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Novel genetic targets in endometrial cancer

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Abstract

Worldwide, ~74,000 women die from endometrial cancer each year. Understanding the somatic genomic alterations that drive endometrial tumorigenesis may provide new opportunities to identify targeted therapies for specific subsets of patients.

Since 2012, the use of next generation sequencing to decode the mutational landscape of endometrial tumors has not only confirmed prior knowledge of established genetic targets for serous and endometrioid endometrial carcinomas, but has also uncovered novel significantly mutated genes, referred to herein as novel genetic targets, which represent candidate cancer genes in these tumors. This editorial summarizes the novel genetic targets that have been identified in serous and endometrioid ECs, according to their unifying functional characteristics. An expert opinion section comments on remaining knowledge gaps that will undoubtedly be filled in future genomic studies of endometrial cancer.

1. Introduction

Most endometrial cancers are endometrial carcinomas (ECs), which are further classified into numerous histopathological subtypes including endometrioid and serous ECs (reviewed in [1]). Endometrioid tumors account for ~80% of newly diagnosed ECs. Although they have a good overall prognosis, improved therapeutic strategies are needed to treat recurrent and advanced-stage endometrioid tumors. Likewise, alternative therapeutic approaches are needed for the treatment of serous ECs, which have a poor overall prognosis. In the era of precision medicine, comprehensive interrogations of tumor exomes and genomes for somatic alterations have been driven by the hope that they will reveal novel genetic targets that might ultimately guide treatment. For the purposes of this editorial, the consideration of novel genetic targets is limited to mutated genes; other classes of genomic and epigenomic alterations also represent novel genetic targets but are beyond the scope of this discussion.

2. Novel genetic targets in endometrioid and serous ECs

Recent massively parallel sequencing of endometrioid and serous ECs by individual laboratories [2-6], and by The Cancer Genome Atlas (TCGA) [7], has uncovered novel, statistically significantly mutated genes (SMGs) in these tumors; that is, genes that are mutated at a statistically significantly higher rate than background and which therefore

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represent candidate cancer genes. Furthermore, the integrated genomic analysis of endometrioid and serous ECs by TCGA revealed that they can be reclassified into four distinct molecular subgroups: ultramutated/POLE-mutant, hypermutated/microsatellite instability (MSI), copy number low/microsatellite stable (MSS), and copy number high/serous-like [7]. The abundance of SMGs in the ultramutated subgroup precludes their discussion in this Editorial. Among the remaining three subgroups, 32 SMGs, including 20 novel genetic targets (**Table 1**), have been described [7]. For ease of discussion herein, these novel genetic targets are loosely categorized according to their major ascribed functions.

2.1 Transcriptional regulation

Six novel SMGs, *CTCF*, *ZFHX3*, *SOX17*, *BCOR*, *MECOM*, and *TAF1*, encode transcriptional regulators. *CTCF* (CCCTC-binding factor) encodes a zinc-finger transcription factor that regulates transcriptional activation and repression, and influences chromatin architecture (Reviewed in [8]). Frequent truncating mutations within *CTCF* in MSI+ endometrioid ECs, and the unstable nature of the truncated transcripts, has lead to the proposal that *CTCF* may be a haploinsufficient tumor suppressor gene in these tumors [9]. Another transcription factor gene, *ZFHX3* (Zinc Finger Homeobox 3), is significantly mutated in hypermutated/MSI ECs [7]. *ZFHX3* is a putative tumor suppressor gene based on its location within a common region of 16q22 deletion in human cancer and the occurrence of frequent somatic mutations in prostate cancer [10]. *SOX17* (SRY (sex determining region Y)-box 17), a SMG in copy number low/MSS ECs, encodes an HMG box transcription factor that, amongst other effects, negatively regulates WNT/β-catenin signaling [11]. In copy number low/MSS ECs, *SOX17* mutations are mutually exclusive with other genetic aberrations affecting the WNT/β-catenin pathway, suggesting that they likely perturb WNT signaling [7]. *BCOR* (BCL6 corepressor), which encodes a corepressor of BCL6, is significantly mutated in copy number low/MSS ECs [7]. *MECOM* (MDS1 and EVI1 Complex Locus), a protooncogene that encodes a zinc finger transcription factor, is significantly mutated in copy number low/MSS ECs [7]. Although the functional impact of *MECOM* mutations in EC is unknown, it is noteworthy that MECOM inhibitors are being developed [12]. Finally, *TAF1* (TAF1 RNA Polymerase II, TATA Box Binding Protein (TBP)-Associated Factor, 250kDa) encodes a subunit of the TFIID basal transcription factor and is a SMG in serous EC [4].

2.2 Chromatin remodeling and chromatin organization

CHD4 (chromodomain helicase DNA binding protein 4) and *ARID5B* (AT rich interactive domain 5B (MRF1-like)) are novel SMGs involved in chromatin remodeling [3, 7]. *CHD4* was first implicated in EC by virtue of its designation as a SMG in serous tumors [3]. CHD4 is a subunit of the NuRD complex, which is a transcriptional activator and repressor, and is implicated in the DNA damage response [13]. *ARID5B* (AT rich interactive domain 5B (MRF1-like) is a SMG in hypermutated/MSI ECs and encodes a DNA-binding protein that complexes with PHF2 (PHD finger protein 2), a lysine demethylase. The DNA-binding activity of ARID5B is believed to direct the ARID5B-PHF2 complex to specific gene promoters resulting in histone demethylation and transcriptional activation [14]. Another SMG in hypermutated/MSI ECs is *HIST1H2BD* (histone cluster 1, H2bd), which encodes a core component of the nucleosome.

2.3 Ubiquitin-mediated protein degradation

FBXW7 (F-Box And WD Repeat Domain Containing 7, E3 Ubiquitin Protein Ligase) and *SPOP* (Speckle-Type POZ Protein), which encode the substrate recognition components of the SKP1-CUL1-FBXW7 and SPOP-CUL3 ubiquitin ligase complexes respectively, are SMGs in serous ECs [2-4]. FBXW7 is a *bona fide* tumor suppressor and SPOP is a putative tumor suppressor. Many of the *FBXW7* mutations documented in EC encode dominant-negative or loss-of -function mutants in other tumor types and it is therefore anticipated that *SPOP* mutations in EC may function similarly [3]. In certain cellular contexts, loss of FBXW7 function is associated with in vitro sensitivity to sorafenib and resistance to antitubulin chemotherapeutics (reviewed in [15]), or sensitivity to an HDAC inhibitor [16]. However, the relevance of those observations to *FBXW7*-mutant endometrial cancers remains to be elucidated.

2.4 RNA binding or RNA modification

Four novel genetic targets, *RPL22*, *RBMX*, *CSDE1*, and *METTL14*, have RNA binding capability or RNA modification activity. *RPL22* (Ribosomal Protein L22) encodes a ribosomal protein and is believed to be a tumor suppressor gene in T-ALL [17]. *RPL22* mutations are extraordinarily frequent (52%) in MSI+ EECs, and are attributed to a recurrent frameshift mutation (c.43delA) suggesting loss of function [18]. *RBMX* (RNA binding motif protein, X-linked) encodes an RNA-binding protein that regulates pre-mRNA splicing [19], and is implicated in the DNA damage response [20], mitotic sister chromatid cohesion [21], and the regulation of Tumor Necrosis Factor Receptor 1 release. *RBMX* is a SMG in hypermutated/MSI ECs, exhibiting recurrent in-frame deletions encompassing the translation start site. *CSDE1* (cold shock domain containing E1, RNA-binding), a SMG in hypermutated/MSI EC, encodes an RNA- and single-stranded DNA-binding protein that regulates mRNA turnover and translation (reviewed in [22]). Most *CSDE1* mutations in EC are missense mutations, including three recurrently mutated residues (R174, R726, R774). Finally, *METTL14* (Methyltransferase Like 14) is significantly mutated in hypermutated/MSI ECs [7], and encodes a methyltransferase that complexes with METTL3 and methylates m^6A on nuclear RNA [23]. The majority of *METTL14* mutations in EC are missense mutations within the methyltransferase domain, including a recurrent R298P mutation [7].

2.5 Other functions

NKAP, *GIGYF2*, *LIMCH1*, *TNFAIP6*, and *SGK1* are novel genetic targets that do not precisely fit into the previously discussed categories. NKAP (NFKB Activating Protein) regulates NF kappa B activation induced by TNF and IL-1 [24], is a transcriptional corepressor for Notch [25], and has been implicated in RNA splicing [26]. *NKAP* is significantly mutated in hypermutated/MSI ECs [7]. GIGYF2 (GRB10 Interacting GYF Protein 2), encoded by a SMG in hypermutated/MSI ECs, is involved in IGF-I receptor signaling [27], and is implicated in the regulation of protein translation [28]. *LIMCH1* (LIM and Calponin Homology Domains 1) encodes a protein with a poorly defined function and is significantly mutated in hypermutated/MSI ECs [7]. The R421fs frameshift mutation accounts for almost all *LIMCH1* mutations in hypermutated/MSI ECs and is predicted to

encode a truncated protein lacking the LIM domain. *TNFAIP6* (Tumor necrosis factor, alpha-induced protein 6) is significantly mutated in hypermutated/MSI ECs. The encoded protein interacts with components of the extracellular matrix including hyaluronan [29], and is involved in the inflammatory response and tissue remodeling [30]. Finally, *SGK1* (Serum/glucocorticoid regulated kinase 1), a SMG in copy number low/MSS ECs, encodes a kinase implicated in the regulation of a wide range of cellular processes including tumor cell survival. Although *SGK1* has received attention as a potential druggable target in cancer (reviewed in [31]), the biological and therapeutic relevance of *SGK1* mutations in EC remain unknown.

3. Mutation patterns between SMGs

Patterns of mutations between genes can provide insights into their possible functional effects. Here, the pattern of mutations among the 32 SMGs, identified in non-ultramutated ECs in TCGA, was obtained via the cBioPortal for Cancer Genomics [32, 33] (Supplementary Tables 1-4). As shown in **Table 2**, mutations in a number of novel SMGs showed a tendency for mutually exclusive or co-occurring mutations, suggesting, respectively, possible functional redundancy or cooperativity.

4. Expert opinion

With novel genetic targets for serous and endometrioid EC now in hand, the challenge will be to determine whether any of these targets are therapeutically relevant. This can take the form of biochemical and biological studies of mutant proteins in their proper cellular and genetic context, systems biology approaches to functionalize the genome [5], as well as systematic searches for gene-drug interactions. One strategy to prioritize genetic targets for further analysis is to focus on the most frequently mutated of the SMGs, which, if proven to be druggable, would theoretically maximize the number of patients who might gain clinical benefit. Alternatively, SMGs that have reported gene-drug interactions and/or are being evaluated as druggable targets in preclinical studies within other cellular contexts, such as *FBXW7*, *MECOM*, and *SGK1*, could be prioritized for assessment of their therapeutic relevance to EC. In terms of seeking druggable targets, it is noteworthy that catalogues of SMGs are dynamic rather than static and depend on the assumptions and parameters used in statistical calculations as well as user-defined statistical cut-offs. Moreover, current catalogues of genetic targets in serous and endometrioid ECs have principally been derived from analyses of primary tumor tissues resected prior to treatment. As such, there may be additional genetic targets yet to be discovered within recurrent or persistent tumors that are refractory to therapy, or in metastatic disease. Additionally, the genomic landscape of other histological subtypes of endometrial carcinoma remains to be elucidated. Finally, it remains to be seen whether additional novel genetic targets will emerge from sequencing of larger numbers of tumors corresponding to each of the four recently defined molecular subgroups of serous and endometrioid EC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Dedes KJ, Wetterskog D, Ashworth A, et al. Emerging therapeutic targets in endometrial cancer. Nat Rev Clin Oncol. 2011; 8:261–71. • This article provides an excellent review of targeted therapies currently being evaluated for endometrial cancer. [PubMed: 21221135]
2. Kuhn E, Wu RC, Guan B, et al. Identification of molecular pathway aberrations in uterine serous carcinoma by genome-wide analyses. J Natl Cancer Inst. 2012; 104:1503–1513. • The first published whole exome sequencing analysis of serous endometrial carcinomas, which documented high-frequency somatic mutations in the *FBXW7* tumor suppressor gene. [PubMed: 22923510]
3. Le Gallo M, O'Hara AJ, Rudd ML, et al. Exome sequencing of serous endometrial tumors identifies recurrent somatic mutations in chromatin-remodeling and ubiquitin ligase complex genes. Nat Genet. 2012; 44:1310–15. • This study identified somatic mutations in serous endomerial carcinomas using whole exome sequencing, and extended their analysis of novel candidate driver genes to both clear cell and endometrioid endometrial carcinomas; this was the first study to identify the chromatin remodelling gene *CHD4*, and the ubiquitin ligase complex gene *SPOP* as candidate driver genes in serous tumors. [PubMed: 23104009]
4. Zhao S, Choi M, Overton JD, et al. Landscape of somatic single-nucleotide and copy-number mutations in uterine serous carcinoma. ProcA Natl Acad Sci USA. 2013; 110:2916–21. • This study describes the systematic identification of somatic mutations and copy number alterations among a large series of serous endometrial carcinomas and cell lines.
5. Liang H, Cheung LW, Li J, et al. Whole-exome sequencing combined with functional genomics reveals novel candidate driver cancer genes in endometrial cancer. Genome Res. 2012; 22:2120–9. • This study employed a unique systems biology approach to search for pathogenic driver genes in endometrial carcinomas. [PubMed: 23028188]
6. Kinde I, Bettegowda C, Wang Y, et al. Evaluation of DNA from the Papanicolaou test to detect ovarian and endometrial cancers. Sci Transl Med. 2013; 5:167–164. • This manuscript highlights the potential utility of molecular based diagnostics for endometrial cancer.
7. Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013; 497:67–73. •• Landmark study reporting the genomic and epigenomic landscape of endometrioid and serous endometrial carcinomas. [PubMed: 23636398]
8. Lee BK, Iyer VR. Genome-wide studies of CCCTC-binding factor (CTCF) and cohesin provide insight into chromatin structure and regulation. J Biol Chem. 2012; 287:30906–13. [PubMed: 22952237]
9. Zighelboim I, Mutch DG, Knapp A, et al. High frequency strand slippage mutations in CTCF in MSI-positive endometrial cancers. Hum Mutat. 2014; 35:63–5. [PubMed: 24130125]
10. Sun X, Frierson HF, Chen C, et al. Frequent somatic mutations of the transcription factor ATBF1 in human prostate cancer. Nat Genet. 2005; 37:407–12. [PubMed: 15750593]
11. Sinner D, Kordich JJ, Spence JR, et al. Sox17 and Sox4 differentially regulate beta-catenin/T-cell factor activity and proliferation of colon carcinoma cells. Mol Cell Biol. 2007; 27:7802–15. [PubMed: 17875931]
12. Zhang Y, Sicot G, Cui X, Vogel M, Wuertzer CA, Lezon-Geyda K, Wheeler J, Harki DA, Muzikar KA, Stolper DA, et al. Targeting a DNA binding motif of the EVI1 protein by a pyrrole-imidazole polyamide. Biochemistry. 2011; 50:10431–41. [PubMed: 22039883]
13. O'Shaughnessy A, Hendrich B. CHD4 in the DNA-damage response and cell cycle progression: not so NuRDy now. Biochem Soc Trans. 2013; 41:777–82. [PubMed: 23697937]
14. Baba A, Ohtake F, Okuno Y, et al. PKA-dependent regulation of the histone lysine demethylase complex PHF2-ARID5B. Nat Cell Biol. 2011; 13:668–75. [PubMed: 21532585]
15. Inuzuka H, Fukushima H, Shaik S, Liu P, Lau AW, Wei W. Mcl-1 ubiquitination and destruction. Oncotarget. 2011; 2:239–44. [PubMed: 21608150]
16. Garnett MJ, Edelman EJ, Heidorn SJ, et al. Systematic identification of genomic markers of drug sensitivity in cancer cells. Nature. 2012; 483:570–5. [PubMed: 22460902]
17. Rao S, Lee SY, Gutierrez A, et al. Inactivation of ribosomal protein L22 promotes transformation by induction of the stemness factor, Lin28B. Blood. 2012; 120:3764–73. [PubMed: 22976955]

18. Novetsky AP, Zighelboim I, Thompson DM Jr. et al. Frequent mutations in the RPL22 gene and its clinical and functional implications. Gynecol Oncol. 2013; 128:470–4. [PubMed: 23127973]
19. Heinrich B, Zhang Z, Raitskin O, et al. Heterogeneous nuclear ribonucleoprotein G regulates splice site selection by binding to CC(A/C)-rich regions in pre-mRNA. J Biol Chem. 2009; 284:14303–15. [PubMed: 19282290]
20. Adamson B, Smogorzewska A, Sigoillot FD, et al. A genome-wide homologous recombination screen identifies the RNA-binding protein RBMX as a component of the DNA-damage response. Nat Cell Biol. 2012; 14:318–28. [PubMed: 22344029]
21. Matsunaga S, Takata H, Morimoto A, et al. RBMX: a regulator for maintenance and centromeric protection of sister chromatid cohesion. Cell Rep. 2012; 1:299–308. [PubMed: 22832223]
22. Mihailovich M, Militti C, Gabaldon T, et al. Eukaryotic cold shock domain proteins: highly versatile regulators of gene expression. Bioessays. 2010; 32:109–18. [PubMed: 20091748]
23. Liu J, Yue Y, Han D, et al. A METTL3-METTL14 complex mediates mammalian nuclear RNA N(6)-adenosine methylation. Nat Chem Biol. 2014; 10:93–5. [PubMed: 24316715]
24. Chen D, Li Z, Yang Q, et al. Identification of a nuclear protein that promotes NF-kappaB activation. Biochem Biophys Res Commun. 2003; 310:720–4. [PubMed: 14550261]
25. Pajerowski AG, Nguyen C, Aghajanian H, et al. NKAP is a transcriptional repressor of notch signaling and is required for T cell development. Immunity. 2009; 30:696–707. [PubMed: 19409814]
26. Burgute BD, Peche VS, Steckelberg AL, et al. NKAP is a novel RS-related protein that interacts with RNA and RNA binding proteins. Nucleic Acids Res. 2014; 42:3177–93. [PubMed: 24353314]
27. Giovannone B, Lee E, Laviola L, et al. Two novel proteins that are linked to insulin-like growth factor (IGF-I) receptors by the Grb10 adapter and modulate IGF-I signaling. J Biol Chem. 2003; 278:31564–73. [PubMed: 12771153]
28. Morita M, Ler LW, Fabian MR, et al. A novel 4EHP-GIGYF2 translational repressor complex is essential for mammalian development. Mol Cell Biol. 2012; 32:3585–93. [PubMed: 22751931]
29. Lee TH, Wisniewski HG, Vilcek J. A novel secretory tumor necrosis factor-inducible protein (TSG-6) is a member of the family of hyaluronate binding proteins, closely related to the adhesion receptor CD44. J Cell Biol. 1992; 116:545–57. [PubMed: 1730767]
30. Milner CM, Higman VA, Day AJ. TSG-6: a pluripotent inflammatory mediator? Biochem Soc Trans. 2006; 34:446–50. Pt 3. [PubMed: 16709183]
31. Lang F, Voelkl J. Therapeutic potential of serum and glucocorticoid inducible kinase inhibition. Expert Opin Investig Drugs. 2013; 22:701–14.
32. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, Jacobsen A, Byrne CJ, Heuer ML, Larsson E, et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012; 2:401–404. [PubMed: 22588877]
33. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, Sun Y, Jacobsen A, Sinha R, Larsson E, et al. Integrative Analysis of Complex Cancer Genomics and Clinical Profiles Using the cBioPortal. Sci Signal. 2013; 6:pl1. [PubMed: 23550210]

Table 1

Mutation frequency of novel significantly mutated protein-encoding genes identified among serous and non-ultramutated endometrioid ECs

Gene symbol[¶]	Frequency of somatic mutations[§]						Reference
	Histological subtype		Molecular subgroup [7]				
	Endometrioid	Serous	Ultramutated	Hypermutated/ MSI	Copy number low/MSS	Copy number high/serous-like	
ARID5B	9%-18%	0%	47%	23%	6%	0%	[6, 7]
BCOR	4%-10%	0%	65%	17%	7%	0%	[6, 7]
CHD4	7%-13%	13%-18%	65%	6%	12%	13%	[3, 4, 6, 7]
CSDE1	7%	0%	59%	15%	1%	0%	[7]
CTCF	15%-29%	0%	41%	23%	21%	0%	[6, 7, 9]
FBXW7	7%-27%	20%-29%	82%	9%	6%	22%	[2-4, 6, 7]
GIGYF2	8%-14%	6%	59%	20%	0%	7%	[6, 7]
HIST1H2BD	2%	0%	0%	8%	1%	0%	[7]
LIMCH1	6%-9%	0%	53%	12%	0%	0%	[6, 7]
MECOM	4%	0%	24%	5%	4%	0%	[7]
METTL14	3%	0%	24%	5%	3%	0%	[7]
NKAP	4%	0%	18%	11%	1%	0%	[6, 7]
RBMX	4%	0%	24%	12%	0%	0%	[7]
RPL22	10%-52%	0%	29%	37%	0%	0%	[7, 21]
SGK1	4%	2%	35%	3%	6%	2%	[7]
SOX17	2%	0%	0%	0%	8%	0%	[7]
SPOP	0%-6%	4%-8%	29%	6%	10%	5%	[3, 4, 6, 7]
TAF1	11%-27%	4%-9%	82%	25%	1%	5%	[4, 6, 7]
TNFAIP6	2%	0%	29%	2%	1%	0%	[7]
ZFHX3	13%-36%	6%	82%	31%	2%	7%	[6, 7]

¶ MIR1277 is significantly mutated but is not shown in Table 1 because it is not a protein-encoding gene

§ Mutation frequencies for the TCGA dataset were obtained from Kandoth et al [7] and via the cBioPortal for Cancer Genomics [32, 33]

¶ *CSMD3* is a novel SMG in EC but is not shown in Table 1 because it may be a false-positive

Table 2

Statistically significant trends in mutation patterns[§] involving novel SMGs identified in non-ultramutated ECs in the TCGA study [7]

Molecular Subgroup	Gene Pair	Trend in Mutation Pattern[§]	p-value[§]
Hypermutated/MSI	*ARID5B-ZFHX3*	Co-occurrence	0.035
	CTCF-FGFR2	Co-occurrence	0.025
	FBXW7-LIMCH1	Co-occurrence	0.021
	BCOR- PPP2R1A	Co-occurrence	0.006
	HIST1H2BD -RPL22	Co-occurrence	0.005
	SPOP-RPL22	Co-occurrence	0.016
	SPOP-CCND1	Co-occurrence	0.005
	SPOP-PPP2R1A	Co-occurrence	0.040
	MECOM-PPP2R1A	Co-occurrence	0.021
	MECOM-ATR	Co-occurrence	0.0004
	METTL14-FGFR2	Co-occurrence	0.048
	METTL14-PPP2R1A	Co-occurrence	0.021
	SGK1-RBMX	Co-occurrence	0.013
	TNFAIP6-MECOM	Co-occurrence	0.046
	TNFAIP6-METTL14	Co-occurrence	0.046
Copy number low/MSS	*SPOP-PTEN*	Mutual exclusivity	0.029
	SOX17-CTNNB1	Mutual exclusivity	0.043
	FBXW7-CTNNB1	Mutual exclusivity	0.022
	FBXW7-SOX17	Co-occurrence	0.047
	MECOM-PIK3R1	Co-occurrence	0.011
Copy number high/serous-like	*CHD4-FBXW7*	Co-occurrence	0.009
	GIGYF2-TP53	Mutual exclusivity	0.001
Ultramutated	*ZFHX3-PIK3CA*	Co-occurrence	0.015
	ZFHX3-ATR	Co-occurrence	0.029
	GIGYF2-CSDE1	Co-occurrence	0.004
	SGK1-CTNNB1	Co-occurrence	0.017
	ATR-CTNNB1	Co-occurrence	0.017
	CSDE1-FGFR2	Co-occurrence	0.041
	GIGYF2-FGFR2	Co-occurrence	0.041
	LIMCH1-PPP2R1A	Co-occurrence	0.020
	SPOP-KRAS	Mutual exclusivity	0.009
	RBMX-KRAS	Mutual exclusivity	0.029
	CCND1-RPL22	Co-occurrence	0.014

[§]Data were obtained from the cBioCancer Genomics Portal [32,33]; SMGs identified in the ultramutated subgroup were not included in the input query. Only gene-pairs demonstrating a p-value <0.05, as derived via Fisher's Exact test are shown; p-values are not adjusted for FDR.