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Provider Information

Physician	Dr. Natalie Amidala
Institution	ACME General Hospital
Case Id	GL-1234

Patient Information

Name	Harrison Solo
Gender	Male
Date of Birth	7/13/1942
Id	1234

Sample

Sample Site	Blood	**Avg. Read Depth**	5152x
Sample Type	Blood	**Collection Date**	2/2/2016
Collection Met…	Peripheral Draw	**Receipt Date**	2/2/2016
Panel Coverage	86.23%	**Report Date**	2/2/2016

Results

Positive: Mutations with an establish somatic link detected.

Affected Genes

ABL1 (0)	*ASXL1* (0)	*ATRX* (0)	*BCOR* (0)	*BCOR1* (0)	***BRAF* (1)**	*CALR* (0)	*CBL* (0)	*CBLB* (0)	*CBLC* (0)	*CDKN2A* (0)
CEBPA (0)	***CUX1* (1)**	*EGFR* (0)	*JAK2* (0)	*JAK3* (0)	*KDM6A* (0)	*KIT* (0)	***TET2* (3)**	***TP53* (1)**		

Genetic Variants

Gene	Zygosity	Variant	Exon	Pathogenicity
BRAF	Heterozygous	NM_004333.4:c.1799T>A(NP_004324.2:p.Val600Glu)	15	Pathogenic

Interpretation Summary

Although BRAF is most commonly associated with malignat melanoma, Lee et al. (2004) showed that BRAF is occasionally mutated in leukemias. As the patient presented acute leukemia and a mutation associated with leukemia was found in the BRAF gene, we recommend treatment take advantage of known drugs targeting mutations in this gene.

Recommendations

The recommended drugs targeting the BRAF mutation are included in the table below as well as 10 of the clinical trials currently underway. Investigation of the incidental findings may also lead to a mutation that can be targeted with a drug to treat the cancer.

OncoMD Drug Summary

BRAF

Drug	Generic	Response Rate
Tafinlar + Mekinist	Dabrafenib + Trametinib	83%
Tafinlar	Dabrafenib	60%
Sutent	Sunitinib	0%
Mekinist	Trametinib	33%
Zelboraf	Vemurafenib	55%
Yervoy	Ipilimumab	0%
Nexavar	Sorafenib	4%

OncoMD Trial Summary

BRAF

Cancer Type	Country	Drugs	Inclusion Criterion	Status	Trial Number
Neoplasms	Australia	Sorafenib (Nexavar, BAY43-9006)	BRAF MUTATION	Recruiting	NCT00625378
Soft Tissue Sarcoma	Australia	Sunitinib malate	BRAF MUTATION	Recruiting	NCT00753727
Neoplasms	Belgium	Sorafenib (Nexavar, BAY43-9006)	BRAF MUTATION	Recruiting	NCT00625378
Neoplasms	Brazil	Sorafenib (Nexavar, BAY43-9006)	BRAF MUTATION	Recruiting	NCT00625378
Hepatocellular Carcinoma	Brunei Darussalam	Sorafenib tosylate	BRAF MUTATION	Recruiting	NCT01135056
Neoplasms	Canada	Sorafenib (Nexavar, BAY43-9006)	BRAF MUTATION	Recruiting	NCT00625378
Paraganglioma	Canada	Sunitinib	BRAF MUTATION	Recruiting	NCT00843037
Kidney Cancer	Canada	sunitinib malate	BRAF MUTATION	Recruiting	NCT01099423
Hepatocellular Carcinoma	China	Sorafenib tosylate	BRAF MUTATION	Recruiting	NCT01135056
Hepatectomy	China	sorafenib	BRAF MUTATION	Recruiting	NCT01409499

Individual Variant Interpretations

NP_004324.2:p.Val600Glu in Exon 15 of *BRAF* (NM_004333.4:c.1799T>A) Pathogenic

This is a Missense Variant located in the BRAF gene.

The val600-to-glu (V600E) mutation caused by a 1799T-A transversion in the BRAF gene was previously designated VAL599GLU (1796T-A). Kumar et al. (2003) noted that an earlier version of the BRAF sequence showed a discrepancy of 3 nucleotides in exon 1; based on the corrected sequence, they proposed a change in nucleotide numbering after nucleotide 94 (the ATG codon) by +3 and a corresponding codon change of +1.

---Malignant Melanoma

Davies et al. (2002) identified a 1799T-A transversion in exon 15 of the BRAF gene that leads to a val600-to-glu (V600E) substitution. This mutation accounted for 92% of BRAF mutations in malignant melanoma (see 155600). The V600E mutation is an activating mutation resulting in constitutive activation of BRAF and downstream signal transduction in the MAP kinase pathway.

To evaluate the timing of mutations in BRAF during melanocyte neoplasia, Pollock et al. (2003) carried out mutation analysis on microdissected melanoma and nevi samples. They observed mutations resulting in the V600E amino acid substitution in 41 (68%) of 60 melanoma metastases, 4 (80%) of 5 primary melanomas, and, unexpectedly, in 63 (82%) of 77 nevi. The data suggested that mutational activation of the RAS/RAF/MAPK pathway in nevi is a critical step in the initiation of melanocytic neoplasia but alone is insufficient for melanoma tumorigenesis.

Lang et al. (2003) failed to find the V600E mutation as a germline mutation in 42 cases of familial melanoma studied. Their collection of families included 15 with and 24 without detected mutations in CDKN2A (600160). They did, however, find the V600E mutation in 6 (27%) of 22 samples of secondary (metastatic) melanomas studied. Meyer et al. (2003) found no V600E mutation in 172 melanoma patients comprising 46 familial cases, 21 multiple melanoma patients, and 106 cases with at least 1 first-degree relative suffering from other cancers. They concluded, therefore, that the common somatic BRAF mutation V600E does not contribute to polygenic or familial melanoma predisposition.

Kim et al. (2003) stated that V600E, the most common of BRAF mutations, had not been identified in tumors with mutations of the KRAS gene (190070). This mutually exclusive relationship supports the hypothesis that BRAF (V600E) and KRAS mutations exert equivalent effects in tumorigenesis (Rajagopalan et al., 2002; Singer et al., 2003).

Flaherty et al. (2010) reported complete or partial regression of V600E-associated metastatic melanoma in 81% of patients treated with an inhibitor (PLX4032) specific to the V600E mutation. Among 16 patients in a dose-escalation cohort, 10 had a partial response, and 1 had a complete response. Among 32 patients in an extension cohort, 24 had a partial response, and 2 had a complete response. The estimated median progression-free survival among all patients was more than 7 months. Responses were observed at all sites of disease, including bone, liver, and small bowel. Tumor biopsy specimens from 7 patients showed markedly reduced levels of phosphorylated ERK (600997), cyclin D1 (168461), and Ki67 (MKI67; 176741) at day 15 compared to baseline, indicating inhibition of the MAP kinase pathway. Three additional patients with V600E-associated papillary thyroid also showed a partial or complete response.

Bollag et al. (2010) described the structure-guided discovery of PLX4032 (RG7204), a potent inhibitor of oncogenic BRAF kinase activity. PLX4032 was cocrystallized with a protein construct that contained the kinase domain of BRAF(V600E). In a clinical trial, patients exposed to higher plasma levels of PLX4032 experienced tumor regression; in patients with tumor regressions, pathway analysis typically showed greater than 80% inhibition of cytoplasmic ERK phosphorylation. Bollag et al. (2010) concluded that their data demonstrated that BRAF-mutant melanomas are highly dependent on BRAF kinase activity.

Patients with BRAF(V600E)-positive melanomas exhibit an initial antitumor response to the RAF kinase inhibitor PLX4032, but acquired drug resistance almost invariably develops. Johannessen et al. (2010) identified MAP3K8 (191195), encoding COT (cancer Osaka thyroid oncogene) as a MAPK pathway agonist that drives resistance to RAF inhibition in BRAF(V600E) cell lines. COT activates ERK primarily through MARK/ERK (MEK)-dependent mechanisms that do not require RAF signaling. Moreover, COT expression is associated with de novo resistance in BRAF(V600E) cultured cell lines and acquired resistance in melanoma cells and tissue obtained from relapsing patients following treatment with MEK or RAF inhibitors. Johannessen et al. (2010) further identified combinatorial MAPK pathway inhibition or targeting of COT kinase activity as possible therapeutic strategies for reducing MAPK pathway activation in this setting.

Nazarian et al. (2010) showed that acquired resistance to PLX4032, a novel class I RAF-selective inhibitor, develops by mutually exclusive PDGFRB (173410) upregulation or NRAS (164790) mutations but not through secondary mutations in BRAF(V600E). Nazarian et al. (2010) used PLX4032-resistant sublines artificially derived from BRAF (V600E)-positive melanoma cell lines and validated key findings in PLX4032-resistant tumors and tumor-matched, short-term cultures from clinical trial patients. Induction of PDGFRB RNA, protein and tyrosine phosphorylation emerged as a dominant feature of acquired PLX4032 resistance in a subset of melanoma sublines, patient-derived biopsies, and short-term cultures. PDGFRB upregulated tumor cells have low activated RAS levels and, when treated with PLX4032, do not reactivate the MAPK pathway significantly. In another subset, high levels of activated N-RAS resulting from mutations lead to significant MAPK pathway reactivation upon PLX4032 treatment. Knockdown of PDGFRB or NRAS reduced growth of the respective PLX4032-resistant subsets. Overexpression of PDGFRB or NRAS(Q61K) conferred PLX4032 resistance to PLX4032-sensitive parental cell lines. Importantly, Nazarian et al. (2010) showed that MAPK reactivation predicts MEK inhibitor sensitivity. Thus, Nazarian et al. (2010) concluded that melanomas escape BRAF(V600E) targeting not through secondary BRAF(V600E) mutations but via receptor tyrosine kinase (RTK)-mediated activation of alternative survival pathway(s) or activated RAS-mediated reactivation of the MAPK pathway, suggesting additional therapeutic strategies.

Poulikakos et al. (2011) identified a novel resistance mechanism for melanomas with BRAF(V600E) treated with RAF inhibitors. The authors found that a subset of cells resistant to vemurafenib (PLX4032, RG7204) express a 61-kD variant form of BRAF(V600E), p61BRAF(V600E), that lacks exons 4 through 8, a region that encompasses the RAS-binding domain. p61BRAF(V600E) showed enhanced dimerization in cells with low levels of RAS activation, as compared to full-length BRAF(V600E). In cells in which p61BRAF(V600E) was expressed endogenously or ectopically, ERK signaling was resistant to the RAF inhibitor. Moreover, a mutation that abolished the dimerization of p61BRAF(V600E) restored its sensitivity to vemurafenib. Finally, Poulikakos et al. (2011) identified BRAF(V600E) splicing variants lacking the RAS-binding domain in the tumors of 6 of 19 patients with acquired resistance to vemurafenib. Poulikakos et al. (2011) concluded that their data supported the model that inhibition of ERK signaling by RAF inhibitors is dependent on levels of RAS-GTP too low to support RAF dimerization and identified a novel mechanism of acquired resistance in patients: expression of splicing isoforms of BRAF(V600E) that dimerize in a RAS-independent manner.

Thakur et al. (2013) investigated the cause and consequences of vemurafenib resistance using 2 independently-derived primary human melanoma xenograft models in which drug resistance is selected by continuous vemurafenib administration. In one of these models, resistant tumors showed continued dependency on BRAF(V600E)-MEK-ERK signaling owing to elevated BRAF(V600E) expression. Thakur et al. (2013) showed that vemurafenib-resistant melanomas become drug-dependent for their continued proliferation, such that cessation of drug administration leads to regression of established drug-resistant tumors. Thakur et al. (2013) further demonstrated that a discontinuous dosing strategy, which exploits the fitness disadvantage displayed by drug-resistant cells in the absence of the drug,

forestalls the onset of lethal drug-resistant disease. Thakur et al. (2013) concluded that their data highlighted the concept that drug-resistant cells may also display drug dependency, such that altered dosing may prevent the emergence of lethal drug resistance. These observations may contribute to sustaining the durability of vemurafenib response with the ultimate goal of curative therapy for the subset of melanoma patients with BRAF mutations.

Using metabolic profiling and functional perturbations, Kaplon et al. (2013) showed that the mitochondrial gatekeeper pyruvate dehydrogenase (PDH; 300502) is a crucial mediator of senescence induced by BRAF(V600E), an oncogene commonly mutated in melanoma and other cancers. BRAF(V600E)-induced senescence is accompanied by simultaneous suppression of the PDH-inhibitory enzyme pyruvate dehydrogenase kinase-1 (PDK1; 602524) and induction of the PDH-activating enzyme pyruvate dehydrogenase phosphatase-2 (PDP2; 615499). The resulting combined activation of PDH enhanced the use of pyruvate in the tricarboxylic acid cycle, causing increased respiration and redox stress. Abrogation of oncogene-induced senescence (OIS), a rate-limiting step towards oncogenic transformation, coincided with reversion of these processes. Further supporting a crucial role of PDH in OIS, enforced normalization of either PDK1 or PDP2 expression levels inhibited PDH and abrogated OIS, thereby licensing BRAF(V600E)-driven melanoma development. Finally, depletion of PDK1 eradicated melanoma subpopulations resistant to targeted BRAF inhibition, and caused regression of established melanomas.

Sun et al. (2014) showed that 6 out of 16 BRAF(V600E)-positive melanoma tumors analyzed acquired EGFR (131550) expression after the development of resistance to inhibitors of BRAF or MEK (176872). Using a chromatin regulator-focused short hairpin RNA (shRNA) library, Sun et al. (2014) found that suppression of SRY-box 10 (SOX10; 602229) in melanoma causes activation of TGF-beta (190180) signaling, thus leading to upregulation of EGFR and platelet-derived growth factor receptor-beta (PDGFRB; 173410), which confer resistance to BRAF and MEK inhibitors. Expression of EGFR in melanoma or treatment with TGF-beta results in a slow-growth phenotype with cells displaying hallmarks of oncogene-induced senescence. However, EGFR expression or exposure to TGF-beta becomes beneficial for proliferation in the presence of BRAF or MEK inhibitors. In a heterogeneous population of melanoma cells that have varying levels of SOX10 suppression, cells with low SOX10 and consequently high EGFR expression are rapidly enriched in the presence of drug treatment, but this is reversed when the treatment is discontinued. Sun et al. (2014) found evidence for SOX10 loss and/or activation of TGF-beta signaling in 4 of the 6 EGFR-positive drug-resistant melanoma patient samples. Sun et al. (2014) concluded that their findings provided a rationale for why some BRAF or MEK inhibitor-resistant melanoma patients may regain sensitivity to these drugs after a 'drug holiday' and identified patients with EGFR-positive melanoma as a group that may benefit from retreatment after a drug holiday.

Boussemart et al. (2014) demonstrated that the persistent formation of the eIF4F complex, comprising the eIF4E (133440) cap-binding protein, the eIF4G (600495) scaffolding protein, and the eIF4A (602641) RNA helicase, is associated with resistance to anti-BRAF (164757), anti-MEK, and anti-BRAF plus anti-MEK drug combinations in BRAF(V600)-mutant melanoma, colon, and thyroid cancer cell lines. Resistance to treatment and maintenance of eIF4F complex formation is associated with 1 of 3 mechanisms: reactivation of MAPK (see 176948) signaling; persistent ERK-independent phosphorylation of the inhibitory eIF4E-binding protein 4EBP1 (602223); or increased proapoptotic BMF (606266)-dependent degradation of eIF4G. The development of an in situ method to detect the eIF4E-eIF4G interactions showed that eIF4F complex formation is decreased in tumors that respond to anti-BRAF therapy and increased in resistant metastases compared to tumors before treatment. Strikingly, inhibiting the eIF4F complex, either by blocking the eIF4E-eIF4G interaction or by targeting eIF4A, synergized with inhibiting BRAF(V600) to kill the cancer cells. eIF4F appeared not only to be an indicator of both innate and acquired resistance, but also a therapeutic target. Boussemart et al. (2014) concluded that combinations of drugs targeting BRAF (and/or MEK) and eIF4F may overcome most of the resistance mechanisms in BRAF(V600)-mutant cancers.

---Colorectal Carcinoma

Rajagopalan et al. (2002) identified the V600E mutation in 28 of 330 colorectal tumors (see 114500) screened for BRAF mutations. In all cases the mutation was heterozygous and occurred somatically.

Domingo et al. (2004) pointed out that the V600E hotspot mutation had been found in colorectal tumors that showed inherited mutation in a DNA mismatch repair (MMR) gene, such as MLH1 (120436) or MSH2 (609309). These mutations had been shown to occur almost exclusively in tumors located in the proximal colon and with hypermethylation of MLH1, the gene involved in the initial steps of development of these tumors; however, BRAF mutations were not detected in those cases with or presumed to have germline mutation in either MLH1 or MSH2. Domingo et al. (2004) studied mutation analysis of the BRAF hotspot as a possible low-cost effective strategy for genetic testing for hereditary nonpolyposis colorectal cancer (HNPCC; 120435). The V600E mutation was found in 82 (40%) of 206 sporadic tumors with high microsatellite instability (MSI-H) but in none of 111 tested HNPCC tumors or in 45 cases showing abnormal MSH2 immunostaining. Domingo et al. (2004) concluded that detection of the V600E mutation in a colorectal MSI-H tumor argues against the presence of germline mutation in either MLH1 or MSH2, and that screening of these MMR genes can be avoided in cases positive for V600E.

Lubomierski et al. (2005) analyzed 45 colorectal carcinomas with MSI and 37 colorectal tumors without MSI but with similar clinical characteristics and found that BRAF was mutated more often in tumors with MSI than without (27% vs 5%, p = 0.016). The most prevalent BRAF alteration, V600E, occurred only in tumors with MSI and was associated with more frequent MLH1 promoter methylation and loss of MLH1. The median age of patients with BRAF V600E was older than that of those without V600E (78 vs 49 years, p = 0.001). There were no BRAF alterations in patients with germline mutations of mismatch repair genes. Lubomierski et al. (2005) concluded that tumors with MSI caused by epigenetic MLH1 silencing have a mutational background distinct from that of tumors with genetic loss of mismatch repair, and suggested that there are 2 genetically distinct entities of microsatellite unstable tumors.

Tol et al. (2009) detected a somatic V600E mutation in 45 (8.7%) of 519 metastatic colorectal tumors. Patients with BRAF-mutated tumors had significantly shorter median progression-free and median overall survival compared to patients with wildtype BRAF tumors, regardless of the use of cetuximab. Tol et al. (2009) suggested that the BRAF mutation may be a negative prognostic factor in these patients.

Inhibition of the BRAF(V600E) oncoprotein by the small-molecule drug PLX4032 (vemurafenib) is highly effective in the treatment of melanoma. However, colon cancer patients harboring the same BRAF(V600E) oncogenic lesion have poor prognosis and show only a very limited response to this drug. To investigate the cause of this limited therapeutic effect in BRAF(V600E) mutant colon cancer, Prahallad et al. (2012) performed an RNA interference-based genetic screen in human cells to search for kinases whose knockdown synergizes with BRAF(V600E) inhibition. They reported that blockade of the epidermal growth factor receptor (EGFR; 131550) shows strong synergy with BRAF(V600E) inhibition. Prahallad et al. (2012) found in multiple BRAF(V600E) mutant colon cancers that inhibition of EGFR by the antibody drug cetuximab or the small-molecule drugs gefitinib or erlotinib is strongly synergistic with BRAF(V600E) inhibition, both in vitro and in vivo. Mechanistically, Prahallad et al. (2012) found that BRAF(V600E) inhibition causes a rapid feedback activation of EGFR, which supports continued proliferation in the presence of BRAF(V600E) inhibition. Melanoma cells express low levels of EGFR and are therefore not subject to this feedback activation. Consistent with this, Prahallad et al. (2012) found that ectopic expression of EGFR in melanoma cells is sufficient to cause resistance to PLX4032. Prahallad et al. (2012) concluded that BRAF(V600E) mutant colon cancers (approximately 8 to 10% of all colon cancers) might benefit from combination therapy consisting of BRAF and EGFR inhibitors.

---Papillary Thyroid Carcinoma

Kimura et al. (2003) identified the V600E mutation in 28 (35.8%) of 78 papillary thyroid cancers (PTC; see 188550); it was not found in any of the other types of differentiated follicular neoplasms arising from the same cell type (0 of 46). RET (see 164761)/PTC mutations and RAS (see 190020) mutations were each identified in 16.4% of PTCs, but there was no overlap in the 3 mutations. Kimura et al. (2003) concluded that thyroid cell transformation to papillary cancer takes place through constitutive activation of effectors along the RET/PTC-RAS-BRAF signaling pathway.

Xing et al. (2004) studied various thyroid tumor types for the most common BRAF mutation, 1799T-A, by DNA sequencing. They found a high and similar frequency (45%) of the 1799T-A mutation in 2 geographically distinct papillary thyroid cancer patient populations, 1 composed of sporadic cases from North America, and the other from Kiev, Ukraine, that included individuals who were exposed to the Chernobyl nuclear accident. In contrast, Xing et al. (2004) found BRAF mutations in only 20% of anaplastic thyroid cancers and in no medullary thyroid cancers or benign thyroid hyperplasia. They also confirmed previous reports that the BRAF 1799T-A mutation did not occur in benign thyroid adenomas or follicular thyroid cancers. They concluded that frequent occurrence of BRAF mutation is associated with PTC, irrespective of geographic origin, and is apparently not a radiation-susceptible mutation.

Nikiforova et al. (2003) analyzed 320 thyroid tumors and 6 anaplastic carcinoma cell lines and detected BRAF mutations in 45 papillary carcinomas (38%), 2 poorly differentiated carcinomas (13%), 3 (10%) anaplastic carcinomas (10%), and 5 thyroid anaplastic carcinoma cell lines (83%) but not in follicular, Hurthle cell, and medullary carcinomas, follicular and Hurthle cell adenomas, or benign hyperplastic nodules. All mutations involved a T-to-A transversion at nucleotide 1799. All BRAF-positive poorly differentiated and anaplastic carcinomas contained areas of preexisting papillary carcinoma, and mutation was present in both the well differentiated and dedifferentiated components. The authors concluded that BRAF mutations are restricted to papillary carcinomas and poorly differentiated and anaplastic carcinomas arising from papillary carcinomas, and that they are associated with distinct phenotypic and biologic properties of papillary carcinomas and may participate in progression to poorly differentiated and anaplastic carcinomas.

Hypothesizing that childhood thyroid carcinomas may be associated with a different prevalence of the BRAF 1799T-A mutation compared with adult cases, Kumagai et al. (2004) examined 31 cases of Japanese childhood thyroid carcinoma and an additional 48 cases of PTC from Ukraine, all of whom were less than 17 years of age at the time of the Chernobyl accident. The BRAF 1799T-A mutation was found in only 1 of 31 Japanese cases (3.4%) and in none of the 15 Ukrainian cases operated on before the age of 15 years, although it was found in 8 of 33 Ukrainian young adult cases (24.2%). Kumagai et al. (2004) concluded that the BRAF 1799T-A mutation is uncommon in childhood thyroid carcinomas.

Puxeddu et al. (2004) found the V600E substitution in 24 of 60 PTCs (40%) but in none of 6 follicular adenomas, 5 follicular carcinomas, or 1 anaplastic carcinoma. Nine of the 60 PTCs (15%) presented expression of a RET/PTC rearrangement. A genetico-clinical association analysis showed a statistically significant correlation between BRAF mutation and development of PTCs of the classic papillary histotype ($P = 0.038$). No link could be detected between expression of BRAF V600E and age at diagnosis, gender, dimension, local invasiveness of the primary cancer, presence of lymph node metastases, tumor stage, or multifocality of the disease. The authors concluded that these data clearly confirmed that BRAF V600E was the most common genetic alteration found to that time in adult sporadic PTCs, that it is unique for this thyroid cancer histotype, and that it might drive the development of PTCs of the classic papillary subtype.

Xing et al. (2004) demonstrated detection of the 1799T-A mutation on thyroid cytologic specimens from fine needle aspiration biopsy (FNAB). Prospective analysis showed that 50% of the nodules that proved to be PTCs on surgical histopathology were correctly diagnosed by BRAF mutation analysis on FNAB specimens; there were no false positive findings.

Xing et al. (2005) studied the relationships between the BRAF V600E mutation and clinicopathologic outcomes, including recurrence, in 219 PTC patients. The authors concluded that in patients with PTC, BRAF mutation is associated with poorer clinicopathologic outcomes and independently predicts recurrence. Therefore, BRAF mutation may be a useful molecular marker to assist in risk stratification for patients with PTC.

In a series of 52 classic PTCs, Porra et al. (2005) found that low SLC5A8 (608044) expression was highly significantly associated with the presence of the BRAF 1799T-A mutation. SLC5A8 expression was selectively downregulated (40-fold) in PTCs of classical form; methylation-specific PCR analyses showed that SLC5A8 was methylated in 90% of classic PTCs and in about 20% of other PTCs. Porra et al. (2005) concluded that their data identified a relationship between the methylation-associated silencing of the tumor-suppressor gene SLC5A8 and the 1799T-A point mutation of the BRAF gene in the classic PTC subtype of thyroid carcinomas.

Vasko et al. (2005) studied the relationship between the BRAF 1799T-A mutation and lymph node metastasis of PTC by examining the mutation in both the primary tumors and their paired lymph node metastases. Their findings indicated that the high prevalence of BRAF mutation in lymph node-metastasized PTC tissues from BRAF mutation-positive primary tumors and the possible de novo formation of BRAF mutation in lymph node-metastasized PTC were consistent with a role of BRAF mutation in facilitating the metastasis and progression of PTC in lymph nodes.

In a patient with congenital hypothyroidism and long-standing goiter due to mutation in the thyroglobulin gene (see TG, 188540; and TDH3, 274700), who was also found to have multifocal follicular carcinoma of the thyroid, Hishinuma et al. (2005) identified somatic heterozygosity for the V600E mutation in the BRAF gene in the cancerous thyroid tissue.

Liu et al. (2007) used BRAF siRNA to transfect stably several BRAF mutation-harboring PTC cell lines, isolated clones with stable suppression of BRAF, and assessed their ability to proliferate, transform, and grow xenograft tumors in nude mice. They found that the V600E mutation not only initiates PTC but also maintains the proliferation, transformation, and tumorigenicity of PTC cells harboring the BRAF mutation, and that the growth of tumors derived from such cells continues to depend on the V600E mutation.

Jo et al. (2006) found that of 161 PTC patients, 102 (63.4%) had the BRAF V600E mutation and that these patients had significantly larger tumor sizes and significantly higher expression of vascular endothelial growth factor (VEGF; 192240) compared to patients without this mutation. The level of VEGF expression was closely correlated with tumor size, extrathyroidal invasion, and stage. Jo et al. (2006) concluded that the relatively high levels of VEGF expression may be related to poorer clinical outcomes and recurrences in BRAF V600E(+) PTC.

Durante et al. (2007) found that the BRAF V600E mutation in PTCs is associated with reduced expression of key genes involved in iodine metabolism. They noted that this effect may alter the effectiveness of diagnostic and/or therapeutic use of radioiodine in BRAF-mutation PTCs.

Lupi et al. (2007) found a BRAF mutation in 219 of 500 cases (43.8%) of PTC. The most common BRAF mutation, V600E, was found in 214 cases (42.8%). BRAF V600E was associated with extrathyroidal invasion (p less than 0.0001), multicentricity (p = 0.0026), presence of nodal metastases (p = 0.0009), class III versus classes I and II (p less than 0.00000006), and absence of tumor capsule (p less than 0.0001), in particular, in follicular- and micro-PTC variants. By multivariate analysis, the absence of tumor capsule remained the only parameter associated (p = 0.0005) with the BRAF V600E mutation. The authors concluded that the BRAF V600E mutation is associated with high-risk PTC and, in particular, in follicular variant with invasive tumor growth.

Flaherty et al. (2010) reported complete or partial regression of V600E-associated papillary thyroid cancer in 3 patients treated with an inhibitor (PLX4032) specific to the V600E mutation.

---Nonseminomatous Germ Cell Tumors

In 3 (9%) of 32 nonseminomatous germ cell tumors (see 273300) with a mixture of embryonal carcinoma, yolk sac tumor, choriocarcinoma, and mature teratoma, Sommerer et al. (2005) identified the activating 1796T-A mutation in the BRAF gene; the mutation was present within the embryonic carcinoma component.

---Astrocytoma

Pfister et al. (2008) identified a somatic V600E mutation in 4 (6%) of 66 pediatric low-grade astrocytomas (see 137800). Thirty (45%) of the 66 tumors had a copy number gain spanning the BRAF locus, indicating a novel mechanism of MAPK (176948) pathway activation in these tumors.

---Variant Function

Brady et al. (2014) showed that decreasing the levels of CTR1 (603085), or mutations in MEK1 (176872) that disrupt copper binding, decreased BRAF(V600E)-driven signaling and tumorigenesis in mice and human cell settings. Conversely, a MEK1-MEK5 (602520) chimera that phosphorylated ERK1/2 independently of copper or an active ERK2 restored the tumor growth of murine cells lacking Ctr1. Copper chelators used in the treatment of Wilson disease (277900) decreased tumor growth of human or murine cells that were either transformed by BRAF(V600E) or engineered to be resistant to BRAF inhibition. Brady et al. (2014) concluded that copper chelation therapy could be repurposed to treat cancers containing the BRAF(V600E) mutation.

This gene has been observed to exhibit Autosomal dominant inheritance pattern.

It has been associated with Adenocarcinoma of lung somatic, Cardiofaciocutaneous syndrome, Colorectal cancer somatic, LEOPARD syndrome 3, Melanoma malignant somatic, Nonsmall cell lung cancer somatic, and Noonan syndrome 7.

Cardiofaciocutaneous (CFC) syndrome is a multiple congenital anomaly disorder characterized by a distinctive facial appearance, heart defects, and mental retardation (summary by Niihori et al., 2006). The heart defects include pulmonic stenosis, atrial septal defect, and hypertrophic cardiomyopathy. Some patients have ectodermal abnormalities such as sparse and friable hair, hyperkeratotic skin lesions, and a generalized ichthyosis-like condition. Typical facial characteristics include high forehead with bitemporal constriction, hypoplastic supraorbital ridges, downslanting palpebral fissures, a depressed nasal bridge, and posteriorly angulated ears with prominent helices. Most cases occur sporadically, but autosomal dominant transmission has been rarely reported (Linden and Price, 2011).

Roberts et al. (2006) provided a detailed review of CFC syndrome, including a discussion of the phenotypic overlap of CFC syndrome with Noonan syndrome (NS1; 163950) and Costello syndrome (218040).

Genetic Heterogeneity of Cardiofaciocutaneous Syndrome

Other forms of cardiofaciocutaneous syndrome include CFC2 (615278), caused by mutation in the KRAS gene (190070); CFC3 (615279), caused by mutation in the MAP2K1 gene (176872); and CFC4 (615280), caused by mutation in the MAP2K2 gene (601263). The protein products of these causative genes, including BRAF, interact in a common RAS/ERK (see 601795) pathway that regulates cell differentiation, proliferation, and apoptosis (summary by Roberts et al., 2006).

Molecular basis is known for 115150 because cardiofaciocutaneous syndrome-1 (CFC1) is caused by heterozygous mutation in the BRAF gene (164757) on chromosome 7q34.

Noonan syndrome is a developmental disorder characterized by reduced postnatal growth, dysmorphic facial features, cardiac defects, and variable cognitive defects (summary by Sarkozy et al., 2009).

Molecular basis is known for 613706 because this form of Noonan syndrome (NS7) is caused by heterozygous mutation in the BRAF gene (164757).

Cardiofaciocutaneous syndrome (CFCS; 115150) and LEOPARD syndrome-3 (613707) can also be caused by mutation in the BRAF gene, indicating that they are allelic disorders.

For a general phenotypic description and a discussion of genetic heterogeneity of Noonan syndrome, see NS1 (163950).

Molecular basis is known for 613707 because of evidence that LEOPARD syndrome-3 (LPRD3) is caused by heterozygous mutation in the BRAF gene (164757) on chromosome 7q34.

For a phenotypic description and a discussion of genetic heterogeneity of LEOPARD syndrome, see 151100.

Incidental Findings

NP_001120680.1:p.Gln644Ter in Exon 3 of *TET2* (NM_001127208.2:c.1930C>T)

This is a Stop Gained located in the TET2 gene.

It has been associated with Myelodysplastic syndrome somatic.

NP_001120680.1:p.Gly1256Asp in Exon 6 of *TET2* (NM_001127208.2:c.3767G>A)

This is a Missense Variant located in the TET2 gene.

It has been associated with Myelodysplastic syndrome somatic.

NP_001120680.1:p.Ile1762Val in Exon 11 of *TET2* (NM_001127208.2:c.5284A>G)

This is a Missense Variant located in the TET2 gene.

It has been associated with Myelodysplastic syndrome somatic.

NP_001904.2:p.Ala464Thr in Exon 16 of *CUX1* (NM_001913.3:c.1390G>A)

This is a Missense Variant located in the CUX1 gene.

NP_000537.3:p.Cys277Arg in Exon 8 of *TP53* (NM_000546.5:c.829T>C)

This is a Missense Variant located in the TP53 gene.

The transcription factor p53 responds to diverse cellular stresses to regulate target genes that induce cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism. In addition, p53 appears to induce apoptosis through nontranscriptional cytoplasmic processes. In unstressed cells, p53 is kept inactive essentially through the actions of the ubiquitin ligase MDM2 (164785), which inhibits p53 transcriptional activity and ubiquitinates p53 to promote its degradation. Numerous posttranslational modifications modulate p53

activity, most notably phosphorylation and acetylation. Several less abundant p53 isoforms also modulate p53 activity. Activity of p53 is ubiquitously lost in human cancer either by mutation of the p53 gene itself or by loss of cell signaling upstream or downstream of p53 (Toledo and Wahl, 2006; Bourdon, 2007; Vousden and Lane, 2007).

This gene has been observed to exhibit Autosomal recessive, Autosomal dominant, Somatic mutation, and Multifactorial inheritance pattern.

It has been associated with Adrenal cortical carcinoma, Breast cancer, Choroid plexus papilloma, Colorectal cancer, Hepatocellular carcinoma, Li-Fraumeni syndrome, Nasopharyngeal carcinoma, Osteosarcoma, Pancreatic cancer, Basal cell carcinoma 7, and Glioma susceptibility 1.

Li-Fraumeni syndrome (LFS) is a clinically and genetically heterogeneous inherited cancer syndrome. LFS is characterized by autosomal dominant inheritance and early onset of tumors, multiple tumors within an individual, and multiple affected family members. In contrast to other inherited cancer syndromes, which are predominantly characterized by site-specific cancers, LFS presents with a variety of tumor types. The most common types are soft tissue sarcomas and osteosarcomas, breast cancer, brain tumors, leukemia, and adrenocortical carcinoma. Classic LFS is defined as a proband with a sarcoma before the age of 45 years and a first-degree relative with any cancer before the age of 45 years and 1 additional first- or second-degree relative in the same lineage with any cancer before the age of 45 years or a sarcoma at any age (Li et al., 1988). Li-Fraumeni-like syndrome (LFL) is defined as a proband with any childhood cancer, or a sarcoma, brain tumor, or adrenocortical tumor before the age of 45 years, plus a first- or second-degree relative in the same lineage with a typical LFS tumor at any age, and an additional first- or second-degree relative in the same lineage with any cancer before the age of 60 years (Birch et al., 1994). A less restrictive definition of LFL is 2 different LFS-related tumors in first- or second-degree relatives at any age (Eeles, 1995). Approximately 70% of LFS cases and 40% of LFL cases contain germline mutations in the p53 gene on chromosome 17p13.1 (Bachinski et al., 2005).

Genetic Heterogeneity of Li-Fraumeni Syndrome

A second form of Li-Fraumeni syndrome (LFS2; 609265) is caused by mutation in the CHEK2 gene (604373), and an LFS locus (LFS3; 609266) has been mapped to chromosome 1q23.

Molecular basis is known for 151623 because Li-Fraumeni syndrome-1 is caused by heterozygous mutation in the p53 gene (TP53; 191170) on chromosome 17p13.1.

Adrenocortical carcinoma (ADCC) is a rare but aggressive childhood tumor, representing about 0.4% of childhood tumors, with a high incidence of associated tumors. ADCC occurs with increased frequency in patients with the Beckwith-Wiedemann syndrome (130650) and is a component tumor in Li-Fraumeni syndrome (LFS; 151623).

Molecular basis is known for 202300 because of evidence that one form of adrenocortical carcinoma is caused by heterozygous mutation in the TP53 gene (191170) on chromosome 17p13.

Choroid plexus tumors are of neuroectodermal origin and range from benign choroid plexus papillomas (CPPs) to malignant choroid carcinomas (CPCs). These rare tumors generally occur in childhood, but have also been reported in adults. Patients typically present with signs and symptoms of increased intracranial pressure including headache, hydrocephalus, papilledema, nausea, vomiting, cranial nerve deficits, gait impairment, and seizures (summary by Safaee et al., 2013).

Molecular basis is known for 260500 because of evidence that one form of choroid plexus papilloma (CPP) results from heterozygous mutation in the p53 gene (TP53; 191170) on chromosome 17p13.

Molecular basis is known for 614740 because susceptibility to basal cell carcinoma (BCC7) is influenced by variation in the TP53 gene (191170) on chromosome 17p13.1.

For a general phenotypic description and a discussion of genetic heterogeneity of basal cell carcinoma, see BCC1 (605462).

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Additional Information

Test

Illumina TruSight Myeloid Sequencing Panel

Indication

The panel targets 54 tumor suppressor genes and oncogenetic hotspots for somatic mutations in hematological malignancies.

Background

The TruSight Myeloid Sequencing Panel uses next-generation sequencing (NGS) technology to provide a comprehensive assessment of 54 genes (tumor suppressor genes and oncogenetic hotspots) in one test. The panel targets mutations with known involvement in acute myeloid leukemia (AML). Myelodsyplastic syndrome (MDS), myelopriliferative neoplasms (MPN), chronic myelogenous leukemia (CML), and juvenile myelomocylic leukemia (JMML). The result is a single assay for accurate, economical, and rapid profiling of liquid tumors for disease status and prognosis, in multiple samples.

Method

TruSight Myeloid features a highly optimized oligo pool specific for investigating genomic changes associated with hematological malignancies. The panel focuses on ~ 141 kb of genomic content consisting of 568 amplicons of ~ 250 bp in length designed against the human NCB37/mg19 reference genome. The oligo pool targets 15 full genes (exons only) plus exonic hotspots of an additional 39 genes, providing nearly 100% coverages of all targeted regions.

This optimized oligo pool provides uniform coverage of the target regions, enabling > 500x coverage for 95% of amplicons at > 5,000x mean coverage.

Sequence data generated from TruSight Myeloid libraries are analyzed using the on-instrument MiSeq Reporter software. After demultiplexing and FASTQ file generation, the software uses a custom banded Smith-Waterman aligner to align the reads against the human hg10 reference genome to create BAM files. The Somatic Variant Caller then performs variant analysis for the specified regions. The outputs are VCF or gVCR files, which are text files that contain SNPs and small indels.

Limitations

This test may not detect all variants in non-coding regions that could affect gene expression or copy number changes encompassing all or a large portion of the gene.

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