	103
114	TNFRSF10C, DcR1	Intron 1	activator	369 to 388bp	A	83.07	104
115	TNFRSF10D, DcR2	Intron 1	activator	351 to 370bp	A	82.02	104
116	TP53, p53	Promoter, 5'-UTR, Exon 1	activator	-12 to 7bp	A, C, S, DNA-R, F+	66.94	105
117	TP53i3, Pig3	5'-UTR, Exon 1	activator	441 to 515bp	DNA-R	66.29	106
118	TP53INP1	Intron 3	activator	10562 to 10581bp	A	73.72	107
119	TP63, TP73L	Promoter	activator	-756 to -734bp	R-	76.02	108
120	TP73, p73	Promoter	activator	-2630 to -2603bp	R-	73.37	109

120	TP73, p73	Promoter	activator	-2612 to -2582bp	R-	68.78	109
121	Tp73:Delta	Promoter	activator	-75 to -45bp	R-	84.87	110
122	TRIAP1, p53CSV	Exon 1, CDS	activator	56 to 75bp	A	76.63	111
123	TRIM22, Staf50	5'-UTR, Intron 1	activator	694 to 713bp	DNA-R	80.91	112
124	TRPM2	Promoter	repressor	-2251 to -2227bp	CNS, C	81.77	4
124	TRPM2	Promoter	repressor	-1878 to -1846bp	CNS, C	82.07	4
124	TRPM2	Promoter	repressor	-2246 to -2227bp	CNS, C	74.96	4
125	TSC2	Intron 11	activator	13579 to 13599bp	R-	84.19	113
125	TSC2	Intron 2	activator	3921 to 3952bp	R-	71.77	113
125	TSC2	Intron 2	activator	2579 to 2598bp	R-	80.62	113
126	TYRP1, TRP-1	Promoter	activator	-122 to -100bp	protective	59.86	114
126	TYRP1, TRP-1	Promoter	activator	-108 to -77bp	protective	54.39	114
126	TYRP1, TRP-1	Promoter	activator	-75 to -56bp	protective	61.9	114
126	TYRP1, TRP-1	Promoter	activator	-134 to -113bp	protective	73.8	114
126	TYRP1, TRP-1	Promoter	activator	-85 to -66bp	protective	60.42	114
127	UBD, FAT10	Promoter	repressor	-239 to -220bp	A	59.67	115
128	VCAN, CSPG2	5'-UTR, Intron 1	activator	684 to 704bp	C	87.31	116
129	VDR	5'-UTR, Intron 1	activator	4720 to 4739bp	C, A	73.09	117
129	VDR	5'-UTR, Intron 1	activator	4707 to 4729bp	C, A	55.95	117

*This table provides additional information on the gene set found in Supplementary information S1 (table). This table provides the relative locations in the gene, the regulation type, the distances to the transcription start site (TSS), the gene functions, the Profile Hidden Markov Model (PHMM) score and the references. The PHMM scores are normalized by the highest possible score (such that the highest possible score is 100). The HG17 release of the human genome sequence was employed to deduce the distances from the TSS. Functions are as follows: A = apoptosis, C = cell cycle control, S = senescence, CytoS = cytoskeleton, E = endosome and exosome compartment, ECM = extracellular matrix, F+/- = positive/negative feedback loops for p53, R+/- = regulation by p53 upon other signal transduction pathways, T = transcription and translation, DNA-R = DNA repair, CytoR = cytokine and inflammatory regulator, CNS = central nervous system regulator, GR = growth factor regulator, HSP = heat shock protein.

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