Somatic Mutations in Human Cancer: Insights from Resequencing the Protein Kinase Gene Family

P.A. FUTREAL, R. WOOSTER, AND M.R. STRATTON

Cancer Genome Project, Wellcome Trust Sanger Institute, Hinxton, CB10 1SA, United Kingdom

All cancers arise due to the accumulation of mutations in critical target genes that, when altered, give rise to selective advantage in the cell and its progeny that harbor them. Knowledge of these mutations is key in understanding the biology of cancer initiation and progression, as well as the development of more targeted therapeutic strategies. We have undertaken a systematic screen of all annotated protein kinases in the human genome for mutations in a series of cancers including breast, non-small-cell lung, and testicular cancer. Our results show a wide diversity in mutation prevalence within and between tumor types. We have identified a mutator phenotype in human breast previously undescribed. The results presented from sequencing the same 1.3 million base pairs through several tumor types suggest that most of the observed mutations are likely to be passenger events rather than causally implicated in oncogenesis. However, this work does provide evidence for the likely existence of multiple, infrequently mutated kinases.

Cancer is a disease of DNA. All cancers arise due to the accumulation of mutations in DNA sequence. These sequence alterations give rise to mutations in critical target genes that ultimately provide a selective growth advantage for the cells harboring them, leading to the clinical manifestations of cancer. The identification of mutated genes in human cancer has been a major focus of cancer research for the past three decades. Identification of these mutations and the cellular pathways that are subverted holds the promise of better diagnostics and more targeted therapies. As well, a more general understanding of mutation prevalence and pattern in cancers will inform on both extrinsic and intrinsic erosive processes that buffet the genome, leading to oncogenesis as well as potential deficits in handling DNA damage.

Mutations in cancer can take the form of chromosomal-scale events such as rearrangements and translocations; subchromosomal alterations in the form of deletions and amplifications; and smaller-scale events comprising insertions, deletions, and base-pair substitutions. As well, the state of DNA methylation can be altered in cancers, providing an epigenetic means for gene deregulation.

Perhaps the least well investigated category of DNA alterations in cancer is that of point mutations—small insertions/deletions and substitutions. Genes primarily targeted by this class of mutation may leave few other positional clues (such as translocation, amplification, germ-line susceptibility alleles) to expedite their identification. Evidence from our recent census of cancer genes suggests that point-mutated genes are underrepresented, particularly in the solid tumors which comprise the bulk of the cancer burden in the population (Futreal et al. 2004). We have undertaken a systematic resequencing approach to ascertain those genes with mutations in this class with the hope of identifying important target genes and to begin to investigate the patterns of somatic mutation in a variety of human cancers.

WHY START WITH PROTEIN KINASES?

We have chosen the family of protein kinases as a first set of genes for resequencing efforts. Genes containing a protein kinase encoding domain are the most frequently mutated in human cancer. Kinases function as key molecular controllers of virtually all cellular processes including cell growth, division and apoptosis—all frequently aberrant in human cancer. As well, kinases have proven to be the most tractable class of proteins for the development of targeted therapeutics in cancer to date. Targeted inhibition of amplified *ERBB2/HER2-neu* receptor in metastatic breast cancer with trastuzumab (Herceptin) (a humanized monoclonal antibody) is the first example of targeted exploitation of a kinase target in cancer therapy (Slamon et al. 2001). The clinical efficacy of imatinib (Gleevec), a small-molecule inhibitor of rearranged and mutated *ABL*, *KIT*, and *PDGFRA/B* kinases, in chronic myelogenous leukemia (CML), gastrointestinal stromal tumors, and idiopathic hypereosinophilic syndrome has established the paradigm for small-molecule-inhibitor-based therapeutics in cancer (Sawyers 2004). Intragenic activating mutations in the *EGFR* gene have been shown to be important mediators of significant response to small-molecule EGFR inhibitors in stage III–IV adenocarcinoma of the lung (Lynch et al. 2004; Paez et al. 2004; Pao et al. 2004), thus extending the imatinib model into an adult epithelial cancer with undoubtedly more complex genetic alterations. Although the responses in lung cancer patients to two EGFR inhibitors, gefitinib (Iressa) and erlotinib (Tarceva), are not as dramatic or durable as those seen in CML with imatinib, they nevertheless show that targeted molecular therapeutics are active in an epithelial cancer which is otherwise refractory to treatment. This potential therapeutic vulnerability of cancers when treated with agents directed at specific mutated genes has been referred to as “oncogene addiction.” In this model, a cancer be-

comes dependent on (addicted to) a particular oncogenically (mutationally) activated pathway for its survival, thus making that pathway particularly attractive for therapeutic intervention (Weinstein 2002).

More recently, the development of clinical resistance to both imatinib in CML and gefitinib in lung adenocarcinoma has been shown to be due to specific point mutations within the kinase domain binding site for the drug, further illustrating the critical role of the target gene in treatment efficacy (Gorre et al. 2001; Kobayashi et al. 2005). Certainly the success of exploiting mutated kinase targets and, conversely, the emergence of clinical resistance when targeting kinases with small-molecule inhibitors, suggest that further identification of mutated kinases in human cancer will provide an important opportunity for both the development of de novo therapeutics and the beginnings of poly-molecular therapy for cancer.

RESEQUENCING THE PROTEIN KINASES— OVERALL RESULTS

The protein kinase family comprises 518 genes (Manning et al. 2002). We have resequenced the coding exons plus splice junctions of the entire family (~1.3 million base pairs [Mb]/sample) in a series of 25 breast cancers, 33 non small-cell lung cancers (NSCLC), and 13 testicular germ-cell tumors (TGCT) (Table 1). In total, 92 Mb of sequence were generated from the 71 samples analyzed, providing the most in-depth analysis of somatic mutations in human cancer undertaken to date.

In each case studied there was a matching DNA sample from normal tissue (usually peripheral blood) from the same individual to verify the somatic nature of the observed mutations. Each coding exon including splice junctions was amplified and sequenced bidirectionally from tumor DNA. Any amplicon containing a sequence variant that was not an obvious single-nucleotide polymorphism (SNP) (present in dbSNP <http://www.ncbi.nlm.nih.gov/SNP/> or previously observed to be a germ-line polymorphism in in-house sequencing efforts) was then amplified from matching normal DNA for the particular case. If the variant was not present in the germ-line DNA, indicating the mutation to be of somatic origin, both tumor and normal were reamplified and sequenced to confirm the somatic mutation. For a subset of genes with somatic mutations, a follow-up study in an independent set of cancers of roughly twice the size of the original screen was undertaken to investigate prevalence.

In total, we identified 279 somatic mutations distributed among 78 genes in the 71 sample (92 megabases) screens under discussion; 185 missense, 25 nonsense, 6 frameshift, 3 in-frame deletion, 12 consensus splice site, and 48 silent mutations were identified (<http://www.sanger.ac.uk/genetics/CGP/Kinases/>) (Bignell et al. 2005; Davies et al. 2005; Stephens et al. 2005). Of note, the rate of silent mutations (unlikely to be under selective pressure) reflects the minimum rate of somatic mutation “noise” to be dealt with in any such large-scale resequencing endeavor.

The most frequently mutated gene was *TTN*, encoding the Titin giant sarcomeric protein, with 15 somatic muta-

tions. Monte Carlo simulation analysis of mutation distribution by coding “footprint” size showed that mutations were not found any more often than predicted by chance when size of coding sequence was taken into account, suggesting that numbers of mutations per se was not a reliable indicator of presumptive oncogenic potential. Additional analyses included manual scrutiny for clustering in genes, for occurrence at conserved positions that are known to be mutated in other kinases, and for tumor type clustering.

To assess potential selection for coding (nonsynonymous) mutations, each nucleotide of the 1.3-Mb coding footprint of the protein kinases was mutated in silico to each of the other three bases (correcting for the observed mutational spectrum and sequence context of mutations), the resulting sequence was translated, and the mutations were classified into missense, nonsense, and silent (synonymous) changes. A higher than expected ratio of non-synonymous:synonymous (nonsyn:syn) changes (which varies from 2:1 to 3:1 depending on the mutational spectrum) suggests that mutations which change the coding sequence are being selected and, hence, that a proportion of mutations detected may be implicated in cancer causation. For both the breast and lung screens, there was evidence for an excess of nonsynonymous changes, suggesting that proportion of mutations identified are likely contributory to oncogenesis, although any one was only mutated at low frequency. Even so, our data suggest that the majority of somatic mutations identified are passenger events and, as such, are significant confounders in trying to identify rare oncogenic mutations. Overall, the screens have not identified a frequently mutated protein kinase in the tumor types examined. However, given the small sample numbers and likely impact of tumor heterogeneity, additional screens are warranted.

The overall distribution of mutations among the samples examined is shown in Figure 1. Most striking is the diversity of mutation prevalence among and between tumor types examined. In general, NSCLC had the most mutations/sample examined, followed by breast cancer, then TGCT. Cancer cell lines tended to have more mutations than the primary cancers examined, but this trend was not particularly exaggerated in the NSCLC. For breast cancers, the cell lines comprised a select subset of breast cancers. All were TP53 mutant, and all but one were derived from a premenopausal breast cancer. However, there was one cell line that had no mutations. For primary tumors, each screen yielded a subset that had no detectable somatic mutations. This was most striking in TGCT, where 12 out of 13 cases had no detectable mutations. Within NSCLC, no carcinoid ($n = 6$) had a somatic mutation. Likewise, the majority of breast cancer primaries (12/16) had no mutations.

TGCT was included in these initial screens due to its unique clinical behavior. It is the only solid tumor curable with chemotherapy in the metastatic setting, despite being markedly aneuploid in nearly all cases (Oosterhuis and Looijenga 2005). We detected only a single somatic point mutation in over 15 Mb of sequence in this tumor type, giving it perhaps the lowest mutation prevalence yet observed. Such evidence is supportive of a model of chemosensitivity where there is demonstrable DNA re-

SOMATIC MUTATIONS IN HUMAN CANCER

45

Table 1. Samples Screened for Somatic Mutations in the Protein Kinases

Sample	Study	Histology	Age at diagnosis	Sex	Smoking status
PD0025a	breast	IDC	83	female	ND
PD0062a	breast	IDC	37	female	ND
PD0091a	breast	IDC	83	female	ND
PD0118a	breast	IDC	78	female	ND
PD0119a	breast	pleomorphic lobular	84	female	ND
PD0127a	breast	IDC	81	female	ND
PD0128a	breast	IDC	85	female	ND
PD1232a	breast	mucinous	85	female	ND
PD1233a	breast	IDC	38	female	ND
PD1234a	breast	IDC	43	female	ND
PD1235a	breast	IDC	38	female	ND
PD1236a	breast	IDC	47	female	ND
PD1237a	breast	IDC	55	female	ND
PD1238a	breast	IDC	36	female	ND
PD1239a	breast	IDC	73	female	ND
PD1241a	breast	IDC	45	female	ND
HCC38	breast	IDC	50	female	ND
HCC1143	breast	IDC	52	female	ND
HCC1187	breast	IDC	41	female	ND
HCC1395	breast	IDC	43	female	ND
HCC1599	breast	IDC	44	female	ND
HCC1937	breast	IDC	23	female	ND
HCC1954	breast	IDC	61	female	ND
HCC2157	breast	IDC	48	female	ND
HCC2218	breast	IDC	38	female	ND
PD0248a	NSCLC	SCC	57	male	previous smoker
PD0250a	NSCLC	carcinoid	61	female	nonsmoker
PD0251a	NSCLC	SCC	57	male	current
PD0252a	NSCLC	BAC	83	male	previous smoker
PD0253a	NSCLC	adeno	60	male	current
PD0263a	NSCLC	LC	81	male	previous smoker
PD0269a	NSCLC	SCC	52	male	current
PD0276a	NSCLC	LC	71	male	previous smoker
PD1240	NSCLC	SCC	69	male	unknown
PD1339a	NSCLC	adeno	65	male	previous smoker
PD1345a	NSCLC	adeno	65	male	current
PD1351a	NSCLC	adeno	67	male	unknown
PD1352a	NSCLC	adeno	58	male	current
PD1353a	NSCLC	adeno	65	male	previous smoker
PD1354a	NSCLC	carcinoid	71	female	nonsmoker
PD1355a	NSCLC	carcinoid	40	male	previous smoker
PD1356a	NSCLC	carcinoid	60	female	previous smoker
PD1359a	NSCLC	carcinoid	52	female	previous smoker
PD1360a	NSCLC	carcinoid	34	female	nonsmoker
PD1362a	NSCLC	LC	64	male	previous smoker
PD1364a	NSCLC	LC	57	female	previous smoker
PD1365a	NSCLC	LC	61	female	nonsmoker
PD1367a	NSCLC	LC	53	male	previous smoker
PD1370a	NSCLC	SCC	68	male	previous smoker
PD1373a	NSCLC	SCC	60	female	previous smoker
PD1379a	NSCLC	SCC	76	male	current
NCI-H1395	NSCLC	adeno	55	female	current
NCI-H1437	NSCLC	adeno	60	male	current
NCI-H1770	NSCLC	adeno	57	male	nonsmoker
NCI-H2009	NSCLC	adeno	68	female	current
NCI-H2087	NSCLC	adeno	69	male	current
NCI-H2122	NSCLC	adeno	46	female	current
NCI-H2126	NSCLC	adeno	65	male	unknown
PD1381a	testis	SGCT	29	male	ND
PD1382a	testis	SGCT	31	male	ND
PD1383a	testis	SGCT	50	male	ND
PD1384a	testis	SGCT	72	male	ND
PD1385a	testis	SGCT	28	male	ND
PD1386a	testis	SGCT	31	male	ND
PD1388a	testis	SGCT	22	male	ND
PD1389a	testis	NSGCT (EC TE YST)	26	male	ND
PD1391a	testis	NSGCT (EC TE YST)	37	male	ND
PD1392a	testis	NSGCT (TE YST)	30	male	ND
PD1394a	testis	NSGCT (EC YST TE)	31	male	ND
PD1395a	testis	NSGCT (YST)	32	male	ND
PD1396a	testis	NSGCT (EC YST TE)	26	male	ND

(NSCLC) Non-small-cell lung cancer; (IDC) infiltrating ductal carcinoma; (SCC) squamous cell carcinoma; (BAC) bronchoalveolar carcinoma; (adeno) adenocarcinoma; (LC) large cell carcinoma; (SGCT) seminomatous germ-cell tumor; (NSGCT) non-seminomatous germ-cell tumor; (EC) embryonal carcinoma; (TE) teratoma; (YST) yolk sac tumor; (ND) no data. PD numbered samples are primary tumors.

Figure 1. Somatic mutations in protein kinases by tumor type. Numbers of somatic mutations detected in resequencing the protein kinase gene are shown for each sample type. Y axis indicates the numbers of somatic mutation in each sample. Arrow brackets are provided to delineate specific sample subsets.

pair deficiency coupled with highly active apoptotic responses such that cells which accrue DNA damage are efficiently killed. Resequencing efforts will begin to provide more data to explore the relationship of somatic mutation prevalence, DNA repair competence, and response to therapy.

These screens allow more precise estimation of the absolute frequency of somatic mutations in cancer genomes as a whole. On the assumption that the 1.3-Mb protein kinase coding sequence is, to some extent, a representative sample of the genome, we can estimate the numbers of somatic mutations in each cancer genome and the numbers of consequent “bystander” amino acid changes. Some individual cancers have as many as 100,000 somatic mutations in their genomes, encoding approximately 1,000 amino acid changes (in 1:30 genes). In contrast, it appears that most breast and testis cancers have fewer than 2,000 somatic point mutations and fewer than 20 bystander amino acid changes.

RESEQUENCING THE PROTEIN KINASES— A NEW BREAST CANCER MUTATOR PHENOTYPE

Our analyses have demonstrated substantial diversity of mutation number and pattern in individual breast cancers. Particularly striking was primary tumor PD0119a (a pleomorphic lobular carcinoma occurring in an 84-year-old woman), which had 52 somatic mutations, more than all other breast cancer samples combined. The cancer was ER⁺, ERBB2⁺, TP53 mutation-negative, and negative for

E-cadherin staining, consistent with a luminal-ductal origin. The mutation spectrum in the cancer is characterized by a high frequency of C:G>G:C transversions occurring at TpC(GpA) dinucleotides (Fig. 2). Inactivating mutations in *BRCA1* or *BRCA2* are not associated with this mutational spectrum, and it is not obviously similar to any reported eukaryotic repair defect. The data suggest the characterization of a novel mutator phenotype in human breast cancer, although formally, the results could be due to a massive exposure. Of note, at least one breast cancer cell line appears to have a similar phenotype, derived from a ductal carcinoma in a 38-year-old (Fig. 2). This observation supports the existence of mutator phenotype in breast cancer. It is important to note that the only way currently to identify and characterize such phenotypes is through in-depth sequencing.

RESEQUENCING THE PROTEIN KINASES— MUTATED GENES

Several genes with somatic mutations identified in the screens are worth highlighting. We detected a single in-frame insertion in the kinase domain of *ERBB2* of a NSCLC primary sample, prompting a further screen of this gene in a larger series of cancers. Data from a larger series of primary NSCLC showed that *ERBB2* mutations are present in about 10% of lung adenocarcinoma (Stephens et al. 2004). This was the first report of intra-genic mutation in this well-studied cancer gene. Mutations were found in the kinase domain affecting the α C-helix region, similar to the deletion mutations found in

SOMATIC MUTATIONS IN HUMAN CANCER

47

Figure 2. Sequence context specificity for the mutator phenotype breast cancer. Arrow and yellow bar indicate the position of C:G>G:C transversion mutations identified. Numbering is relative to the position of the mutation. All mutations were regularized to the “C” strand for this analysis. Note the almost complete predominance of a T residue before the mutated C. The sequence of TP53 C:G>G:C transversion mutations in breast cancer is shown for comparison. Red = T, green = A, blue = C, black = G. TP53 data from <http://www-p53.iarc.fr/>

EFGR (Lynch et al. 2004; Paez et al. 2004; Pao et al. 2004). Mutant *ERBB2* was neither overexpressed nor amplified in the cases examined. We found no obvious correlation with smoking history or sex, unlike subsequent studies (Shigematsu et al. 2005). Additional rare *ERBB2* mutations were found in cases of gastric cancer, ovarian cancer, and glioblastoma. Subsequent studies have reported low-frequency mutations (Sasaki et al. 2005), suggesting that *ERBB2* mutations, like those found in *EGFR*, may be restricted to specific subsets of NSCLC. Further work is needed to more clearly delineate the characteristics of this cohort to investigate the potential for the treatment of this subset of patients with anti-*ERBB2* therapies.

Activating germ-line mutations of the fibroblast growth factor receptors, *FGFR1*, *FGFR2*, and *FGFR3*, have been reported in skeletal dysplasias (Wilkie et al. 2002). Somatic mutations of *FGFR3* found in papillary transitional-cell bladder cancer affect identical positions to germ-line mutations predisposing to thanatophoric dwarfism (Cappellen et al. 1999). Analogous to these data, we identified a somatic mutation in *FGFR1* (pP252T) in a bronchoalveolar NSCLC affecting a key codon known to have mutated in the skeletal dysplasia Pfeiffer syndrome (Human Gene Mutation Database,

<http://archive.uwcm.ac.uk/uwcm/mg/hgmd0.html>). Likewise, a somatic mutation was identified in *FGFR2* (pW290C) in a squamous cell lung carcinoma at an identical position reported for germ-line mutations in the skeletal dysplasias, craniosynostosis, Crouzon, and Pfeiffer syndromes. *FGFR2* point mutations have been previously described only in gastric cancer—again at residues analogous to germ-line mutations. These results strongly suggest that mutations in *FGFR1* and *FGFR2* are likely to play a role, albeit uncommonly, in lung carcinogenesis. Further work is needed to determine the rates and subtype distributions of *FGFR* mutations and the possible role of *FGFR* kinase inhibitors in lung cancer therapy.

Somatic mutations within the catalytic loop (pR678Q, pH677Y) and activation segment (pR721F) in *NTRK3*, encoding a neurotrophic growth factor receptor tyrosine kinase, were detected in breast and NSCLC. Mutations in *NTRK3* were also detected in a screen of the tyrosine kinases in colorectal cancers (Bardelli et al. 2003). The clustering of somatic mutations in key highly conserved residues and between tumor types suggests that *NTRK3* mutations are likely contributory to oncogenesis. Likewise, kinase domain mutations in both the primary and follow-up screen of NSCLC were detected in *AURKC* (*STK13*) encoding the aurora kinase C chromosomal pas-

senger protein implicated in centrosome/spindle regulation during mitosis. The aurora kinases are the target for several inhibitors in clinical development (Andrews 2005). The extent of *AURKC* involvement in breast and lung cancers needs to be further investigated to potentially leverage these new therapeutics for these cancers.

CONCLUSIONS

Our resequencing efforts to date have provided evidence for multiple, infrequently mutated kinases in human cancer. Indeed, commonly mutated protein kinases such as *BRAF*, previously identified in a pilot screen in our laboratory (Davies et al. 2002), may well be the exception rather than the rule. Mutation screening of the protein kinases published for colorectal cancer are in agreement with the data presented here (Bardelli et al. 2003; Parsons et al. 2005). Taken together, the data paint a picture of increasing complexity of human cancer with any number of infrequently mutated protein kinases playing a role in oncogenesis. If such is the case, much larger studies will be needed to garner the statistical genetic support for discriminating between rare oncogenic and passenger mutations. New approaches for functional characterization involving high-throughput cell biological assays will be needed to further investigate the effects of these mutations. Newly developed animal model systems for introduction of multiple mutant alleles into specific tissues of the mouse, such as the Sleeping Beauty transposon system (Collier et al. 2005), will need to be exploited. The development of targeted therapeutics becomes more challenging if multiple small-molecule inhibitors are required to make a major impact on a given cancer type.

The data presented here represent the most in-depth look at the state of cancer genomes at the sequence level published to date. It is hoped that this work will help to inform future large-scale efforts such that we can begin to affect treatment of this complex set of diseases at pace and begin to deliver on the promise of the human genome sequence.

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REFERENCES

- Andrews P.D. 2005. Aurora kinases: Shining lights on the therapeutic horizon? *Oncogene* **24**: 5005.
- Bardelli A., Parsons D.W., Silliman N., Ptak J., Szabo S., Saha S., Markowitz S., Willson J.K.V., Parmigiani G., Kinzler K.W., Vogelstein B., and Velculescu V.E. 2003. Mutational analysis of the tyrosine kinome in colorectal cancers. *Science* **300**: 949.
- Bignell G., Smith R., Hunter C., Stephens P., Davies H., Greenman C., Teague J., Butler A., Edkins S., Stevens C., O'Meara S., Parker A., Avis T., Barthorpe S., Brackenbury L., Buck G., Clements J., Cole J., Dicks E., Edwards K., Forbes S., Gorton M., Gray K., Halliday K., Harrison R., Hills K., Hinton J., Jones D., Kosmidou V., Laman R., Lugg R., Menzies A., Perry J., Petty R., Raine K., Shepherd R., Small A., Solomon H., Stephens Y., Tofts C., Varian J., Webb A., West S., Widaw S., Yates A., Gillis A.J.M., Stoop H.J., Gurr R.J.H.L.M.v., Oosterhuis J.W., Looijenga L.H., Futreal P.A., Wooster R., and Stratton M.R. 2005. Sequence analysis of the protein kinase gene family in human testicular germ-cell tumours of adolescents and adults. *Genes Chromosomes Cancer* **45**: 42.
- Cappellen D., De Oliveira C., Ricol D., de Medina S., Bourdin J., Sastre-Garau X., Chopin D., Thiery J., and Radvanyi F. 1999. Frequent activating mutations of FGFR3 in human bladder and cervix carcinomas. *Nat. Genet.* **23**: 18.
- Collier L.S., Carlson C.M., Ravimohan S., Dupuy A.J., and Largaespada D.A. 2005. Cancer gene discovery in solid tumours using transposon-based somatic mutagenesis in the mouse. *Nature* **436**: 272.
- Davies H., Bignell G.R., Cox C., Stephens P., Edkins S., Clegg S., Teague J., Woffendin H., Garnett M.J., Bottomley W., Davis N., Dicks E., Ewing R., Floyd Y., Gray K., Hall S., Hawes R., Hughes J., Kosmidou V., Menzies A., Mould C., Parker A., Stevens C., Watt S., Hooper S., Wilson R., Jayatilake H., Gusterson B.A., Cooper C., Shipley J., Hargrave D., Pritchard-Jones K., Maitland N., Chenevix-Trench G., Riggins G.J., Bigner D.D., Palmieri G., Cossu A., Flanagan A., Nicholson A., Ho J.W., Leung S.Y., Yuen S.T., Weber B.L., Seigler H.F., Darrow T.L., Paterson H., Marais R., Marshall C.J., Wooster R., Stratton M.R., and Futreal P.A. 2002. Mutations of the BRAF gene in human cancer. *Nature* **417**: 949.
- Davies H., Hunter C., Smith R., Stephens P., Greenman C., Bignell G., Teague J., Butler A., Edkins S., Stevens C., Parker A., O'Meara S., Avis T., Barthorpe S., Brackenbury L., Buck G., Clements J., Cole J., Dicks E., Edwards K., Forbes S., Gorton M., Gray K., Halliday K., Harrison R., Hills K., Hinton J., Jones D., Kosmidou V., Laman R., Lugg R., Menzies A., Perry J., Petty R., Raine K., Shepherd R., Small A., Solomon H., Stephens Y., Tofts C., Varian J., Webb A., West S., Widaw S., Yates A., Brasseur F., Cooper C.S., Flanagan A.M., Green A., Knowles M., Leung S.Y., Looijenga L.H.J., Malkowicz B., Pierotti M.A., Teh B.T., Yuen S.T., Lakhani S.R., Easton D.F., Weber B.L., Goldstraw P., Nicholson A.G., Wooster R., Stratton M.R., and Futreal P.A. 2005. Somatic mutations of the protein kinase gene family in human lung cancer. *Cancer Res.* **65**: 7591.
- Futreal P.A., Coin L., Marshall M., Down T., Hubbard T., Wooster R., Rahman N., and Stratton M.R. 2004. A census of human cancer genes. *Nat. Rev. Cancer* **4**: 177.
- Gorre M.E., Mohammed M., Ellwood K., Hsu N., Paquette R., Rao P.N., and Sawyers C.L. 2001. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. *Science* **293**: 876.
- Kobayashi S., Boggon T.J., Dayaram T., Janne P.A., Kocher O., Meyerson M., Johnson B.E., Eck M.J., Tenen D.G., and Hallmos B. 2005. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med.* **352**: 786.
- Lynch T.J., Bell D.W., Sordella R., Gurubhagavatula S., Oki-moto R.A., Brannigan B.W., Harris P.L., Haserlat S.M., Supko J.G., Haluska F.G., Louis D.N., Christiani D.C., Settleman J., and Haber D.A. 2004. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med.* **350**: 2129.
- Manning G., Whyte D.B., Martinez R., Hunter T., and Sudarsanam S. 2002. The protein kinase complement of the human genome. *Science* **298**: 1912.
- Oosterhuis J.W. and Looijenga L.H.J. 2005. Testicular germ-cell tumours in a broader perspective. *Nat. Rev. Cancer* **5**: 210.
- Paez J.G., Janne P.A., Lee J.C., Tracy S., Greulich H., Gabriel S., Herman P., Kaye F.J., Lindeman N., Boggon T.J., Naoki K., Sasaki H., Fujii Y., Eck M.J., Sellers W.R., Johnson B.E., and Meyerson M. 2004. EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. *Science* **304**: 1497.
- Pao W., Miller V., Zakowski M., Doherty J., Politi K., Sarkaria I., Singh B., Heelan R., Rusch V., Fulton L., Mardis E., Kupfer D., Wilson R., Kris M., and Varmus H. 2004. EGF receptor gene mutations are common in lung cancers from "never smokers"

- and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc. Natl. Acad. Sci.* **101**: 13306.
- Parsons D.W., Wang T.-L., Samuels Y., Bardelli A., Cummins J.M., DeLong L., Silliman N., Ptak J., Szabo S., Willson J.K.V., Markowitz S., Kinzler K.W., Vogelstein B., Lengauer C., and Velculescu V.E. 2005. Colorectal cancer mutations in a signalling pathway. *Nature* **436**: 792.
- Sasaki H., Shimizu S., Endo K., Takada M., Kawahara M., Tanaka H., Matsumura A., Iuchi K., Haneda H., Suzuki E., Kobayashi Y., Yano M., and Fujii Y. 2005. EGFR and erbB2 mutation status in Japanese lung cancer patients. *Int. J. Cancer* **118**: 180.
- Sawyers C. 2004. Targeted cancer therapy. *Nature* **432**: 294.
- Shigematsu H., Takahashi T., Nomura M., Majumdar K., Suzuki M., Lee H., Wistuba I.I., Fong K.M., Toyooka S., Shimizu N., Fujisawa T., Minna J.D., and Gazdar A.F. 2005. Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. *Cancer Res.* **65**: 1642.
- Slamon D.J., Leyland-Jones B., Shak S., Fuchs H., Paton V., Bajamonde A., Fleming T., Eiermann W., Wolter J., Pegram M., Baselga J., and Norton L. 2001. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N. Engl. J. Med.* **344**: 783.
- Stephens P., Hunter C., Bignell G., Edkins S., Davies H., Teague J., Stevens C., O'Meara S., Smith R., Parker A., Barthorpe A., Blow M., Brackenbury L., Butler A., Clarke O., Cole J., Dicks E., Dike A., Drozd A., Edwards K., Forbes S., Foster R., Gray K., Greenman C., Halliday K., Hills K., Kosmidou V., Lugg R., Menzies A., Perry J., Petty R., Raine K., Ratford L., Shepherd R., Small A., Stephens Y., Tofts C., Varian J., West S., Widaa S., Yates A., Brasseur F., Cooper C.S., Flanagan A.M., Knowles M., Leung S.Y., Louis D.N., Looijenga L.H.J., Malkowicz B., Pierotti M.A., Teh B., Chenevix-Trench G., Weber B.L., Yuen S.T., Harris G., Goldstraw P., Nicholson A.G., Futreal P.A., Wooster R., and Stratton M.R. 2004. Lung cancer: Intragenic ERBB2 kinase mutations in tumours. *Nature* **431**: 525.
- Stephens P., Edkins S., Davies H., Greenman C., Cox C., Hunter C., Bignell G., Teague J., Smith R., Stevens C., O'Meara S., Parker A., Tarpey P., Avis T., Barthorpe A., Brackenbury L., Buck G., Butler A., Clements J., Cole J., Dicks E., Edwards K., Forbes S., Gorton M., Gray K., Halliday K., Harrison R., Hills K., Hinton J., Jones D., Kosmidou V., Laman R., Lugg R., Menzies A., Perry J., Petty R., Raine K., Shepherd R., Small A., Solomon H., Stephens Y., Tofts C., Varian J., Webb A., West S., Widaa S., Yates A., Brasseur F., Cooper C.S., Flanagan A.M., Green A., Knowles M., Leung S.Y., Looijenga L.H.J., Malkowicz B., Pierotti M.A., Teh B., Yuen S.T., Nicholson A.G., Lakhani S., Easton D.F., Weber B.L., Stratton M.R., Futreal P.A., and Wooster R. 2005. A screen of the complete protein kinase gene family identifies diverse patterns of somatic mutations in human breast cancer. *Nat. Genet.* **37**: 590.
- Weinstein I.B. 2002. Cancer. Addiction to oncogenes—The Achilles heel of cancer. *Science* **297**: 63.
- Wilkie A., Patey S., Kan S., van den Ouweland A., and Hamel B. 2002. FGFs, their receptors, and human limb malformations: Clinical and molecular correlations. *Am. J. Med. Genet.* **112**: 266.

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P.A. FUTREAL, R. WOOSTER and M.R. STRATTON

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