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Targeting the Met signaling pathway in renal cancer

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Abstract

Renal cell carcinoma (RCC), the most common form of kidney cancer, accounts for 3% of all adult malignancies and its incidence has significantly increased over the last 20 years. RCC claims 13,000 lives annually in the USA and more than 100,000 worldwide. A better understanding of the molecular basis of RCC has facilitated the development of novel and more selective therapeutic approaches. An important role in RCC oncogenesis is played by the receptor for HGF, Met, which has attracted considerable attention, more recently as a molecular target for cancer therapy, and several drugs selectively targeting this pathway are now in clinical trials. This review will focus on efforts to understand the role of the Met signaling pathway in renal cancer and how this has contributed to the development of potent and selective drug candidates.

Keywords

HGF; HPRC; Met; RCC; renal cell carcinoma; targeted therapy; TFE3

Renal cell carcinoma (RCC) represents 85% of all primary renal neoplasms and its incidence has increased significantly over the last 20 years. Approximately 39,000 people will be newly diagnosed in 2008; 13,000 will die in the USA alone and more than 100,000 worldwide annually [1]. Patients who are found to have localized disease can have long-term disease-free survival; however, when the diagnosis is made after the disease has become metastatic, the prognosis is poor, with only a 18% survival rate at 2 years [2]. Immunologic therapy with IL-2 is associated with a dramatic response in 10-20% of patients with advanced disease [3]; however, more effective forms of therapy are needed that will benefit a higher percentage of patients. Moreover, IL-2 therapy is also associated with severe toxicity.

These circumstances clearly highlight the necessity for developing novel therapeutic approaches to improve the outcome of RCC. A better understanding of the molecular pathogenesis of RCC, obtained through the study of families affected with inherited forms of kidney cancer, have allowed better classification of kidney cancer as a number of different types of cancer [4]. Relating these pathogenic features to the more common sporadic renal

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cancers has, in turn, greatly improved our global understanding of RCC. We discuss four types of familial renal cancer syndromes, based on genetic, histologic and clinical criteria.

Clear-cell renal carcinoma is the most common type, accounting for 75% of RCC. Patients affected with von Hippel-Lindau (VHL) disease present with multiple, bilateral kidney cancers of the clear-cell type, accompanied by a number of other different features [5]. The *VHL* tumor-suppressor gene product forms a multimeric complex that includes elongins C and B [6,7], Cul2 [8] and Rbx1 [9], targeting the hypoxia-inducible factors HIF1α and HIF2α for ubiquitination and subsequent degradation [10,11]. Nearly 100% of VHL families have germline mutations of the *VHL* gene [12], and *VHL* inactivation by mutations or promoter hypermethylation has been described in more than 60% of patients with sporadic clear-cell RCC.

Papillary renal carcinoma (PRC) is the second most common type of kidney cancer and has been further divided into two subtypes based upon histological criteria and distinctive gene expression profile: type I (hereditary papillary renal carcinoma [HPRC]) and type II. In HPRC, mutations in the gene encoding the receptor for HGF, *MET*, are associated with the onset of multiple bilateral type I papillary carcinomas [13-15]; these tumors tend to be low grade and have a better prognosis. Type II lesions are generally high grade and have a poorer prognosis.

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is a hereditary syndrome characterized by the occurrence of cutaneous and uterine leiomyomas, and by the development of an aggressive form of kidney cancer [16] that tends to spread early and are histologically classified mostly as type II papillary renal cancer. Defects in the gene encoding the Krebs cycle enzyme fumarate hydratase were identified as causative, and high levels of HIF1α and HIF2α can be found in HLRCC tumor samples [17-19].

Birt-Hogg-Dubé (BHD) syndrome is caused by germline mutations in the *BHD* gene on chromosome 17p11.2 [20,21], acting as a tumor-suppressor gene and encoding the protein folliculin. This syndrome is characterized by the development of pulmonary cysts, cutaneous fibrofolliculomata and multifocal renal tumors [22,23].

The HGF/Met pathway has attracted increasing attention in recent years as a promising molecular target for cancer therapy. An increasing understanding of the involvement of this pathway in kidney development and in renal pathological conditions has suggested the targeting of this pathway as a promising strategy for the treatment of kidney cancer, particularly papillary type I RCC. In addition to direct involvement through germline activating mutations in HPRC type 1, HGF/Met signaling is implicated in the pathogenesis of sporadic RCC in a broader manner, as described later.

HGF/Met signaling in renal cancers

Hereditary renal cell carcinoma type 1 & sporadic papillary RCC

Through clinical, histopathological and cytogenetic analysis of families with multiple members affected by PRC, Zbar *et al.* described an inherited form of PRC characterized by bilateral, multifocal papillary kidney lesions that tend to grow slowly and develop late in life [13,24]; rare cases of early onset have been described more recently [25]. Linkage analysis by Schmidt *et al.* localized the *HPRC* gene to chromosome 7q31-34, where the *MET* gene resides [26].

An oncogenic derivative of the *MET* gene was isolated from a chemically mutagenized human osteogenic sarcoma cell line. The oncogenic activity was due to rearrangement of a sequence on chromosome 1 (containing the translocated promoter region, *TPR*, locus) and the *MET* locus on chromosome 7, generating the chimeric gene *TPR-MET* [27]. This rearrangement was later

found in patients with gastric carcinoma [28]. The full-length *MET* proto-oncogene was found to encode the structural features of a membrane-spanning receptor endowed with intracellular tyrosine kinase (TK) activity [29]. Subsequently, HGF, a pleiotropic heparin-binding protein, was found to be the natural ligand of the Met receptor and capable of stimulating its multiple biological activities, including motility, proliferation, survival and morphogenesis [30,31].

Met is widely expressed in the early phase of development and its expression persists throughout adulthood [32]. Both HGF and Met are upregulated after renal injury, as a general mechanism of tissue repair and regeneration after tissue damage [33]. Upon ligand binding, autophosphorylation at tyrosines Y1234 and Y1235 (all Met residues are numbered per SwissProt Database accession number P08581) within the activation loop of the receptor TK domain significantly increase kinase activity. Phosphorylation on two critical tyrosine residues at the C terminus (Y1349 and Y1356) create a multifunctional docking site [34] that recruits intracellular effectors, such as Grb2, Gab1, PI3K, Shc and Src, among others [32]. In particular, Grb2 directly binds to Y1356, regulating cell cycle progression through the Ras/MAPK pathway, as well as other intracellular pathways involved in cell migration and invasion [35]. Through paracrine signaling, overexpression, autocrine loop formation, receptor mutations and gene rearrangement, HGF and Met are implicated in a wide variety of human malignancies [36].

Several activating missense mutations of the *MET* gene have been described in individuals with PRC and HPRC, and in other human cancers. Schmidt *et al.* described several mutations in the Met tyrosine kinase domain, both in the germline of HPRC families (M1131T, V1188L, D1228N and Y1230C) and in a subset of tumors from patients with sporadic PRCs (L1195V, D1228H, Y1230H and M1250T) [26]. Notably, some of these mutations were located in a codon homologous to a naturally occurring mutation in *KIT* and in the *RET* proto-oncogene. Subsequent experiments introducing these mutations in NIH3T3 cells confirmed their oncogenic role through increased levels of tyrosine autophosphorylation, increased focus forming activity, increased cell motility *in vitro* and tumorigenicity in nude mice [37,38].

Extensive studies of two large North American HPRC families facilitated the identification of a novel oncogenic germline mutation (H1094R) [39]. Using a panel of 79 sporadic PRC specimens, additional mutations were detected, some of which were found also as germline mutations through comparison with matched normal samples [40]. It is noteworthy that most PRC tumors display trisomy 7 even in the absence of *MET* mutations, and HPRC patients with *MET* mutations show selective duplication of the mutant *MET* allele, suggesting that *MET* mutations confer a proliferative advantage through errors in chromosomal replication during cell division [41].

To further define the mechanisms by which *MET* mutations act at the molecular and cellular level, Bardelli *et al.* showed that the M1250T mutation resulted in changes in substrate preferences *in vitro*; in NIH3T3 cells this mutation, as well as the Y1230H and D1228H/N mutations, displayed constitutive association with the key intracellular effector Gab1 [42]. These results showed that oncogenicity is mediated by many known receptor proximal effectors and that interruption of such interactions may be a viable strategy to block mutant Met signaling. Furthermore, different mutations may contribute to disease pathogenesis through distinct downstream molecular pathways [43]. Several lines of evidence suggest that ligand binding may contribute significantly to oncogenesis associated with PRC *MET* mutations [44]. The observation that the kidney is an abundant source of HGF and its activators, may explain, at least in part, why patients with germline *MET* mutations exhibit only kidney cancer. These studies also demonstrated that mutated Met might be more easily activated than wild-type Met and more likely to remain activated for longer periods after stimulation [45].

TFE3 renal carcinoma

A subgroup of RCC with papillary architecture is associated with Xp11.2 translocation (transcription factor 3 [*TFE3*] gene fusions) [46]. This entity, referred to as TFE3 renal carcinoma, has been predominantly reported in children, accounting for 5-20% of RCC in young patients. In young adults, the tumors are more aggressive and prognosis is poor due to the advanced stage at presentation, prompting intense investigation into its pathogenesis [47-49]. The *TFE3* gene is located at Xp11.2 and is a member of the microphthalmia transcription factor (MiTF) family [50]. A number of translocations involving Xp11.2 can occur; fusion of *TFE3* to four distinct genes has been identified (*PRCC*, *ASPL*, *PSF* and *NonO* [51-53], which can result in enhanced levels of transcription of oncoproteins. Several lines of evidence suggest an important role of these fusion proteins in the initiation and maintenance of the oncogenic phenotype in papillary RCC [54], and are consequently potential targets for the treatment of these tumors.

A recent search for transcriptional targets downstream of TFE3 fusion oncoproteins showed that Met activation has an important role in the oncogenesis of several tumors containing the TFE3 fusion, including RCC [55]. Indeed, in contrast to clear-cell RCC, Met protein expression is increased, with phosphorylation at the critical residue pY1234 and pY1235 in the activation loop of the TK domain, as well as phosphorylation at residue pY1349 in the C terminus [56]. Such hyperphosphorylation is associated with the malignant behavior of TFE3 renal carcinoma and its poor survival rates, consistent with other oncogenic phenotypes associated with HGF/Met aberrant signaling. Treatment with the Met selective inhibitor PHA665752 strongly inhibited HGF-dependent Met phosphorylation at pY1234 and pY1235 [55]. Also, the prominent phosphorylation of Met in the multifunctional docking site induced the recruitment and activation of several downstream effectors, including Akt and P44/42 MAPK, further validating Met as a potential and tractable therapeutic target for tumors with the TFE3 fusion.

Clear-cell RCC

As mentioned earlier, loss of the *VHL* tumor-suppressor gene function is responsible for familial and most sporadic clear-cell carcinoma, leading to abnormal expression of genes involved in cell proliferation, invasion and angiogenesis. The protein encoded by *VHL* (pVHL) forms a stable complex with other proteins possessing E3 ubiquitin ligase activity. This complex is best known for targeting hypoxia-inducible factors (HIFs) for polyubiquitination and subsequent proteasomal degradation [57]. Under normoxic conditions, pVHL suppresses HIF protein levels and consequently their activity. Under hypoxic conditions or when the *VHL* gene is mutated or lost, HIFs accumulate and several HIF target genes are upregulated, including VEGF, PDGF, TGF-a, erythropoietin and Met [57,4]. HGF signaling is also increased by hypoxia through other mechanisms, leading to invasive growth in cultured cells and in mouse tumor models [58]. Cultured *VHL*-negative RCC cells accumulate HIF proteins aberrantly and respond to HGF treatment with matrix metalloproteinase production, increased motility, matrix invasion and tubulogenesis [59]. These HGF-driven activities are abolished when wild-type VHL expression is reconstituted in RCC cells, directly linking loss of VHL function to an invasive phenotype [59].

Investigating the mechanism by which *VHL* loss of function resulted in increased HGF-driven invasiveness, Peruzzi *et al.* examined downstream mediators of Met signaling with proven oncogenic potential that might be negatively regulated by ubiquitin-directed proteasomal degradation [60]. Among these candidates is β-catenin [61,62], which links cadherins to the actin cytoskeleton and also functions in the transcriptional activation of genes involved in normal growth and development. β-catenin and E-cadherin are important in mesenchymal-to-epithelial transition processes during renal development, particularly during tubule formation [63,64], and dysregulation of β-catenin signaling can be potently oncogenic [65]. Peruzzi *et*

al. showed that HGF stimulated the redistribution of β-catenin from peripheral to cytoplasmic, perinuclear and nuclear pools, leading to β-catenin target gene activation in *VHL*-negative RCC cells, and that restoration of normal *VHL* expression repressed these activities [60]. Ectopic expression of an ubiquitination-resistant β-catenin mutant in RCC cells transfected with wild-type *VHL* reversed this repression by pVHL, and expression of a dominant-negative form of T-cell factor blocked the invasive response of *VHL*-negative cells [60]. Thus, Met/β-catenin signaling contributes to the invasive phenotype of *VHL*-negative clear-cell RCC, revealing another potential target for biomarker and drug development.

Low levels of pro-HGF are present in the systemic circulation and HGF-induced Met activation at target cell surfaces requires proteolytic processing of HGF to its mature, two-chain form [66-70]. Several serine proteases are capable of activating HGF, including HGF activator [71-73], hepsin [74,75] and plasminogen activators [76]. This process is further controlled by the Kunitz-type inhibitors and HGF activator inhibitor (HAI)-1 and -2 [77-79]. Several groups have demonstrated that an increased ratio of HGF activators to HAI-1 or -2 correlates with malignant progression and poor prognosis in a variety of carcinomas [80-83], emphasizing the important balance between HGF activators and their cognate inhibitors for normal HGF pathway activation in tissue homeostasis. Betsunoh *et al.* showed that hepsin was frequently upregulated in advanced RCC, a feature that correlated with distant metastasis and proved to be a reliable independent prognostic indicator of reduced overall survival [80]. HAI-2 is also implicated in the pathogenesis of clear-cell and non-clear-cell RCC [84], consistent with prior reports of downregulation of HAI-1 and -2 expression in RCC, coupled with Met and HGF activator upregulation [85].

Strategies to target HGF/Met signaling in renal cancers

At least three different strategies have been developed to inhibit Met signaling: antagonism of receptor-ligand interaction, inhibition of the TK catalytic activity and inhibition of the interaction between the receptor and intracellular signaling effectors.

Antagonism of HGF/Met interaction

Several studies suggest that antagonism of ligand binding is a logical and feasible therapeutic strategy for HPRC type 1 and PRC, as well as other malignancies where Met is not mutated but active. The discovery that a naturally occurring truncated HGF variant (HGF/NK2) was a specific competitive mitogenic antagonist, led to the development of HGF/NK4, a larger, more antagonistic HGF fragment [86] and to an uncleavable form of pro-HGF [87], both of which block tumor growth and metastasis in animal models. Similarly, soluble Met ectodomain fragments with pathway neutralizing and anti-tumor activities were engineered following the earlier development of a Met ectodomain-IgG fusion protein with HGF-neutralizing activity [88-90]. OA-5D5, a one-armed humanized anti-Met monoclonal antibody targeting the ligand-binding site, has demonstrated activity in reducing tumor growth of orthotopic pancreatic [91] and glioblastoma [88] xenografts , and is now in human clinical trials. Cao *et al.* [92] and other groups [93] described the anti-tumor activity of neutralizing mouse monoclonal antibodies against human HGF in animal models. More recently, Burgess *et al.* reported the development of a fully human monoclonal antibody with HGF-neutralizing and anti-tumor properties (AMG102), which is currently in Phase II clinical trials as a single agent in RCC and glioblastoma multiforme [94].

Inhibition of Met TK activity

Tyrosine kinase inhibitors have shown success in treating many malignancies. Not surprisingly, the number of pharmaceutical and biotechnology companies that have announced drug development programs targeting the Met TK has grown considerably in the last 10 years.

Several programs to develop highly selective synthetic inhibitors of the Met ATP-binding site have yielded compounds effective in nanomolar concentrations in cultured cells and in various animal models [95]. Of these, the indolinone compounds SU11274 and PHA665752 display a minimum of 50-fold selectivity for Met relative to several other TKs, and potently blocked HGF-stimulated activities in cultured cells and tumorigenicity in Met-driven xenograft models [96,97]. Analysis of SU11274 using cells that express HPRC-associated *MET* mutants revealed interesting differences in sensitivity [96]: this compound was able to inhibit the Met mutant M1250T, but other mutations, such as L1195V and Y1230H, were insensitive. Another novel, orally available Met small-molecule inhibitor, PF2341066, evaluated against a panel of NIH3T3 cells expressing various Met mutations, demonstrated a markedly diminished activity against mutants Y1230C and Y1235D in the TK domain activation loop, compared with wild-type or other TK domain mutations [98]. More recently, similar drugs with conserved or enhanced activity against mutants have been described [99,100]. The drug XL880/GSK1363089, a multikinase inhibitor with potent anti-Met activity that is currently in Phase II clinical trials in patients with PRC, was found to be effective in a gefitinib/erlotinib-resistant lung tumor cell line with acquired *MET* amplification [101]. Increased sensitivity to the inhibitor PHA665752 was observed in gastric cancer cells with *MET* gene amplification [102], strongly reinforcing the concept that knowledge of genetic alterations should help predict the efficacy of Met TK inhibitors for specific patient groups.

Inhibition of Met/effector interactions

Disrupting the interaction between Met and intracellular signaling effectors is another attractive strategy to target this pathway. Several signal transducers, such as Gab1, PI3K, Grb2 and STAT3, are important in Met-driven cell transformation and constitute potential targets [34, 42,43]. In particular, the SH2 domain of the adaptor protein Grb2 has been successfully targeted, taking advantage of its unique structure among SH2 domains [103], providing the basis for the development of small selective binding antagonists [35]. Further refinement of these early structures has yielded compounds that block HGF-stimulated cell motility, matrix invasion and morphogenesis in normal and tumor-derived cultured cells, as well as vascular endothelial cells, at low nanomolar concentrations [104,105]. The same compounds have been shown to inhibit tumor metastasis in two animal models [106]. Other downstream signaling proteins activated by Met or other receptors have been successfully targeted; one notable example is the serine/threonine kinase mTOR. mTOR inhibition has been explored in a variety of cancers, including RCC, and the inhibitor temsirolimus was approved by the US FDA in 2007 for advanced RCC [107].

The PI3K/Akt signaling cascade, important for survival and mitogenic signaling, is another potential therapeutic target for RCC. Higher PI3K expression has been reported in late-stage and high-grade RCC and correlates with poor survival [108]. At present, no PI3K or Akt inhibitors are approved for clinical use in RCC, but studies are underway that explore this possibility [109].

Treatment combinations

Finally, as a strategy to overcome drug resistance and toxicity, combinations of treatments targeting the Met pathway with other agents or therapeutic approaches are under investigation. Compounds that block HSP90/client interactions, such as geldanamycin [110], also potently block Met oncogenic signaling [111,112]. For several cancers where the Met pathway is active, clinical trials of geldanamycin-related compounds are ongoing [113]. Combining agents, such as geldanamycin, which attenuate the supply of new receptors to the cell surface, with inhibitors of other specific receptor functions such as kinase activity, could lower the effective dose of each, reducing the likelihood of drug toxicity and the selection pressure for drug-resistant mutations.

Several other signaling pathways can enhance HGF-driven Met activation, and *MET* gene amplification can result in ligand-independent Met kinase activation. In light of this, combination strategies have been explored with other TK inhibitors [114,115]. Recent findings that gefitinib-resistant nonsmall-cell lung cancers develop *MET* amplification [116], further reinforce the rationale of these combinations, and clinical trials combining Met and EGFR TK inhibitors are currently under consideration. Tumor angiogenesis is another important feature of RCC. Currently, the use of bevacizumab (a monoclonal antibody directed against VEGF) and interferon is the only combination approved by the FDA, but other similar combination strategies are also currently under investigation [115].

Combining Met-targeted therapy with traditional chemotherapy is another option. AMG102 combined with temozolomide or docetaxel [117], and cisplatin and SU11274 [118], have been shown to be effective in models of glioblastoma. Further preclinical evaluation of these combinations is needed to identify which will be more effective at the bedside. Finally, changes in Met signaling as an effect of ionizing radiation [119] and evidence that Met activation can interfere with cell death induced by ionizing radiation treatment [120,121], suggest that combining HGF/Met-selective targeted therapies with radiotherapy may make tumor cells more responsive. Interestingly, it has been demonstrated that a Met-activating mutation (Y1235D) in oropharyngeal cancer can interfere with the normal response to radiotherapy [122]; it will be interesting to extend these studies to other mutations found in RCC tumors.

Expert commentary

Building on the knowledge derived from more than two decades of intense investigation, refined approaches to targeting Met and its signaling pathway have been developed [95]. The study of families with inherited forms of kidney cancer has provided critical genetic insights into oncogenesis, and now offers an opportunity to target this pathway in genetically defined disease populations. The use of rationally targeted therapies for cancer necessitates the accurate assessment of patients prior to treatment in order to identify those most likely to benefit from a given selective therapy. Ultimately, panels of biomarkers may be needed to predict the best choice of therapeutics.

Several novel drugs targeting HGF and Met are entering the clinical arena and their efficacy will provide some indication as to the importance of this pathway in different tumors. Of particular interest will be investigations of these agents in RCC tumors bearing Met mutations or other genetic evidence of pathway activation. Together with structural studies of novel Met drugs bound to various Met mutant forms, the information obtained from these studies will contribute to the development of more refined Met inhibitors, the development of improved pharmacodynamic indicators of drug activity, insights into effective drug combinations and strategies to overcome drug resistance.

Five-year view

Several novel HGF- and Met-targeted drugs are under preclinical and clinical investigation. In the near future we expect these efforts to result in the approval of several new therapeutics with greater efficacy and reduced toxicity. It will become progressively important to identify the specific mechanisms of Met activation present in each patient to reduce the risk of ineffective treatments and increase disease stasis and/or reversal. Additional molecular prognostic and pharmacodynamic markers that are practical to use in patient-care settings, and that provide precise measurements over a substantial dynamic range and over time are urgently needed. Finally, continued basic research into the molecular basis of kidney cancer should reveal concomitantly activated signaling pathways and novel molecular targets for developing the most effective drug combinations.

Key issues

- Met signaling has been shown to be important in renal cell carcinoma (RCC).
- The rational design and development of *MET* inhibitors for the treatment of RCC and other cancers has yielded a considerable increase in the number of potent and selective agents.
- Hereditary papillary renal cell carcinoma, where *MET* mutations drive the pathology, is an ideal RCC tumor for the study of *MET*-targeted therapies.
- *MET* mutants respond differentially to various *MET* inhibitors.
- *MET* is a direct transcription target in transcription factor 3-renal carcinomas and represents another rational target for therapy of this form of RCC.
- The receptor encoded by *MET*, as an *HIF* target gene, is also a potential target in clear-cell RCC.
- Prescreening patients with RCC for genetic and molecular defects will become progressively more important in selecting among targeted therapies.
- Combinations of targeted therapies or combining these therapies with more traditional cytotoxic therapies, based on the specific molecular patterns expressed in patient tumors, may provide more effective treatment regimes.

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Table 1

Characteristics of renal cell carcinoma subtypes.

Type/histology	Frequency (%)*	Gene‡	Tumor multiplicity	Age of onset
Clear cell	75	*VHL*	Multiple, bilateral	Adolescence
Papillary type 1	5	*MET* proto-oncogene	Multiple, bilateral	40-49 years
HLRCC/papillary type 2	10	*FH*	Single or multiple	10-20 years
Chromophobe/oncocytoma	5-10	*BHD*/Folliculin	Multiple, bilateral	30-39 years

HLRCC: Hereditary leiomyomatosis and renal cell cancer.

*Indicates portion of total annual renal cell carcinoma cases.

‡Indicates the genetic defect associated with the hereditary form of renal cell carcinoma, and by implication and direct evidence, in the corresponding sporadic form.

Table 2

Summary of *MET* tyrosine kinase domain mutations.

Swissprot	Genbank	Germline/somatic	Ref.
H1094R	H1112R	Germline	[39]
M1131T	M1149T	Germline	[123]
V1188L	V1206L	Germline	[26]
L1195V	L1213V	Somatic	[26]
D1228N	D1246N	Germline	[26]
D1228H	D1246H	Somatic	[26]
Y1230C	Y1248C	Germline	[26]
Y1230H	Y1248H	Somatic	[26]
Y1235D	Y1253D	Somatic	[124,125]
M1250T	M1268T	Somatic	[26]

Mutations are listed by codon position in SwissProt (accession P08581) or Genbank (accession J02958) sequence contexts.