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Functional and mutational landscape of cell polarity complex genes in cutaneous melanoma: A comprehensive bioinformatic analysis

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Cutaneous melanoma is the most aggressive type of skin cancer, known for its high metastatic potential and molecular heterogeneity. This study explores the functional significance of polarity complex proteins in melanoma by analyzing their roles in epithelial polarity maintenance and directional cell migration. Genomic mutation and gene expression data from the TCGA-SKCM cohort were evaluated using bioinformatic tools including PolyPhen-2, SIFT, Mutation Assessor, and AlphaMissense. A total of 347 mutations were identified in 12 polarity-related genes, with 128 predicted as pathogenic or oncogenic. Many mutations were located in PDZ domains and were associated with disruptions in key signaling pathways such as TGF-β and Hippo. STRING-based protein interaction analysis supported these associations. Differential expression analysis revealed significant downregulation of LLGL2, CRB3, PATJ, and PARD3 in melanoma samples compared to normal tissue ($P < 0.01$). Pathway enrichment analysis showed involvement of these genes in cancer hallmark pathways, particularly those related to invasion, metastasis, and immune evasion. The study suggests that polarity proteins can act as either tumor suppressors or oncogenes depending on mutation context. These findings provide valuable insights into melanoma pathogenesis and suggest polarity complex components as potential prognostic biomarkers and therapeutic targets in SKCM.

Keywords: Cell polarity complex, Cutaneous melanoma, mutation, gene expression

Introduction

Skin cutaneous melanoma (SKCM) originates from melanocytes, pigment-producing cells derived from the neuroectoderm, characterized by a highly polarized dendritic morphology. These cells reside in close contact with keratinocytes, the predominant cell type of the epidermis. Studies have shown that keratinocytes secrete soluble factors that modulate melanocyte growth, motility, and differentiation[1,2]. While the keratinocyte–melanocyte cross-talk plays a pivotal role in maintaining the epidermal melanin unit, the precise mechanisms by which the epidermal microenvironment influences melanomagenesis remain incompletely understood[3,4].

Cell polarity is fundamental to various biological processes, including cell growth, migration, intracellular transport, and fate determination. Profound and dynamic changes in cell adhesion, polarity, and tissue architecture are integral to oncogenic transformation. Central to these processes are evolutionarily conserved polarity protein complexes, namely the Crumbs (CRB) complex, the Partitioning-defective (PAR) complex, and the Scribble (SCRIB) complex[3–5]. The SCRIB complex, which includes Scribble, Discs large (DLG), and Lethal giant larvae (LGL), localizes to the basolateral membrane in epithelial cells and is essential for maintaining basolateral identity. In contrast, the PAR complex composed of PAR3, PAR6, atypical protein kinase C (aPKC), and the small GTPase cdc42 and the CRB complex consisting of the transmembrane protein CRB3, Pals1, and PATJ function in establishing and maintaining apical polarity[5–7]. Importantly, these complexes exhibit mutually antagonistic interactions, maintaining the spatial organization of epithelial polarity. Loss of cell polarity is widely recognized as an early and enabling event in tumor initiation and progression. Given their role as fundamental determinants of cell and tissue architecture, dysregulation of polarity proteins and their signaling pathways can significantly contribute to melanoma carcinogenesis[3–8]. Therefore, the present study aims to identify potential molecular targets

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involved in the pathogenesis and progression of cutaneous melanoma by comprehensively analyzing oncogenic mutations and mRNA expression profiles of genes encoding polarity complex proteins critical determinants of epithelial architecture in malignant melanoma.

Material and Methods

Patient data acquisition

Demographic, clinical, and genomic data for patients with skin cutaneous melanoma (SKCM; n=442) were obtained from the cBioPortal for Cancer Genomics (https://www.cbioportal.org). Details of the SKCM cohort are presented in Table 1, and raw data are publicly accessible via the platform. Data were downloaded on December 27, 2024.

Mutation profile analysis

Mutation profiles were analyzed using the cBioPortal, which provides open-access genomic data, including mutation information, mRNA expression (from microarray and RNA-seq), and clinical annotations derived from The Cancer Genome Atlas (TCGA)[9]. The SKCM (n=442) dataset was selected, and mutations in genes encoding polarity complex proteins were comprehensively investigated.

Table 1 — Demographic, clinical and genetic data of patients with SKCM cohort.

Characteristic	Patient data n: 442(%)
Gender	
Male/Female/NA	273/169
Diagnosis age, years	(1-90)
Diagnosis type	
Metastasis	361
Primary	81
Metastasis Stage Code	
M0	390 (88.2)
M1	5 (1.1)
M1A	2 (0.9)
M1B	5 (1.1)
M1C	10(2.3)
NA/other	28 (6.3)
Overall Survival Status	
Living	222
Deceased	213
NA	26
Total Mutation Frequency in SKCM	Case (Frequency%)
LLGL1 genetic alteration	5
LLGL2 genetic alteration	10
SCRIB genetic alteration	10
DLG1 genetic alteration	6
CRB1 genetic alteration	25
CRB2 genetic alteration	9
CRB3 genetic alteration	0
PATJ genetic alteration	13
PALS1 genetic alteration	4
PARD3 genetic alteration	9
PARD6A genetic alteration	1

In silico functional pathogenicity and oncogenicity prediction

To assess the pathogenicity and potential clinical relevance of mutations detected in polarity complex genes, four bioinformatic tools were used: PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) predicts the possible impact of amino acid substitutions on protein structure and function based on comparative evolutionary analysis and protein structural features[10]. SIFT (https://sift.bii.a-star.edu.sg/) estimates whether an amino acid substitution affects protein function using sequence homology and physicochemical properties[11]. Mutation Assessor (http://mutationassessor.org/r3/) evaluates the functional impact of missense mutations in proteins, particularly those observed in cancers[12]. AlphaMissense assigns a pathogenicity score (0–1) to amino acid substitutions by considering protein structure and functional context, categorizing them as "probably pathogenic," "uncertain," or "probably benign"[13].

Gene expression profiling and survival analysis

Gene expression levels and survival outcomes were analyzed using GEPIA (http://gepia.cancer-pku.cn/), which integrates RNA-seq data from 9736 tumor and 8587 normal tissue samples across TCGA and GTEx databases[14]. In this study, expression data from SKCM tumor samples (n=461) and normal tissues (n=558) were compared. The impact of differential gene expression on overall survival was analyzed using Kaplan–Meier curves and the log-rank test via GEPIA.

Promoter methylation analysis

Promoter methylation levels of polarity complex genes were evaluated using the UALCAN portal (http://ualcan.path.uab.edu/analysis-prot.html)[15]. Methylation data were obtained from TCGA using the Illumina Infinium Human Methylation450 Bead Chip. Differences in methylation levels between tumor and normal tissues were assessed using Welch's t-test.

Cancer hallmark pathway analysis

Cancer hallmark enrichment analysis was conducted to determine the biological relevance of polarity complex genes in melanoma. In the resulting visualization, each hallmark is represented by colored slices, where the size and color intensity reflect the degree and statistical significance of pathway enrichment compared to a reference gene set[16].

Protein–protein interaction (ppi) network analysis

Protein interactions were analyzed using the STRING database (http://string-db.org), which identifies both physical and functional associations between proteins[17]. The polarity complex gene products were queried to construct a PPI network and explore their biological relationships in tumorigenesis**.**

Statistical analysis

All statistical analyses were conducted using embedded tools within the bioinformatics platforms mentioned above. mRNA expression differences between SKCM and normal tissues were analyzed via one-way ANOVA in GEPIA. Survival differences between high and low expression groups were evaluated using Kaplan–Meier survival curves and compared using the log-rank test. Statistical significance was defined as $P < 0.05$.

Results

Mutation profile analysis

In the SKCM cohort (n = 442), all target genes except CRB3 were found to harbor mutations. The CRB1 gene exhibited the highest mutation frequency (25%), while PARD6A had the lowest (1%). The identified mutations included missense, nonsense, and frameshift mutations, as well as gene amplifications and deep deletions. A total of 347 mutations were detected across 12 genes, with the detailed characteristics presented in Table 2. Statistically significant co-occurrence of mutations was observed among the following gene pairs: LLGL2–CRB1, CRB1–PATJ, CRB1–CRB2, PARD3–PATJ, and PRKCI–CRB1 (P<0.001). No putative driver mutations were identified in any of the target genes. Additionally, gene amplification events were detected in all target genes except CRB3, while deep deletions resulting in homozygous loss were observed in all genes except CRB3, SCRIB, and PARD6A. (Fig. 1A & B) depict the frequency of mutations in the target genes within the SKCM cohort, while (Fig. 2A & B) illustrates the localization of mutations within specific domains of the encoded proteins.

Scribble complex gene analysis

The Scribble protein complex comprising Scribble, Lgl, and Dlg proteins is highly conserved across species, from Drosophila to *Caenorhabditis*

Table 2 — Characteristics of mutations detected in target genes in TCGA SKCM cohort

							Clinic Impact			
No	Gene	Nt alteration	Rs Number/ Cosmic ID	Alteration Type	Localization	AA position	Poly-Phen2 (Score)	SIFT (Score)	Mutaion Assesor (Score)	Alpha Missense (Score)
M-1	LLGL1	c.1805C>T	rs3514903	Missense mutation	Exon-14	T602I	Probably Damaging (1.00)	Deleterious (0.00)	High (7.13)	Pathogenic (0.99)
M-2	LLGL1	c.1205C>T	NA	Missense mutation	Exon-10	A402V	Benign (0.21)	Deleterious (0.00)	Low (4.92)	Benign (0.13)
M-3	LLGL1	c.598T>G	rs3889391	Missense mutation	Exon-6	S200A	Benign (0.00)	Tolerated (1.00)	Low (4.92)	Benign (0.7)
M-4	LLGL1	c.1054G>A	rs3514900	Missense mutation	Exon-9	E352K	Benign (0.18)	Tolerated (0.12)	Low(3.88)	Benign (0.9)
M-5	LLGL1	c.1892C>A	NA	Missense mutation	Exon-14	P631H	Possibly Damaging (0.83)	Tolerated (0.7)	Medium (5.35)	Benign (0.21)
M-6	LLGL1	c.928G>T	NA	Missense mutation	Exon-9	G310C	Probably Damaging (1.00)	Deleterious (0.00)	High (7.19)	Pathogenic (0.96)
M-7	LLGL1	c.1768C>A	NA	Missense mutation	Exon-14	R590S	Benign (0.00)	Tolerated (0.7)	Low(2.98)	Benign (0.17)
M-8	LLGL1	c.1538C>T	NA	Missense mutation	Exon-13	P513L	Probably Damaging (0.97)	Deleterious (0.00)	High (7.13)	Pathogenic (0.98)
M-9	LLGL1	c.2297G>A	NA	Missense mutation	Exon-17	G766D	Benign (0.08)	Tolerated (0.10)	Low(4.51)	Benign (0.11)
M-10	LLGL1	c.1690G>T	NA	Nonsense mutation	Exon-14	E564*	NA	NA	NA	NA
M-11	LLGL1	c.1332G>T	NA	Missense mutation	Exon-11	Q444H	Possibly Damaging (0.56)	Deleterious (0.03)	Medium (4.98)	Benign (0.14)
M-12	LLGL1	c.218G>T	rs3402647	Missense mutation	Exon-3	R73L	Benign (0.04)	Tolerated (0.11)	Medium (5.19)	Benign (0.14)
M-13	LLGL1	c.860C>A	NA	Missense mutation	Exon-8	P287H	Probably Damaging (1.00)	Deleterious (0.01)	Medium (5.17)	Pathogenic (0.94)

(*Contd.*)

Table 2 — Characteristics of mutations detected in target genes in TCGA SKCM cohort (*Contd*.)

No	Gene	Nt alteration	Rs Number/ Cosmic ID	Alteration Type	Localization	AA position	Clinic Impact			
							Poly-Phen2 (Score)	SIFT (Score)	Mutaion Assesor (Score)	Alpha Missense (Score)
M-14	LLGL1	c.2508C>A	NA	Missense mutation	Exon-18	F836L	Probably Damaging (0.97)	Deleterious (0.01)	Medium (6.09)	Pathogenic (1.00)
M-15	LLGL1	c.130C>T	NA	Missense mutation	Exon-2	P44S	Benign (0.00)	Deleterious (0.04)	Low(3.28)	Benign (0.15)
M-16	LLGL1	c.131C>T	rs141705015	Missense mutation	Exon-2	P44L	Benign (0.18)	Deleterious (0.01)	Low(5.06)	Benign (0.26)
M-17	LLGL1	c.1819C>A	NA	Missense mutation	Exon-14	H607N	Probably Damaging (0.99)	Deleterious (0.01)	Medium (5.20)	Benign (0.01)
M-18	LLGL1	c.2246C>T	rs373022414	Missense mutation	Exon-17	S749L	Probably Damaging (0.99)	Deleterious (0.02)	Medium (6.00)	Ambiguous (0.44)
M-19	LLGL2	NA	NA	Fusion mutation	NA	LLGL2-CDR2L Fusion	NA	NA	NA	NA
M-20	LLGL2	c.1190C>T	rs893540567	Missense mutation	Exon-11	P397L	Possibly Damaging (0.71)	Deleterious (0.01)	NA	Ambiguous (0.39)
M-21	LLGL2	c.484C>T	rs138074005	Missense mutation	Exon-6	R162C	Benign (0.00)	Deleterious (0.03)	NA	Benign (0.08)
M-22	LLGL2	c.1724C>T	NA	Missense mutation	Exon-8	P575L	Benign (0.01)	Deleterious (0.01)	NA	Benign (0.19)
M-23	LLGL2	c.2755G>A	NA	Missense mutation	Exon-21	E919K	Probably Damaging (0.98)	Deleterious (0.00)	NA	Pathogenic (0.99)
M-24	LLGL2	c.958G>A	rs34553577	Missense mutation	Exon-10	D320N	Benign (0.01)	Tolerated (0.21)	NA	Benign (0.07)
M-25	LLGL2	c.2380G>A	rs1422808547	Missense mutation	Exon-19	E794K	Probably Damaging (0.98)	Deleterious (0.00)	NA	Pathogenic (0.79)
M-26	LLGL2	c.836C>T	NA	Missense mutation	Exon-9	P279L	Probably Damaging (0.99)	Deleterious (0.00)	NA	Pathogenic (0.58)
M-27	LLGL2	c.1508C>T	rs755124108	Missense mutation	Exon-14	P503L	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0.79)
M-28	LLGL2	c.808C>T	rs761736519	Missense mutation	Exon-8	R270C	Possibly Damaging (0.60)	Deleterious (0.04)	NA	Benign (0.09)
M-29	LLGL2	c.1679G>A	NA	Missense mutation	Exon-14	G560E	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0.98)
M-30	LLGL2	c.1351G>A	NA	Missense mutation	Exon-15	D451N	Possibly Damaging (0.65)	Tolerated (0.10)	NA	Benign (0.17)
M-31	LLGL2	c.75+1_75+2 dup	NA	Frame Shift Deletion	NA	-25fs	NA	NA	NA	NA
M-32	LLGL2	c.2276C>T	rs150971482	Missense mutation	Exon-18	P759L	Benign (0.00)	Tolerated (0.21)	NA	Benign (0.08)
M-33	LLGL2	c.2567C>T	NA	Missense mutation	Exon-20	A856V	Benign (0.00)	Tolerated (0.39)	NA	Benign (0.08)
M-34	LLGL2	c.881G>A	NA	Missense mutation	Exon-9	G294E	Possibly Damaging (0.68)	Tolerated (0.16)	NA	Benign (0.21)
M-35	LLGL2	c.2630C>T	rs764009284	Missense mutation	Exon-20	S877L	Possibly Damaging (0.70)	Deleterious (0.00	NA	Benign (0.28)
M-36	LLGL2	c.2630C>T	rs963325779	Missense mutation	Exon-20	P883S	Benign (0.14)	Tolerated (0.15)	NA	Benign (0.10)
M-37	LLGL2	:c.2647C>T	NA	Missense mutation	Exon-20	G860W	Possibly Damaging (0.60)	Deleterious (0.01)	NA	Benign (0.19)
M-38	LLGL2	c.1118C>A	NA	Missense mutation	Exon-11	P373Q	Benign (0.00)	Tolerated (0.08)	NA	Benign (0.11)
M-39	LLGL2	c.705C>A	rs1211391232	Missense mutation	Exon-8	N235K	Benign (0.04)	Deleterious (0.01)	NA	Ambiguous (0.51)
M-40	LLGL2	c.596G>A	rs201009590	Missense mutation	Exon-7	R199Q	Benign (0.00)	Tolerated (0.07)	NA	Benign (0.07)
M-41	LLGL2	c.1664G>A	NA	Missense mutation	Exon-15	G555D	Benign (0.26)	Tolerated (0.06)	NA	Benign (0.28)
M-42	LLGL2	c.1077G>T	NA	Missense mutation	Exon-11	E359D	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0.90)

(*Contd.*)

Table 2 — Characteristics of mutations detected in target genes in TCGA SKCM cohort (*Contd*.)

No	Gene	Nt alteration	Rs Number/ Cosmic ID	Alteration Type	Localization	AA position	Clinic Impact			
							Poly-Phen2 (Score)	SIFT (Score)	Mutaion Assesor (Score)	Alpha Missense (Score)
M-43	LLGL2	c.947C>A	NA	Nonsense mutation	Exon-10	S316*	NA	NA	NA	NA
M-44	LLGL2	c.596G>T	NA	Missense mutation	Exon-7	R199L	Benign (0.00)	Tolerated (0.37)	NA	Benign (0.10)
M-45	LLGL2	c.211C>T	NA	Nonsense mutation	Exon-4	Q71*	NA	NA	NA	NA
M-46	LLGL2	c.75G>A	NA	Splice region mutation	Exon-2	X25_splice	NA	NA	NA	NA
M-47	LLGL2	c.3031G>T	NA	Missense mutation	Exon-25	G1011W	Possibly Damaging (0.47)	Deleterious (0.00)	NA	Benign (0.16)
M-48	LLGL2	c.2771C>T	NA	Missense mutation	Exon-21	S924F	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0.97)
M-49	LLGL2	c.238C>T	NA	Missense mutation	Exon-4	H80Y	Benign (0.34)	Tolerated (0.28)	NA	Benign (0.08)
M-50	SCRIB	c.892G>A	NA	Missense mutation	Exon-9	E298K	Probably Damaging (0.91)	Deleterious (0.00)	NA	Pathogenic (0.98)
M-51	SCRIB	c.4568C>T	rs782160875	Missense mutation	Exon-33	S1523F	Probably Damaging (0.99)	Deleterious (0.00)	Medium (6.44)	Ambiguous (0.35)
M-52	SCRIB	c.3064T>A	NA	Missense mutation	Exon-22	S1022T	Probably Damaging (1.00)	Tolerated (0.22)	Low (3.44)	Benign (0.20)
M-53	SCRIB	c.401C>T	rs1815869157	Missense mutation	Exon-4	A134V	Probably Damaging (0.94)	Deleterious (0.00)	NA	Pathogenic (0.92)
M-54	SCRIB	c.401C>T	rs1815692361	Missense mutation	Exon-11	L382F	Probably Damaging (1.00)	Deleterious (0.00)	High (7.06)	Pathogenic (0.91)
M-55	SCRIB	c.1144C>T	NA	Missense mutation	Exon-30	P1374L	Possibly Damaging (0.54)	Deleterious (0.01)	Medium (5.97)	Benign (0.17)
M-56	SCRIB	c.4121C>T	NA	Missense mutation	Exon-30	P1374S	Possibly Damaging (0.56)	Deleterious (0.01)	Low (4.61)	Benign (0.20)
M-57	SCRIB	c.4120C>T	NA	Missense mutation	Exon-27	L1271V	Benign (0.01)	Deleterious (0.03)	Low (3.87)	Benign (0.09)
M-58	SCRIB	c.3811C>G	NA	Missense mutation	Exon-5	S165P	Probably Damaging (0.96)	Deleterious (0.01)	NA	Pathogenic (0.95)
M-59	SCRIB	c.493T>C	NA	Missense mutation	Exon-10	P352L	Benign (0.22)	Deleterious (0.01)	Medium (5.36)	Benign (0.12)
M-60	SCRIB	c.1055C>T	NA	Missense mutation	Exon-35	S1575F	Benign (0.02)	Tolerated (0.65)	NA	Benign (0.12)
M-61	SCRIB	c.4724C>T	NA	Missense mutation	Exon-8	G217W	Probably Damaging (1.00)	NA	NA	Pathogenic (0.97)
M-62	SCRIB	c.649G>T	NA	Missense mutation	Exon-8	R948L	Benign (0.28)	Deleterious (0.00)	High (7.06)	Pathogenic (0.88)
M-63	SCRIB	c.649G>T	NA	Nonsense mutation	Exon-10	G309*	NA	NA	NA	NA
M-64	SCRIB	c.2843G>T	NA	Missense mutation	Exon-4	R128L	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0.72)
M-65	SCRIB	c.2843G>T	NA	Splice region mutation	Exon-34	X1565_splice	NA	NA	NA	NA
M-66	SCRIB	c.925G>T	NA	Missense mutation	Exon-30	R1355L	Possibly Damaging (0.55)	Deleterious (0.00)	Medium (6.22)	Pathogenic (0.67)
M-67	SCRIB	c.383G>T	NA	Missense mutation	Exon-11	P421T	Benign (0.01)	Tolerated (0.43)	Low (3.39)	Benign (0.07)
M-68	SCRIB	c.4695G>T	NA	Missense mutation	Exon-3	E99*	NA	NA	NA	NA
M-69	SCRIB	c.4064G>T	NA	Missense mutation	Exon-25	R1229L	Probably Damaging (1.00)	Deleterious (0.00)	Medium (6.12)	Benign (0.22)
M-70	SCRIB	c.1261C>A	NA	Missense mutation	Exon-10	R343M	Probably Damaging (1.00)	Deleterious (0.00)	High (7.06)	Pathogenic (1.00)
M-71	SCRIB	c.295G>T	NA	Missense mutation	Exon-10	L342F	Probably Damaging (0.98)	Deleterious (0.00)	Medium (6.42)	Pathogenic (0.86)
M-72	SCRIB	c.3686G>T	NA	Missense mutation	Exon-16	E723D	Probably Damaging (0.97)	Deleterious (0.02)	Low (4.70)	Pathogenic (0.78)

(*Contd*.)

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No	Gene	Nt alteration	Rs Number/ Cosmic ID	Alteration Type	Localization	AA position	Clinic Impact Poly-Phen2 (Score)	SIFT (Score)	Mutaion Assesor (Score)	Alpha Missense (Score)
M-73	SCRIB	c.1531-1G>T	NA	Splice region mutation	NA	X511_splice	NA	NA	NA	NA
M-74	DLG1	c.205C>T	rs753543349	Missense mutation	Exon-4	R69C	Benign (0.12)	Deleterious (0.04)	NA	
M-75	DLG1	c.1493G>A	NA	Missense mutation	Exon-14	G498E	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0.99)
M-76	DLG1	c.1640C>T	NA	Missense mutation	Exon-15	P547L	Probably Damaging (0.91)	Deleterious (0.01)	NA	Pathogenic (0.80)
M-77	DLG1	c.347C>T	NA	Missense mutation	Exon-5	P116L	Benign (0.00)	Tolerated (0.11)	NA	Benign (0.06)
M-78	DLG1	c.346C>T	rs761445608	Missense mutation	Exon-5	P116S	Benign (0.00)	Tolerated (0.29)	NA	Benign (0.07)
M-79	DLG1	c.1864G>A	NA	Missense mutation	Exon-17	E622K	Probably Damaging (0.98)	Deleterious (0.00)	NA	Pathogenic (0.99)
M-80	DLG1	c.2233C>T	rs746862777	Missense mutation	Exon-22	H745Y	Possibly Damaging (0.73)	Deleterious (0.00)	NA	Pathogenic (0.97)
M-81	DLG1	c.2645A>G	NA	Missense mutation	Exon-26	N882S	Benign (0.03)	Tolerated (0.61)	NA	Benign (0.07)
M-82	DLG1	c.856G>T	rs1178053626	Missense mutation	Exon-10	D286Y	Probably Damaging (0.97)	Deleterious (0.00)	NA	Ambiguous (0.40)
M-83	DLG1	c.326G>T	NA	Missense mutation	Exon-5	R109M	Possibly Damaging (0.49)	Deleterious (0.00)	NA	Benign (0.31)
M-84	DLG1	c.2621G>A	NA	Missense mutation	Exon-26	G874E	Possibly Damaging (0.89)	Deleterious (0.02)	NA	Pathogenic (0.90)
M-85	DLG1	c.395C>A	NA	Missense mutation	Exon-5	P132Q	Benign (0.37)	Deleterious (0.02)	NA	Benign (0.22)
M-86	DLG1	c.2517-1G>T	NA	Splice region mutation	NA	X839_splice	NA	NA	NA	NA
M-87	DLG1	c.1765C>A	NA	Missense mutation	Exon-17	L589I	Possibly Damaging (0.90)	Deleterious (0.03)	NA	Pathogenic (0.57)
M-88	DLG1	c.2011C>T	NA	Missense mutation	Exon-19	P671S	Benign (0.00)	Tolerated (1.00)	NA	Benign (0.10)
M-89	DLG1	c.116A>G	NA	Missense mutation	Exon-3	N39S	Benign (0.00)	Tolerated (0.52)	NA	Benign (0.05)
M-90	DLG1	c.1801C>T	rs1451447881	Missense mutation	Exon-17	P601S	Possibly Damaging (0.90)	Deleterious (0.00)	NA	Pathogenic (0.98)
M-91	CRB1	c.1793C>T	rs1314024688	Missense mutation	NA	P598L	Probably Damaging (0.94)	Tolerated (1.00)	NA	Benign (0.07)
M-92	CRB1	c.1361G>A	NA	Missense mutation	NA	G454E	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0.73)
M-93	CRB1	c.146C>T	NA	Missense mutation	Exon-2	S49L	Benign (0.20)	Tolerated (0.71)	NA	Benign (0.07)
M-94	CRB1	c.2867G>A	rs267598279	Missense mutation	Exon-9	G956E	Benign (0.03)	Tolerated (0.13)	NA	Benign (0.09)
M-95	CRB1	c.1832C>T	NA	Missense mutation	Exon-6	S611F	Probably Damaging (0.95)	Deleterious (0.03)	NA	Benign (0.23)
M-96	CRB1	c.3172G>A	rs564754426	Missense mutation	Exon-9	E1058K	Benign (0.04)	Tolerated (0.70)	NA	Benign (0.06)
M-97	CRB1	c.1786C>T	rs1230478193	Missense mutation	Exon-6	P596S	Benign (0.02)	Tolerated (0.61)	NA	Benign (0.07)
M-98	CRB1	c.2020G>A	rs868258281	Missense mutation	Exon-6	D674N	Possibly Damaging (0.88)	Tolerated (0.61)	NA	Benign (0.10)
M-99	CRB1	c.3364G>A	rs1392028577	Missense mutation	Exon-9	E1122K	Benign (0.01)	Tolerated (0.25)	NA	Benign (0.06)
M-100	CRB1	c.2735C>T	NA	Missense mutation	Exon-8	S912F	Benign (0.04)	Deleterious (0.01)	NA	Benign (0.12)
M-101	CRB1	c.817C>T	rs1324068019	Missense mutation	Exon-3	H273Y	Possibly Damaging (0.65)	Tolerated (0.09)	NA	Benign (0.08)
M-102	CRB1	c.1471G>A	rs937362854	Missense mutation	Exon-6	D491N	Benign (0.00)	Tolerated (1.00)	NA	Benign (0.06)

(*Contd*.)

Table 2 — Characteristics of mutations detected in target genes in TCGA SKCM cohort (*Contd*.)

No	Gene	Nt alteration	Rs Number/ Cosmic ID	Alteration Type	Localization	AA position	Clinic Impact Poly-Phen2 (Score)	SIFT (Score)	Mutaion Assesor (Score)	Alpha Missense (Score)
M-103	CRB1	c.2722G>A	NA	Missense mutation	Exon-8	D908N	Benign (0.43)	Deleterious (0.00)	NA	Benign (0.10)
M-104	CRB1	c.3455G>A	NA	Missense mutation	Exon-9	G1152E	Probably Damaging (1.00)	Deleterious (0.00)	NA	Ambiguous (0.52)
M-105	CRB1	c.1856G>A	NA	Missense mutation	Exon-6	G619E	Benign (0.06)	Tolerated (0.14)	NA	Benign (0.06)
M-106	CRB1	c.2029G>A	rs867230786	Missense mutation	Exon-6	E677K	Benign (0.06)	Tolerated (0.17)	NA	Benign (0.08)
M-107	CRB1	c.1690G>A	rs757279881	Missense mutation	Exon-6	D564N	Benign (0.14)	Deleterious (0.04)	NA	Benign (0.11)
M-108	CRB1	c.1913C>T	rs267598278	Missense mutation	Exon-6	S638L	Probably Damaging (1.00)	Deleterious (0.02)	NA	Benign (0.15)
M-109	CRB1	c.745G>A	rs1461964160	Missense mutation	Exon-3	D249N	Possibly Damaging (0.91)	Tolerated (0.33)	NA	Benign (0.07)
M-110	CRB1	c.2620C>T	NA	Missense mutation	Exon-7	L874F	Benign (0.10)	Tolerated (0.61)	NA	Benign (0.07)
M-111	CRB1	:c.3737G>A	NA	Missense mutation	Exon-2	E204K	Benign (0.21)	Deleterious (0.00)	NA	Benign (0.09)
M-112	CRB1	c.1765G>A	NA	Missense mutation	Exon-6	E589K	Benign (0.01)	Tolerated (0.16)	NA	Benign (0.09)
M-113	CRB1	c.1976C>T	rs986645649	Missense mutation	Exon-6	S659L	Benign (0.01)	Tolerated (0.22)	NA	Benign (0.09)
M-114	CRB1	c.3737G>A	NA	Missense mutation	Exon-9	G1246E	Probably Damaging (0.93)	Deleterious (0.00)		Ambiguous (0.41)
M-115	CRB1	c.2129-1G>A	NA	Splice region mutation	NA	X710_splice	NA	NA	NA	NA
M-116	CRB1	c.1676C>T	NA	Missense mutation	Exon-6	S559F	Probably Damaging (0.94)	Tolerated (0.07)	NA	Benign (0.17)
M-117	CRB1	c.322G>A	NA	Missense mutation	Exon-2	E108K	Benign (0.04)	Tolerated (0.08)	NA	Benign (0.09)
M-118	CRB1	c.2261C>T	rs764359208	Missense mutation	Exon-7	A754V	Possibly Damaging (0.70)	Tolerated (0.17)	NA	Benign (0.14)
M-119	CRB1	c.3235G>A	rs1200731853	Missense mutation	Exon-9	D1079N	Benign (0.10)	Tolerated (0.14)	NA	Benign (0.08)
M-120	CRB1	c.310G>T	rs934010730	Missense mutation	Exon-2	G104W	Probably Damaging (1.00)	Deleterious (0.00)	NA	Ambiguous (0.53)
M-121	CRB1	c.2224T>C	NA	Missense mutation	Exon-7	F742L	Probably Damaging (0.97)	Deleterious (0.11)	NA	Pathogenic (0.83)
M-122	CRB1	c.3206G>A	NA	Missense mutation	Exon-9	G1069E	Probably Damaging (1.00)	Deleterious (0.00)	NA	Ambiguous (0.35)
M-123	CRB1	c.2490C>G	rs2125484844	Missense mutation	Exon-7	I830M	Benign (0.06)	Deleterious (0.04)	NA	Benign (0.11)
M-124	CRB1	c.2885T>C	NA	Missense mutation	Exon-9	L962S	Possibly Damaging (0.64)	Tolerated (0.22)	NA	Benign (0.14)
M-125	CRB1	c.4126C>T	NA	Nonsense mutation	Exon-12	Q1376*	NA	NA	NA	NA
M-126	CRB1	c.1276G>A	NA	Missense mutation	Exon-6	D426N	Benign (0.43)	Tolerated (0.30)	NA	Benign (0.09)
M-127	CRB1	c.1942A>G	NA	Missense mutation	Exon-6	I648V	Benign (0.17)	Tolerated (0.76)	NA	Benign (0.11)
M-128	CRB1	c.3824C>A	rs551798394	Missense mutation	Exon-10	T1275K	Possibly Damaging (0.46)	Deleterious (0.00)	NA	Benign (0.23)
M-129	CRB1	c.3823A>C	NA	Missense mutation	Exon-10	T1275P	Possibly Damaging (0.71)	Deleterious (0.00)	NA	Benign (0.23)
M-130	CRB1	c.4206G>A	NA	Missense mutation	Exon-12	M1402I	Benign (0.00)	Tolerated (0.14)	NA	Benign (0.08)
M-131	CRB1	c.2215C>T	rs771762730	Missense mutation	Exon-7	L739F	Possibly Damaging (0.66)	Deleterious (0.02)	NA	Benign (0.11)
M-132	CRB1	c.2524G>A	NA	Missense mutation	Exon-7	E842K	Probably Damaging (1.00)	Tolerated (0.35)	NA	Benign (0.08)

(*Contd*.)

Table 2 — Characteristics of mutations detected in target genes in TCGA SKCM cohort (*Contd*.)

No	Gene	Nt alteration	Rs Number/ Cosmic ID	Alteration Type	Localization	AA position	Clinic Impact Poly-Phen2 (Score)	SIFT (Score)	Mutaion Assesor (Score)	Alpha Missense (Score)
M-133	CRB1	c.2155G>A	NA	Missense mutation	Exon-7	D719N	Benign (0.01)	Tolerated (0.35)	NA	Benign (0.08)
M-134	CRB1	c.2761G>A	rs987199796	Missense mutation	Exon-8	A921T	Benign (0.35)	Tolerated (0.21)	NA	Benign (0.08)
M-135	CRB1	c.910C>T	NA	Missense mutation	Exon-4	L304F	Benign (0.35)	Tolerated (0.19)	NA	Benign (0.09)
M-136	CRB1	c.3106G>A	rs563857130	Missense mutation	Exon-9	E1036K	Benign (0.04)	Tolerated (0.14)	NA	Benign (0.06)
M-137	CRB1	c.2465G>A	NA	Nonsense mutation	Exon-7	W822*	NA	NA	NA	NA
M-138	CRB1	c.2443G>A	NA	Missense mutation	Exon-7	G815R	Probably Damaging (0.98)	Deleterious (0.00)	NA	Ambiguous (0.42)
M-139	CRB1	c.2107G>A	rs2125472121	Missense mutation	Exon-6	E703K	Benign (0.00)	Tolerated (0.75)	NA	Benign (0.07)
M-140	CRB1	c.4130G>A	rs1052327653	Missense mutation	Exon-12	G1377E	Probably Damaging (1.00)	Deleterious (0.00)	NA	Ambiguous (0.42)
M-141	CRB1	c.1750G>A	rs1664322968	Missense mutation	Exon-6	D584N	Possibly Damaging (0.66)	Deleterious (0.02)	NA	Benign (0.12)
M-142	CRB1	c.1463T>A	NA	Missense mutation	Exon-6	F488Y	Probably Damaging (0.99)	Deleterious (0.01)	NA	Ambiguous (0.52)
M-143	CRB1	c.1792C>T	NA	Missense mutation	Exon-6	P598S	Benign (0.29)	Tolerated (0.43)	NA	Benign (0.08
M-144	CRB1	c.1639C>T	NA	Missense mutation	Exon-6	Q547*	NA	NA	NA	NA
M-145	CRB1	c.493G>A	NA	Missense mutation	Exon-2	D165N	Probably Damaging (1.00)	Tolerated (0.12)	NA	Benign (0.14)
M-146	CRB1	c.3013G>A	NA	Missense mutation	Exon-9	D1005N	Benign (0.04)	Tolerated (0.40)	NA	Benign (0.07)
M-147	CRB1	c.3094G>A	NA	Missense mutation	Exon-6	G1032S	Probably Damaging (0.98)	Deleterious (0.00)	NA	Benign (0.10)
M-148	CRB1	c.1649A>T	NA	Missense mutation	Exon-6	N550I	Possibly Damaging (0.58)	Deleterious (0.01)	NA	Benign (0.17)
M-149	CRB1	c.3376C>T	rs149390998	Missense mutation	Exon-9	L1126F	Probably Damaging (1.00)	Deleterious (0.02)	NA	Benign (0.10)
M-150	CRB1	c.2533G>A	NA	Missense mutation	Exon-7	G845S	Benign (0.32)	Tolerated (0.08)	NA	Benign (0.18)
M-151	CRB1	c.3812G>A	rs1665276651	Missense mutation	Exon-10	G1271E	Possibly Damaging (0.74)	Tolerated (0.06)	NA	Benign (0.10)
M-152	CRB1	c.4075C>T	rs1427358329	Missense mutation	Exon-12	L1359F	Benign (0.11)	Tolerated (0.10)	NA	Benign (0.07)
M-153	CRB1	c.3020G>A	NA	Missense mutation	Exon-9	R1007K	Benign (0.31)	Tolerated (0.10)	NA	Benign (0.08)
M-154	CRB1	c.2110G>A	NA	Missense mutation	Exon-6	G704S	Probably Damaging (1.00)	Deleterious (0.00)	NA	Benign (0.27)
M-156	CRB1	c.1115C>T	rs1244838953	Missense mutation	Exon-5	S372F	Possibly Damaging (0.83)	Tolerated (0.10)	NA	Benign (0.09)
M-157	CRB1	c.2459C>T	rs762823359	Missense mutation	Exon-7	S820F	Possibly Damaging (0.77)	Deleterious (0.01)	NA	Benign (0.14)
M-158	CRB1	c.1988C>T	NA	Missense mutation	Exon-6	S663L	Possibly Damaging (0.62)	Deleterious (0.00)	NA	Benign (0.10)
M-159	CRB1	c.2891G>A	NA	Missense mutation	Exon-9	R964K	Benign (0.00)	Tolerated (0.06)	NA	Benign (0.12)
M-160	CRB1	c.3319C>T	NA	Missense mutation	Exon-9	L1107F	Probably Damaging (1.00)	Deleterious (0.00)	NA	Benign (0.32)
M-161	CRB1	c.1901C>T	NA	Missense mutation	Exon-6	P634L	Benign (0.01)	Tolerated (0.65)	NA	Benign (0.09)
M-162	CRB1	c.2093G>A	NA	Missense mutation	Exon-6	C698Y	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0.91)
M-163	CRB1	c.407G>A	rs752559648	Missense mutation	Exon-2	C136Y	Probably Damaging (1.00)	Deleterious (0.01)	NA	Pathogenic (0.88)

(*Contd.*)

Table 2 — Characteristics of mutations detected in target genes in TCGA SKCM cohort (*Contd*.)

No	Gene	Nt alteration	Rs Number/ Cosmic ID	Alteration Type	Localization	AA position	Clinic Impact Poly-Phen2 (Score)	SIFT (Score)	Mutaion Assesor (Score)	Alpha Missense (Score)
M-164	CRB1	c.839G>A	rs930465675	Missense mutation	Exon-3	G280E	Benign (0.01)	Tolerated (0.34)	NA	Benign (0.07)
M-165	CRB1	c.3137C>A	NA	Missense mutation	Exon-9	S1046Y	Possibly Damaging (0.47)	Deleterious (0.00)	NA	Benign (0.13)
M-166	CRB1	c.527C>A	NA	Missense mutation	Exon-2	P176Q	Probably Damaging (1.00)	Deleterious (0.00)	NA	Ambiguous (0.45)
M-167	CRB1	c.275G>T	NA	Missense mutation	Exon-2	R92M	Probably Damaging (0.91)	Tolerated (0.12)	NA	Benign (0.10)
M-168	CRB1	c.3139C>A	NA	Missense mutation	Exon-9	Q1047K	Benign (0.33)	Deleterious (0.02)	NA	Benign (0.08)
M-169	CRB1	c.2512A>T	NA	Nonsense mutation	Exon-8	K838*	NA	NA	NA	NA
M-170	CRB1	c.664G>A	rs114846212	Missense mutation	Exon-3	E222K	Benign (0.27)	Deleterious (0.00)	NA	Benign (0.29)
M-171	CRB1	c.2242C>T	NA	Missense mutation	Exon-7	P748S	Benign (0.18)	Tolerated (0.51)	NA	Benign (0.10)
M-172	CRB1	c.535C>T	NA	Nonsense mutation	Exon-2	Q179*	NA	NA	NA	NA
M-173	CRB1	c.2308G>T	rs1320599	Missense mutation	Exon-7	G770C	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0.67)
M-174	CRB1	c.875G>A	NA	Missense mutation	Exon-4	G292E	Probably Damaging (1.00)	Deleterious (0.00)	NA	Benign (0.11)
M-175	CRB1	c.3622G>T	NA	Missense mutation	Exon-9	G1208C	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0.81)
M-176	CRB1	c.3233C>A	NA	Missense mutation	Exon-9	T1078K	Probably Damaging (0.97)	Deleterious (0.00)	NA	Benign (0.23)
M-177	CRB1	c.3680C>T	NA	Missense mutation	Exon-9	A1227V	Probably Damaging (1.00)	Deleterious (0.00)	NA	Ambiguous (0.42)
M-178	CRB1	:c.385C>A	NA	Missense mutation	Exon-2	P129T	Benign (0.07)	Tolerated (0.41)	NA	Benign(0.07)
M-179	CRB1	c.3301G>A	rs1665083389	Missense mutation	Exon-9	E1101K	Benign (0.43)	Tolerated (0.07)	NA	Benign (0.09)
M-180	CRB1	c.4193C>T	NA	Missense mutation	Exon-12	P1398L	Benign (0.06)	Tolerated (0.09)	NA	Benign (0.08)
M-181	CRB1	c.895G>A	NA	Missense mutation	Exon-4	E299K	Possibly Damaging (0.58)	Deleterious (0.00)	NA	Benign (0.19)
M-182	CRB1	c.1804G>A	rs778242034	Missense mutation	Exon-6	D602N	Benign (0.01)	Tolerated (0.51)	NA	Benign (0.06)
M-183	CRB2	c.1714G>T	NA	Missense mutation	Exon-3	G572W	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0.63)
M-184	CRB2	c.472G>A	NA	Missense mutation	Exon-2	P135L	Benign (0.05)	Tolerated (0.36)	NA	Benign (0.09)
M-185	CRB2	c.404C>T	NA	Missense mutation	Exon-3	G158R	Probably Damaging (1.00)	Deleterious (0.00)	NA	Benign (0.19)
M-186	CRB2	c.404C>T	NA	Missense mutation	Exon-7	R466C	Probably Damaging (0.99)	Deleterious (0.03)	NA	Benign (0.18)
M-187	CRB2	c.1627C>T	NA	Missense mutation	Exon-7	R543W	Benign (0.00)	Deleterious (0.05)	NA	Benign (0.23)
M-188	CRB2	c.2090C>G	NA	Missense mutation	Exon-8	T697R	Benign (0.42)	Tolerated (0.06)	NA	Benign (0.18)
M-189	CRB2	c.461C>T	NA	Missense mutation	Exon-3	P154L	Probably Damaging (1.00)	Deleterious (0.00)	NA	Ambiguous (0.43)
M-190	CRB2	c.790G>A	NA	Missense mutation	Exon-5	E264K	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0. 59)
M-191	CRB2	c.232C>T	NA	Missense mutation	Exon-2	H78Y	Possibly Damaging (0.74)	Deleterious (0.00)	NA	Benign (0.18)
M-192	CRB2	c.1391G>A	NA	Missense mutation	Exon-7	R464K	Possibly Damaging (0.86)	Deleterious (0.01)	NA	Benign (0.31)
M-193	CRB2	c.224C>T	NA	Missense mutation	Exon-2	P75L	Probably Damaging (0.98)	Deleterious (0.00)	NA	Benign (0.22)

(*Contd*.)

Table 2 — Characteristics of mutations detected in target genes in TCGA SKCM cohort (*Contd*.)

No	Gene	Nt alteration	Rs Number/ Cosmic ID	Alteration Type	Localization	AA position	Clinic Impact Poly-Phen2 (Score)	SIFT (Score)	Mutaion Assesor (Score)	Alpha Missense (Score)
M-194	CRB2	c.1096C>T	NA	Missense mutation	Exon-7	P366S	Probably Damaging (1.00)	Deleterious (0.00)	NA	Ambiguous (0.42)
M-195	CRB2	c.3811G>A	NA	Missense mutation	Exon-13	E1271K	Probably Damaging (1.00)	Deleterious (0.00)	NA	NA
M-196	CRB2	c.1181C>T	NA	Missense mutation	Exon-7	S394F	Possibly Damaging (0.78)	Deleterious (0.00)	NA	Pathogenic (0. 88)
M-197	CRB2	c.1494G>A	NA	Nonsense mutation	Exon-7	W498*	NA	NA	NA	NA
M-198	CRB2	c.1360C>T	NA	Missense mutation	Exon-7	P454S	Benign (0.43)	Deleterious (0.00)	NA	Benign (0,09)
M-199	CRB2	c.1295G>A	NA	Missense mutation	Exon-7	G432E	Probably Damaging (0.94)	Deleterious (0.00)	NA	Ambiguous (0.50)
M-200	CRB2	c.794G>A	NA	Missense mutation	Exon-5	C265Y	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0. 93)
M-201	CRB2	c.1630C>T	NA	Missense mutation	Exon-7	L544F	Possibly Damaging (0.78)	Deleterious (0.004	NA	Benign (0,12)
M-202	CRB2	c.2276G>A	NA	Missense mutation	Exon-5	F298V	Benign (0.01)	Deleterious (0.04)	NA	Ambiguous (0.51)
M-203	CRB2	c.892T>G	NA	Missense mutation	Exon-9	V862I	Possibly Damaging (0.56)	Deleterious (0.04)	NA	Benign (0,14)
M-204	CRB2	c.3416G>A	NA	Missense mutation	Exon-11	S1139N	Benign (0.00)	Tolerated (0.06)	NA	Benign (0,12)
M-205	CRB2	c.1112G>A	NA	Missense mutation	Exon-7	G371E	Probably Damaging (0.99)	Deleterious (0.00)	NA	Pathogenic (0. 77)
M-206	CRB2	c.1852G>T	NA	Missense mutation	Exon-7	G618W	Probably Damaging (0.99)	Deleterious (0.00)	NA	Pathogenic (0. 57)
M-207	CRB2	c.3257G>T	NA	Missense mutation	Exon-10	W1086L	Probably Damaging (0.98)	Deleterious (0.00)	NA	Pathogenic (0. 68)
M-208	CRB2	c.1415G>A	NA	Missense mutation	Exon-7	G472E	Probably Damaging (0.98)	Deleterious (0.00)	NA	Pathogenic (0. 61)
M-209	CRB2	c.341C>T	NA	Missense mutation	Exon-2	S114F	Probably Damaging (0.99)	Deleterious (0.00)	NA	Pathogenic (0. 80)
M-210	CRB2	c.1453G>T	NA	Nonsense mutation	Exon-7	E485*	NA	NA	NA	NA
M-211	CRB2	c.3855C>G	NA	Missense mutation	Exon-13	I1285M	Probably Damaging (1.00)	Deleterious (0.00)	NA	Ambiguous (0.44)
M-212	CRB2	c.1280C>A	NA	Missense mutation	Exon-7	P427Q	Benign (0.09)	Tolerated (0.52)	NA	Benign (0,12)
M-213	CRB2	c.1325C>A	NA	Missense mutation	Exon-7	S442Y	Probably Damaging (0.98)	Deleterious (0.00)	NA	Pathogenic (0. 92)
M-214	CRB2	c.3409G>T	NA	Nonsense mutation	Exon-11	E1137*	NA	NA	NA	NA
M-215	CRB2	c.2276G>A	NA	Nonsense mutation	Exon-8	W759*	NA	NA	NA	NA
M-216	PATJ	c.2390C>T	rs1404651157	Missense mutation	Exon 19	S797L	Benign (0.00)	Tolerated (0.18)	NA	NA
M-217	PATJ	c.4597C>T	NA	Missense mutation	Exon 35	P1533S	Benign (0.00)	Tolerated (0.42)	NA	NA
M-218	PATJ	c.4868G>T	NA	Missense mutation	Exon 37	R1623M	Possibly Damaging (0.83)	Deleterious (0.01)	NA	NA
M-219	PATJ	c.2501G>A	NA	Missense mutation	Exon 20	G834E	Probably Damaging (0.99)	Tolerated (0.07)	NA	NA
M-220	PATJ	c.4814G>A	NA	Missense mutation	Exon 37	G1605E	Probably Damaging (1.00)	Deleterious (0.00)	NA	NA
M-221	PATJ	c.575C>T	NA	Missense mutation	Exon 6	P192L	Benign (0.05)	Deleterious (0.04)	NA	NA
M-222	PATJ	c.1060C>T	rs1239232941	Missense mutation	Exon 8	P354S	Benign (0.01)	Tolerated (0.35)	NA	NA
M-223	PATJ	c.2906G>A	NA	Missense mutation	Exon 21	R969K	Benign (0.08)	Tolerated (0.89)	NA	NA

(*Contd*.)

Table 2 — Characteristics of mutations detected in target genes in TCGA SKCM cohort (*Contd*.)

No	Gene	Nt alteration	Rs Number/ Cosmic ID	Alteration Type	Localization	AA position	Poly-Phen2 (Score)	Clinic Impact SIFT (Score)	Mutaion Assesor (Score)	Alpha Missense (Score)
M-224	PATJ	c.3007C>T	rs747595265	Missense mutation	Exon 22	P1003S	Benign (0.08)	Deleterious (0.01)	NA	NA
M-215	PATJ	c.3839G>A	rs373112517	Missense mutation	Exon 22	R1280Q	Probably Damaging (1.00)	Deleterious (0.00)	NA	NA
M-225	PATJ	c.4322C>T	rs1659719044	Missense mutation	Exon 33	S1441F	Probably Damaging (0.97)	Deleterious (0.00)	NA	NA
M-226	PATJ	c.2206C>T	rs770908960	Missense mutation	Exon 18	R736C	Probably Damaging (1.00)	Deleterious (0.00)	NA	NA
M-227	PATJ	:c.3077C>T	NA	Missense mutation	Exon 22	S1026F	Benign (0.05)	Tolerated (0.08)	NA	NA
M-228	PATJ	c.4393C>T	NA	Missense mutation	Exon 34	H1465Y	Possibly Damaging (0.62)	Deleterious (0.00)	NA	NA
M-229	PATJ	c.1727C>T	NA	Missense mutation	Exon 15	S576F	Probably Damaging (0.98)	Deleterious (0.00)	NA	NA
M-230	PATJ	c.1852C>T	rs774855207	Nonsense mutation	Exon 16	R618*	NA	NA	NA	NA
M-231	PATJ	c.518_520del	NA	Frame Shift Deletion	Exon 5	A173del	NA	NA	NA	NA
M-232	PATJ	c.517G>A	rs1230481578	Missense mutation	Exon 5	A173T	Probably Damaging (1.00)	Deleterious (0.00)	NA	NA
M-233	PATJ	c.3694G>A	NA	Missense mutation	Exon 28	D1232N	Possibly Damaging (0.76)	Deleterious (0.03)	NA	NA
M-234	PATJ	c.3283A>G	NA	Missense mutation	Exon-24	N1095D	Probably Damaging (0.97)	Deleterious (0.00)	NA	NA
M-235	PATJ	c.3630T>A		Missense mutation	Exon-27	D1210E	Benign (0.00)	Tolerated (1.00)	NA	NA
M-236	PATJ	c.2533G>A	rs1665077135	Missense mutation	Exon-20	E845K	Benign (0.01)	Tolerated (0.08)	NA	NA
M-237	PATJ	c.4853C>T	NA	Missense mutation	Exon-37	S1618F	Possibly Damaging (0.71)	Deleterious (0.01)	NA	NA
M-238	PATJ	c.1378C>T	NA	Missense mutation	Exon-11	P460S	Benign (0.01)	Tolerated (0.58)	NA	NA
M-239	PATJ	c.2631G>C	NA	Missense mutation	Exon-20	E877D	Benign (0.00)	Tolerated (0.49)	NA	NA
M-240	PATJ	c.4982C>T	NA	Missense mutation	NA	S1661L	Benign (0.10)	Deleterious (0.05)	Low (3.28)	NA
M-241	PATJ	c.3571-1G>A	NA	Splice region mutation	NA	X1191_splice	NA	NA	NA	NA
M-242	PATJ	c.3573G>C	rs765172796	Missense mutation	Exon-27	R1191S	Benign (0.12)	Tolerated (0.05)	NA	NA
M-243	PATJ	c.5401G>A	NA	Missense mutation	Exon-43	D1801N	Benign (0.00)	Tolerated (0.11)	NA	NA
M-244	PATJ	c.2659G>A	NA	Missense mutation	Exon-20	E887K	Benign (0.00)	Tolerated (0.49)	NA	NA
M-245	PATJ	c.496G>A	rs1646474403	Missense mutation	Exon-5	D166N	Benign (0.05)	Deleterious (0.00)	NA	NA
M-246	PATJ	c.4308G>A	NA	Missense mutation	Exon-33	M1436I	Benign (0.04)	Tolerated (0.11	NA	NA
M-247	PATJ	c.5206G>A	NA	Missense mutation	Exon-41	D1736N	Probably Damaging (1.00)	Deleterious (0.00)	Medium (5.62)	NA
M-248	PATJ	c.1989C>A	rs1467193684	Missense mutation	Exon-17	H663Q	Benign (0.00)	Tolerated (0.60)	NA	NA
M-249	PATJ	c.4081G>A	rs570517908	Missense mutation	Exon-31	E1361K	Benign (0.02)	Tolerated (0.17)	NA	NA
M-250	PATJ	c.2470G>A	NA	Missense mutation	Exon-20	E824K	Probably Damaging (0.99)	Deleterious (0.01)	NA	NA
M-251	PATJ	c.1069-1G>A	NA	Splice region mutation	NA	X357_splice	NA	NA	NA	NA
M-252	PATJ	c.4991C>T	NA	Missense mutation	Exon-38	S1664F	Benign (0.01)	Deleterious (0.04)	Low (4.75)	NA

(*Contd*.)

Table 2 — Characteristics of mutations detected in target genes in TCGA SKCM cohort (*Contd*.)

No	Gene	Nt alteration	Rs Number/ Cosmic ID	Alteration Type	Localization	AA position	Poly-Phen2 (Score)	Clinic Impact SIFT (Score)	Mutaion Assesor (Score)	Alpha Missense (Score)
M-253	PATJ	c.4991C>T	NA	Missense mutation	Exon-20	G814E	Benign (0.00)	Tolerated (0.45)	NA	NA
M-254	PATJ	c.2371G>A	NA	Missense mutation	Exon-19	E791K	Benign (0.00)	Tolerated (0.45)	NA	NA
M-255	PATJ	c.2749G>A	NA	Missense mutation	Exon-20	E917K	Benign (0.00)	Tolerated (0.16)	NA	NA
M-257	PATJ	c.4361G>A	NA	Missense mutation	Exon-33	G1454E	Probably Damaging (1.00)	Deleterious (0.04)	NA	NA
M-258	PATJ	c.1942G>A	NA	Missense mutation	Exon-16	E648K	Possibly Damaging (0.53)	Deleterious (0.00)	NA	NA
M-259	PATJ	c.3821C>A	NA	Missense mutation	Exon-28	P1274H	Probably Damaging (1.00)	Deleterious (0.00)	NA	NA
M-260	PATJ	c.4030G>T	NA	Nonsense mutation	Exon-30	E1344*	NA	NA	NA	NA
M-261	PATJ	c.2863C>A	NA	Missense mutation	Exon-21	L955I	Benign (0.01)	Tolerated (0.05)	NA	NA
M-262	PATJ	c.4571G>T	NA	Missense mutation	Exon-35	R1524L	Benign (0.09)	Deleterious (0.01)	NA	NA
M-263	PATJ	c.2888G>A	NA	Missense mutation	Exon-21	G963E	Benign (0.44)	Tolerated (0.05)	NA	NA
M-264	PATJ	c.3287G>A	NA	Missense mutation	Exon-24	G1096E	Probably Damaging (1.00)	Deleterious (0.00)	NA	NA
M-265	PATJ	c.5306C>A	NA	Missense mutation	Exon-42	A1769D	Benign (0.00)	Deleterious (0.01)	Low (4.69)	NA
M-266	PATJ	c.33G>T	NA	Missense mutation	Exon-3	Q11H	Probably Damaging (1.00)	Deleterious (0.03)	NA	NA
M-267	PATJ	c.3389G>T	NA	Missense mutation	Exon-25	G1130V	Probably Damaging (1.00)	Deleterious (0.00)	NA	NA
M-268	PATJ	c.1427C>A	rs773065062	Missense mutation	Exon-12	P476Q	Benign (0.06)	Tolerated (0.38)	NA	NA
M-269	PATJ	c.2323-3C>T	NA	Splice region mutation	NA	X775_splice	NA	NA	NA	NA
M-270	PATJ	c.1056G>T	NA	Missense mutation	Exon-8	K352N	Benign (0.01)	Tolerated (0.32)	NA	NA
M-271	PATJ	c.4798C>A	NA	Missense mutation	Exon-36	L1600I	Probably Damaging (0.98)	Deleterious (0.00)	NA	NA
M-272	PATJ	c.2206C>A	NA	Missense mutation	Exon-18	R736S	Probably Damaging (1.00)	Deleterious (0.00)	NA	NA
M-273	PATJ	c.3365G>A	rs866800533	Missense mutation	Exon-24	G1122E	Probably Damaging (0.99)	Deleterious (0.00)	NA	NA
M-274	PATJ	c.2500G>A	NA	Missense mutation	Exon-20	G834R	Probably Damaging (0.99)	Deleterious (0.04)	NA	NA
M-275	PATJ	c.690C>G	NA	Missense mutation	Exon-6	S230R	Benign (0.05)	Tolerated (0.10)	NA	NA
M-276	PATJ	c.2221A>C	NA	Missense mutation	Exon-18	N741H	Probably Damaging (1.00)	Deleterious (0.00)	NA	NA
M-277	PALS1	c.16A>C	NA	Missense mutation	Exon-3	M6L	Benign (0.00)	Tolerated (0.11)	NA	Benign (0.03)
M-278	PALS1	c.2003G>T	NA	Missense mutation	Exon-15	W668L	Probably Damaging (0.99)	Deleterious (0.00)	Medium (6.46)	Pathogenic (0. 99)
M-279	PALS1	c.1025C>A	NA	Missense mutation	Exon-8	P342H	Possibly Damaging (0.47)	Deleterious (0.03)	Low (3.18)	Benign (0.14)
M-280	PALS1	c.577-1G>T	NA	Splice region mutation	Exon-15	X193_splice	NA	NA	NA	NA
M-281	PALS1	c.2004G>T	NA	Missense mutation	Exon-15	W668C	Probably Damaging (1.00)	Deleterious (0.00)	Mediım (6.46)	Pathogenic (1.00)
M-282	PALS1	c.654G>T	NA	Missense mutation	Exon-5	Q218H	Probably Damaging (0.97)	Deleterious (0.00)	Mediım (5.75)	Benign (0.23)
M-283	PALS1	c.118C>A	NA	Missense mutation	Exon-3	P40T	Probably Damaging (0.99)	Deleterious (0.00)	Low (3.90)	Pathogenic (0.69)

(*Contd.*)

Table 2 — Characteristics of mutations detected in target genes in TCGA SKCM cohort (*Contd*.)

No	Gene	Nt alteration	Rs Number/ Cosmic ID	Alteration Type	Localization	AA position	Poly-Phen2 (Score)	Clinic Impact SIFT (Score)	Mutaion Assesor (Score)	Alpha Missense (Score)
M-284	PALS1	c.79G>T	NA	Nonsense mutation	Exon-3	E27*	NA	NA	NA	NA
M-285	PALS1	c.1970G>T	NA	Missense mutation	Exon-15	R657M	Probably Damaging (0.98)	Deleterious (0.02)	Low (5.13)	Pathogenic (0.68)
M-286	PALS1	c.1991C>A	NA	Missense mutation	Exon-15	T664N	Benign (0.07)	Tolerated (0.56)	Low (4.84)	Pathogenic (0.62)
M-287	PALS1	c.1597C>T	NA	Missense mutation	Exon-13	R533W	Probably Damaging (1.00)	Deleterious (0.00)	Mediım (6.12)	Pathogenic (0.57)
M-288	PALS1	c.1732C>T	NA	Missense mutation	Exon-13	R578C	Possibly Damaging (0.6 87)	Deleterious (0.00)	Mediım (5.17)	Benign (0.19)
M-289	PARD3	NA	NA	NA	NA	PARD3-FAM83B Fusion	NA	NA	NA	NA
M-290	PARD3	c.955C>T	rs746189923	Missense mutation	Exon-8	R319C	Benign (0.00)	Deleterious (0.02)	NA	Benign (0.07)
M-291	PARD3	c.508C>T	rs1314904995	Missense mutation	Exon-4	P170S	Possibly Damaging (0.68)	Deleterious (0.03)	NA	Ambiguous (0.52)
M-292	PARD3	c.3202C>T	rs1262435673	Nonsense mutation	Exon-22	R1068*	NA	NA	NA	NA
M-293	PARD3	c.3137C>T	NA	Missense mutation	Exon-22	S1046F	Benign (0.31)	Tolerated (0.06)	NA	Benign (0.17)
M-294	PARD3	c.482C>T	NA	Missense mutation	Exon-21	S161F	Benign (0.31)	Deleterious (0.00)	NA	Benign (0.14)
M-295	PARD3	c.2956G>A	NA	Missense mutation	Exon-13	D986N	Benign (0.01)	Tolerated (0.11	NA	Benign (0.10)
M-296	PARD3	c.404-1G>A	NA	Splice region mutation	Exon-15	X135_splice	NA	NA	NA	NA
M-297	PARD3	c.3088C>T	rs201444228	Nonsense mutation	Exon-21	R1030*	NA	NA	NA	NA
M-298	PARD3	c.1783G>A	NA	Missense mutation	Exon-13	D595N	Possibly Damaging (0.89)	Deleterious (0.00)	NA	Pathogenic (0.87)
M-299	PARD3	c.2161G>A	NA	Missense mutation	Exon-15	G721R	Possibly Damaging (0.84)	Tolerated (0.06)	NA	Ambiguous (0.47)
M-300	PARD3	c.2986G>A	NA	Missense mutation	Exon-20	G996R	Possibly Damaging (0.84)	Tolerated (0.36)	NA	Benign (0.23)
M-301	PARD3	c.2642C>T	rs1325227684	Missense mutation	Exon-19	S881F	Probably Damaging (0.89)	Deleterious (0.02)	NA	Ambiguous (0.55)
M-302	PARD3	c.854G>A	NA	Missense mutation	Exon-7	G285E	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (1.00)
M-303	PARD3	c.2135G>A	rs771607063	Missense mutation	Exon-15	R712Q	Probably Damaging (0.92)	Tolerated (0.05)	NA	Ambiguous (0.42)
M-304	PARD3	c.3707C>T	rs772939644	Missense mutation	Exon-25	S1236F	Probably Damaging (1.00)	Deleterious (0.00)	NA	Ambiguous (0.43)
M-305	PARD3	c.4036C>A	NA	Missense mutation	Exon-25	Q1346K	Benign (0.11)	Tolerated (0.10)	NA	Benign (0.20)
M-306	PARD3	c.1663G>A	NA	Missense mutation	Exon-11	E555K	Benign (0.08)	Deleterious (0.00)	NA	Pathogenic (0.66)
M-307	PARD3	c.3955C>T	rs573679528	Missense mutation	Exon-25	P1319S	Benign (0.12)	Deleterious (0.01)	NA	Benign (0.07)
M-308	PARD3	c.4057C>T	NA	Missense mutation	Exon-10	A499V	Probably Damaging (0.99)	Deleterious (0.00)	NA	Pathogenic (0.99)
M-309	PARD3	c.1496C>T	NA	Nonsense mutation	Exon-23	Q1162*	NA	NA	NA	NA
M-310	PARD3	c.3484C>T	NA	Missense mutation	Exon-11	G521C	Probably Damaging (0.95)	Deleterious (0.00)	NA	Pathogenic (0.69)
M-311	PARD3	c.1561G>T	NA	Missense mutation	Exon-23	P1148T	Possibly Damaging (0.83)	Tolerated (0.06)	NA	Benign (0.25)
M-312	PARD3	c.3442C>A	NA	Missense mutation	Exon-20	Q982K	Benign (0.04)	Tolerated (0.80)	NA	Benign (0.10)

(*Cont*d.)

Table 2 — Characteristics of mutations detected in target genes in TCGA SKCM cohort (*Contd*.)

No	Gene	Nt alteration	Rs Number/ Cosmic ID	Alteration Type	Localization	AA position	Clinic Impact Poly-Phen2 (Score)	SIFT (Score)	Mutaion Assesor (Score)	Alpha Missense (Score)
M-313	PARD3	c.2944C>A	NA	Missense mutation	Exon-24	R1226L	Benign (0.12)	Deleterious (0.00)	NA	Pathogenic (0.92)
M-314	PARD3	c.3677G>T	rs1429728150	Missense mutation	Exon-25	P1334L	Probably Damaging (0.99)	Deleterious (0.00)	NA	Pathogenic (0.95)
M-315	PARD3	c.4001C>T	NA	Missense mutation	Exon-25	P1334S	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0.95)
M-316	PARD3	c.4000C>T	rs372887395	Missense mutation	Exon-15	G721W	Probably Damaging (0.97)	Deleterious (0.00)	NA	Benign (0.24)
M-317	PARD3	c.2546A>C	NA	Missense mutation	Exon-17	K849T	Benign (0.23)	Tolerated (0.19)	NA	Pathogenic (0.97)
M-318	PARD3	c.2161G>T	NA	Missense mutation	Exon-15	G721V	Possibly Damaging (0.46)	Deleterious (0.00)	NA	Pathogenic (0.62)
M-319	PARD3	c.2162G>T	NA	Missense mutation	Exon-17	L842F	Probably Damaging (0.99)	Tolerated (0.13)	NA	Pathogenic (0.77)
M-320	PARD3	c.1400-1G>T	NA	Splice region mutation	NA	X467_splice	NA	NA	NA	NA
M-321	PARD3	c.3295G>T	NA	Missense mutation	Exon-22	G1099W	Possibly Damaging (0.85)	Deleterious (0.00)	NA	Benign (0.34)
M-322	PARD3	c.3229G>T	NA	Missense mutation	Exon-22	E1077*	NA	NA	NA	NA
M-323	PARD3	c.2711G>T	NA	Missense mutation	Exon-19	G904V	Possibly Damaging (0.89)	Deleterious (0.00)	NA	Pathogenic (0.66)
M-324	PARD6A	c.1013G>T	NA	Missense mutation	Exon-3	R338L	Benign (0.04)	Deleterious (0.00)	NA	Benign (0.10)
M-325	PARD6A	c.925C>A	NA	Missense mutation	Exon-3	P309T	Benign (0.00)	Deleterious (0.00)	NA	Benign (0.07)
M-326	PARD6A	c.1001G>T	rs766459239	Missense mutation	Exon-3	G334V	Benign (0.35)	Deleterious (0.00)	NA	Benign (0.10)
M-327	PARD6A	c.211C>A	NA	Missense mutation	Exon-2	L71I	Benign (0.04)	Tolerated (1.00)	NA	Benign (0.11)
M-328	PRKC1	c.832C>T	rs1428010723	Missense mutation	Exon-9	R278C	Benign (0.26)	Tolerated (0.12)	Low (4.60)	Benign (0.26)
M-329	PRKC1	c.653C>T	NA	Missense mutation	Exon-8	P218L	Benign (0.01)	Deleterious (0.04)	Low (4.00)	Benign (0.10)
M-330	PRKC1	c.450G>T	NA	Missense mutation	Exon-5	R150S	Possibly Damaging (0.54)	Deleterious (0.04)	Low (2.73)	Pathogenic (0.99)
M-331	PRKC1	c.1634G>T	rs1458271182	Missense mutation	Exon-17	G545V	Benign (0.21)	Tolerated (0.07)	High (7.06)	Ambiguos (0.48)
M-332	PRKC1	c.959C>T	rs3590030	Missense mutation	Exon-10	S320F	Probably Damaging (1.00)	Deleterious (0.01)	Mediun (6.65)	Pathogenic (1.00)
M-333	PRKC1	c.943C>T	rs1693795	Missense mutation	Exon-10	L315F	Probably Damaging (1.00)	Deleterious (0.01)	Mediun (6.35)	Pathogenic (1.00)
M-334	PRKC1	c.242C>T	rs3590028	Missense mutation	Exon-3	S81L	Probably Damaging (0.95)	Tolerated (0.01)	NA	Ambiguos (0.54)
M-335	PRKC1	c.1012G>A	rs3590031	Missense mutation	Exon-11	G338R	Probably Damaging (1.00)	Deleterious (0.00)	High (7.74)	Pathogenic (1.00)
M-336	PRKC1	c.1418T>A	rs3590031	Missense mutation	Exon-15	V473D	Probably Damaging (0.99)	Deleterious (0.00)	High (7.06)	Pathogenic (1.00)
M-337	PRKC1	c.1051C>T	rs3915348	Missense mutation	Exon-11	P351S	Probably Damaging (0.99)	Deleterious (0.03)	Low (4.07)	Ambiguos (0.53)
M-339	PRKC1	c.1759C>T	rs2108853706	Missense mutation	Exon-18	P587S	Probably Damaging (1.00)	Deleterious (0.03)	Low (4.49)	Pathogenic (0.99)
M-340	PRKC1	c.581C>T	NA	Missense mutation	Exon-6	S194F	Benign (0.02)	Tolerated (0.29)	Low (4.29)	Benign (0.11)
M-341	PRKC1	c.1445C>A	NA	Missense mutation	Exon-15	P482Q	Probably Damaging (0.93)	Deleterious (0.00)	High (7.72)	Pathogenic (0.99)
M-342	PRKC1	c.356G>T	NA	Missense mutation	Exon-4	G119V	Probably Damaging (1.00)	Deleterious (0.00)	NA	Pathogenic (0.97)

(*Contd*.)

Table 2 — Characteristics of mutations detected in target genes in TCGA SKCM cohort (*Contd*.)

No	Gene	Nt alteration	Rs Number/ Cosmic ID	Alteration Type	Localization	AA position	Poly-Phen2 (Score)	SIFT (Score)	Clinic Impact Mutaion Assesor (Score)	Alpha Missense (Score)
M-343	PRKC1	c.1613C>A	NA	Missense mutation	Exon-18	P538H	Probably Damaging (1.00)	Deleterious (0.00)	Mediun (6.49)	Pathogenic (0.98)
M-344	PRKC1	c.1515G>T	NA	Missense mutation	Exon-16	L505F	Probably Damaging (1.00)	Deleterious (0.00)	High (6.83)	Pathogenic (0.92)
M-345	PRKC1	c.1559C>A	NA	Missense mutation	Exon-16	P520Q	Benign (0.09)	Tolerated (0.07)	Low (4.89)	Benign (0.17)
M-346	PRKC1	c.727G>T	NA	Missense mutation	Exon-9	G243C	Possibly Damaging (0.71)	Deleterious (0.01)	Low (4.83)	Benign (0.13)
M-347	PRKC1	c.1506G>T	rs1178271455	Missense mutation	Exon-16	K502N	Benign (0.01)	Tolerated (0.30)	Low (3.43)	Ambiguos (0.44)

Abbreviations: M: Mutation; NA: Not available; c: complementary: Nt: Nucleotid; AA: Amino acid; rs: Reference SNP cluster ID

Fig. 1 — (A) Distribution of mutations in target genes in TCGA SKCM cohort from cBioPortal. Percentages of overall mutations for each gene are given on the left. (B) Distribution of all mutation types detected in the SKCM cohort.

elegans and mammals. This complex plays a critical role in establishing basolateral identity in epithelial cells with apical-basal polarity and serves as a scaffold for various signaling pathways.

The Lgl gene family encodes Lgl, a cortical cytoskeletal protein essential for maintaining cell polarity and epithelial integrity. In the SKCM cohort, LLGL1 harbors 18 distinct mutations, including 17 missense and 1 nonsense mutation, with a somatic mutation frequency of 4.4%. The p.E564* nonsense mutation, located within the WD-40 repeats domain, is of particular interest due to its potential to cause premature termination of the polypeptide, likely resulting in a truncated and non-functional protein. WD-40 repeat domains are involved in processes such as signal transduction, cytoskeleton organization, and cell division.

The LLGL2 gene exhibits a somatic mutation frequency of 8.0%, with 30 different mutations identified: 26 missense, 1 fusion, 2 nonsense, 1 frameshift insertion, and 1 splice site mutation. Among these, the p.S316* and p.Q71* nonsense mutations, as well as the -25fs frameshift mutation, are particularly significant as they may disrupt the early reading frame and lead to truncated protein products. Notably, the frameshift mutation occurs in close proximity to the X25_splice site mutation, both of which may result in the generation of aberrant mRNA transcripts and the production of non-functional proteins.

DLG1, a member of the membrane-associated guanylate kinase (MAGUK) family, functions as a molecular scaffold. In the SKCM cohort, DLG1 has a somatic mutation frequency of 4.4%, with 16 mutations identified (15 missense and 1 splice site mutation). The p.X839_splice mutation, located within the highly conserved GUK domain, is particularly noteworthy as it may lead to the

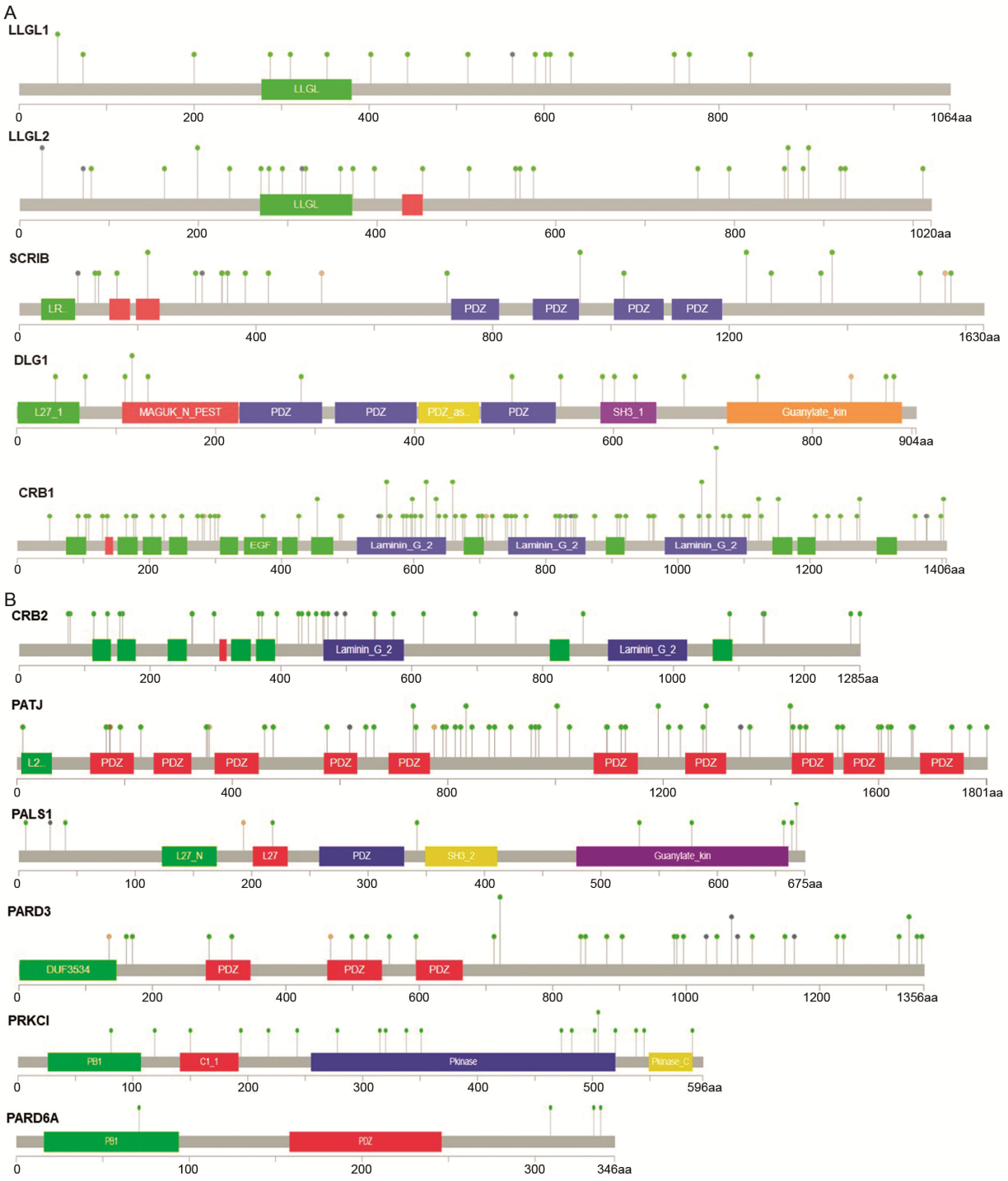


Fig. 2 — The localization of mutations detected in the domains of proteins belonging to the study genes in TCGA SKCM cohort.

formation of truncated transcripts and disrupt mRNA expression. Although the GUK domain lacks enzymatic activity, it is critical for mediating protein-protein interactions.

The SCRIB gene encodes a protein responsible for regulating apico-basal polarity in epithelial cells. A total of 27 mutations (24 missense, 2 nonsense, and 1 splice site) have been identified, corresponding to a somatic mutation frequency of 6.1%. The p.S1523F missense mutation occurs at a phosphorylation site, which may affect post-translational regulation. Additionally, the p.X1565_splice and p.X511_splice

mutations, located at evolutionarily conserved splice sites, could result in the formation of aberrant transcripts and altered mRNA expression. The nonsense mutations p.E99*, located in exon 3, and p.G309*, located in exon 10, may prevent the formation of critical functional domains such as the LRR (leucine-rich repeat) and PDZ domains thus potentially leading to non-functional protein products.

Crumbs complex gene analysis

The Crumbs polarity complex comprises CRB1, CRB2, CRB3, PALS1, and PATJ. The CRB family consists of key apical determinants responsible for maintaining apico-basal polarity in epithelial cells. CRB1, CRB2, and CRB3 are located on chromosomes 1q31.3, 9q33.3, and 19p13.3, respectively. CRB1 and CRB2 encode large transmembrane proteins with extensive extracellular domains composed of laminin A G-like and EGF-like domains, and a conserved 37-amino acid cytoplasmic tail. In contrast, CRB3 encodes a smaller 120-amino-acid protein, lacking extracellular domains but sharing a similar cytoplasmic region with CRB1 and CRB2.

In the CRB1 gene, 74 distinct mutations have been identified (67 missense, 5 nonsense, and 2 splice site mutations), with a somatic mutation frequency of 22.6% in the SKCM cohort. Among these, the p.Q1376* mutation in exon 12 may impair the function of the C-type lectin domain. Similarly, nonsense mutations such as p.Q179* (exon 2), p.Q547* (exon 6), and p.K838* (exon 7) may disrupt EGF-like domain function. Splice site mutations p.X710_splice and p.X283_splice, located at highly conserved regions, may result in aberrant mRNA transcripts and non-functional protein products.

In CRB2, 33 mutations have been identified (29 missense, 4 nonsense), with a somatic mutation frequency of 8.5%. Nonsense mutations p.E485* and p.W498* in exon 7 may compromise the Laminin G-like 1 domain, while p.W759* in exon 8 targets the Laminin G-like 2 domain. The p.E1137* mutation in exon 11 may impair EGF-like domain function. No mutations or genomic anomalies were detected in the CRB3 gene.

PATJ encodes a scaffolding protein that establishes cell polarity by mediating interactions between PALS1 and CRB proteins via its protein-protein interaction domains. In the SKCM cohort, 60 mutations have been detected (55 missense, 2 nonsense, 2 splice site mutations and 1 frameshift deletion), with a somatic mutation frequency of 12.1%. PATJ contains one L27 domain and ten PDZ domains. The p.Q11H mutation occurs in the L27 domain, whereas p.A173del, found in exon 5, maps to the second PDZ domain crucial for interactions with AMOT and TSC2 proteins. Other relevant missense mutations include p.N166D and p.P192L. Mutations p.G1096E, p.G1122E, p.G1130V, p.S1441F, p.G1454E, and p.H1465Y affect the sixth and eighth PDZ domains, which are responsible for binding ZO-3 and Claudin. Nonsense mutations p.R618* and p.E1344* may result in premature protein truncation, potentially disrupting key PDZ domains.

PALS1, a member of the MAGUK family, functions as a signal adaptor protein containing two L27, one PDZ, one SH3, one Hook, and one Guanylate Kinase (GUK) domain. In the SKCM cohort, 12 mutations were identified (10 missense, 1 splice and 1 nonsense), with a somatic mutation frequency of 3.0%. The p.E27* nonsense mutation and p.X193_splice may disrupt PDZ domain formation, thus interfering with PATJ interaction and leading to defective mRNA transcripts.

Par complex gene analysis

PARD3 is a key regulator of the PAR polarity complex, capable of forming major complexes through its self-homologous binding domain. A total of 34 mutations (27 missense, 1 fusion, 5 nonsense and 2 splice site mutations) have been identified in PARD3, which encodes a 1,356-amino-acid protein with an N-terminal domain, C-terminal domain, three PDZ domains (PDZ1, PDZ2, PDZ3), and an aPKC binding region. The p.X135_splice mutation, located in the CR1 domain, may disrupt self-association with other PARD3 proteins, leading to non-functional transcripts and altered mRNA expression. Critical missense mutations in the PDZ domains, such as p.G285E, p.A499V, p.G521C, and p.D595N, may interfere with protein-protein binding. Additionally, the region between amino acids 712-936, which binds aPKC, contains 7 significant missense mutations. Nonsense mutations such as p.R1030*, p.R1068*, p.E1077* and p.Q1162* may cause premature transcript termination.

PRKC1 (also known as aPKC1) is a kinase involved in cell signaling. It contains several functional domains, including RM (regulatory module), PB1 (Phox and Bem1 domain), PSS (pseudo-substrate sequence), BSL (beta-zinc binding),

and KD (kinase domain). In the SKCM cohort, PRKC1 has a somatic mutation frequency of 5.0%, with 19 missense mutations identified. Notable mutations within the kinase domain include p.L315F, p.S320F, p.G338R, p.P351S, p.V473D, p.P482Q and p.L505F. The PARD6A gene, which encodes a protein containing PB1, PDZ, IQ, and CRIB domains, has four missense mutations, with a somatic mutation frequency of 1.1%.

In silico functional pathogenicity and oncogenicity prediction results

Based on pathogenicity/oncogenicity prediction using PolyPhen-2, SIFT, Mutation Assessor, and AlphaMissense tools, 128 out of the 347 identified mutations were predicted to be potentially pathogenic or oncogenic by at least two tools. These mutations are detailed in Table 2.

Gene expression profiling and survival analysis results

In the SKCM cohort (n = 163), comparison of gene expression levels between tumor samples and healthy controls revealed that LLGL2, CRB3, PATJ, and PARD3 were significantly downregulated in tumor tissues (P<0.001) (Fig. 3A). However, no statistically significant association was found between gene expression levels and patient survival.

Promoter methylation analysis results

Promoter methylation analysis revealed that LLGL1 and LLGL2 were significantly hypermethylated in metastatic tissues compared to healthy controls ($P = 1.00 \times 10^{-2}$ and $P = 2.23 \times 10^{-3}$, respectively). DLG1 was found to be hypermethylated in both primary tumor and metastatic tissues ($P = 8.8 \times 10^{-16}$ and $P = 1.62 \times 10^{-12}$, respectively). No significant promoter methylation differences were detected for the other target genes across tissue types (Fig. 3B).

Cancer hallmark enrichment analysis

Using a bioinformatics tool, a visual representation of enrichment in cancer hallmark features was generated for LLGL1, LLGL2, SCRIB, DLG1, CRB1, CRB2, CRB3, PATJ, PALS1, PRKCI, PARD3 and PARD6A (Fig. 4A). These genes were significantly associated with hallmark features such as "*Sustaining Proliferative Signaling*" (P = 0.00084)

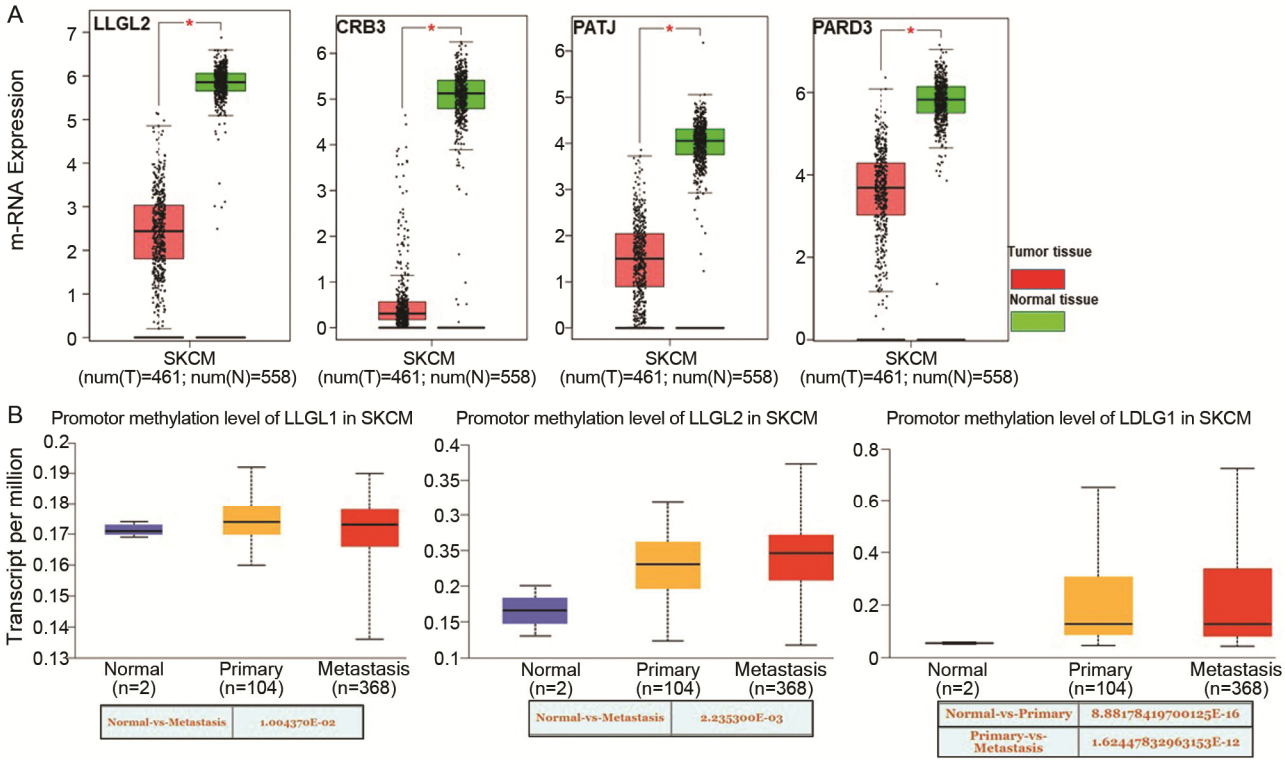
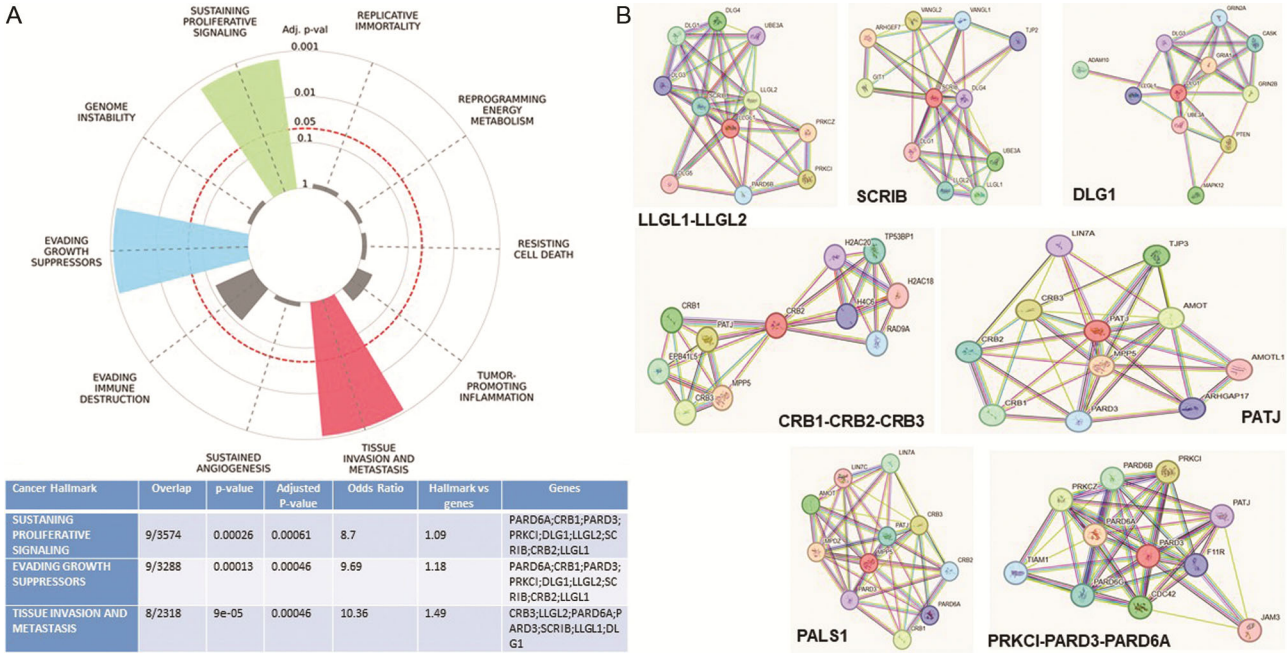


Fig. 3 — (A) Validation of the m-RNA expression levels of LLGL2, CRB3, PATJ, and PARD3 genes in SKCM tissues and normal tissues using GEPIA. These four box plots are based on 461 SKCM samples (marked in red) and 558 normal samples (marked in green), SKCM=Skin Cutaneous Melanoma, (*indicates P < 0.01). (B) Promoter region methylation levels of LLGL1, LLGL2, and DLG1 genes. Created using UALCAN tool.



Cancer Hallmark	Overlap	p-value	Adjusted P-value	Odds Ratio	Hallmark vs genes	Genes
SUSTAINING PROLIFERATIVE SIGNALING	9/3574	0.00026	0.00061	8.7	1.09	PARD6A;CRB1;PARD3;PRKCI;DLG1;LLGL2;SCRIB;CRB2;LLGL1
EVADING GROWTH SUPPRESSORS	9/3288	0.00013	0.00046	9.69	1.18	PARD6A;CRB1;PARD3;PRKCI;DLG1;LLGL2;SCRIB;CRB2;LLGL1
TISSUE INVASION AND METASTASIS	8/2318	9e-05	0.00046	10.36	1.49	CRB3;LLGL2;PARD6A;PARD3;SCRIB;LLGL1;DLG1

Fig. 4 — (A) The cancer hallmark enrichment plot compares the target genes to the reference set of genes and shows the significance of this comparison with colored slices. The red dotted line indicates where statistical significance reaches $P = 0.05$, and only significantly enriched cancer hallmarks are shown in color. (B) Schematic representation of known and predicted protein-protein interactions with the target proteins. Each line has features. [Red line-indicates the presence of fusion evidence; Green line- neighborhood evidence; Blue line- cooccurrence evidence; Purple lineexperimental evidence; Yellow line- textmining evidence; Light blue line database evidence; Black line coexpression evidence.]

and "Evading Growth Suppressors" (P = 0.00046). Additionally, CRB3, LLGL2, PARD6A, PARD3, SCRIB, LLGL1 and DLG1 showed strong enrichment in the "*Tissue Invasion and Metastasis*" hallmark.

Protein-protein interaction analysis results

STRING network analysis was used to examine functional protein–protein interactions of the selected polarity complex components (Fig. 4B). LLGL1, LLGL2 and SCRIB interact with UBE3A, an E3 ubiquitin ligase involved in protein degradation. CRB2 interacts with 53BP1 (encoded by *TP53BP1*), a key DNA damage response protein. DLG1 interacts with PTEN, a tumor suppressor that negatively regulates the PI3K/AKT/mTOR pathway. PATJ and PALS1 interact with Angiomotin (AMOT), implicated in tumor proliferation and invasion. CRB1, CRB2, and CRB3 interact with histone proteins HIST1H4F and H2AC20 and the DNA repair regulator RAD9A, suggesting involvement in chromatin remodeling and DNA damage response pathways.

Discussion

Cell polarity is a fundamental biological process that governs cell growth, migration, invasion, molecular transport, and cell fate determination. Disruption of polarity regulators has been implicated in the development and progression of various cancers[4-8,18,19]. In this study, we provide genetic evidence linking functional mutations and expression changes in polarity complex genes key epithelial polarity regulators with the pathogenesis of skin cutaneous melanoma (SKCM). Our findings suggest that these genes may function either as tumor suppressors or oncogenes depending on the context, reflecting their pivotal roles in maintaining epithelial homeostasis. Using genomic data from 442 SKCM patients in The Cancer Genome Atlas (TCGA), we characterized mutation profiles of twelve core polarity complex genes. We identified 347 mutations in total comprising 313 missense, 18 nonsense, 11 splice site, 2 frame-shift and 2 fusion mutations. Among these genes, CRB1 was the most frequently mutated, while CRB3 exhibited no detectable mutations. Functional impacts of these mutations were further explored through analyses of gene expression, promoter methylation, survival associations, and protein–protein interactions.

The Scribble complex activates multiple signaling cascades to establish apical-basal and planar cell polarity, regulating essential cellular processes. Many

studies have reported that the SCRIB gene, which encodes the Scribble protein, acts as a tumor suppressor due to its role in tumor-related mechanisms and its regulation of tumor development and metastasis[6-8,20]. SCRIB is a large scaffold protein containing 16 Leucine-Rich Repeat (LRR) and 4 PDZ protein interaction domains, and these domains interact with DLG1-4 and LL1/2 to form the Scribble complex. The LRR and PDZ domains are crucial for SCRIB's localization and stabilization at the plasma membrane, and SCRIB acts as a tumor suppressor by interacting with proteins like ZO-2, PHLPP1, Vangl2, APC, and ERK to regulate processes such as cell proliferation, differentiation, apoptosis, and migration[5,6,20,21]. The p.E99* and p.G309* nonsense mutations determined in this study may eliminate potential protein-protein interactions by disrupting the formation of non-functional LRR and PDZ domains. Both patients carrying these mutations were metastatic. Protein-protein interaction results also showed direct interactions with VANGL1 and VANGL2, planar cell polarity proteins involved in tissue morphogenesis and key scaffolding proteins of the WNT signaling pathway. This pathway is known to be important for the establishment and maintenance of polarity in epithelial tissues and for critical cell mobility events necessary for proper embryonic development[20,21].

LLGL2, an important component of the Scribble complex, interacts with the Scribble protein through its LRR domain, and inhibition of the ERK, Hippo, and Wnt pathways occurs via the LRR repeat domains[4-6,22]. In this study, we identified 8 different missense mutations on the LRR domain that could potentially affect these critical interactions. The p.S1022T mutation detected on the PDZ3 domain is located on the binding region of the TRIP6 protein, which increases chemotherapy resistance, promotes proliferation and invasion, and contributes to tumor progression. This mutation was found in a 45-year-old male patient with metastasis.

LLGL proteins play significant roles in regulating polarity in various cell types and function as tumor suppressors. In epithelial cells, LLGL1 and LLGL2 are localized to the lateral membrane beneath tight junctions. The N-terminal sequence of LLGL proteins contains various WD40 motifs that serve as protein interaction modules[4-6,22]. LLGL2, through its WD40 repeats, directly interacts with PARD6 at amino acid residues p.S655, p.S659 and p.S663 to form multi-protein complexes involved in migration, polarity, and cell adhesion. In this study, we detected an E564* truncating mutation on exon 14, coding for the WD40 motif, which may lead to a non-functional transcript by eliminating the PARD6 binding sites. Additionally, p.X25_splice, p.-25fs mutations and p.Q71* nonsense mutations were found in the C-terminal region of LLGL2. This region is known to be involved in direct protein-protein interactions with N-cadherin, which is essential for the formation of apical junction complexes necessary for cell adhesion in embryonic stem cells[22]. Low LLGL2 expression has been determined in breast cancer, colorectal cancer, gastric cancer, and lung adenocarcinoma, and it has been associated with cancer prognosis[23]. In the SKCM cohort, LLGL2 m-RNA expression was found to be low, consistent with the literature. The cancer hallmark analysis for LLGL2 also revealed significant associations with "*Sustaining Proliferative Signaling*," "*Tissue Invasion and Metastasis*," and "*Evading Growth Suppressors,*" supporting the idea that LLGL2 could be a prognostic factor.

Since epigenetic modulation is thought to be a key factor in the reduction of methylation levels in promoter regions, the promoter methylation status of LLGL1 and LLGL2 was analyzed. It was found that LLGL1 and LLGL2 genes were hypermethylated in metastatic tissue compared to normal tissue. Promoter region hypermethylation leads to silencing of the subsequent gene, and since it is an important mechanism in inactivating tumor suppressor genes, the results confirm that LLGL1 and LLGL2 function as tumor suppressors in SKCM.

DLG1, a member of the MAGUK family of molecular scaffolding proteins[24]. A pathogenic p.R109M missense mutation was detected in the MAGUK domain, which actively clusters and organizes its binding components. The p.X839_splice mutation found in the C-terminal domain of DLG1, which is important for the MAGUK domain function, could alter the functional transcript by modifying the splice site. DLG1 was found to be hypermethylated in both tumor and metastatic tissues compared to normal tissue. DLG1 expression is known to play different and sometimes opposite roles in processes such as differentiation, cytokinesis, proliferation, cell migration and tumor microenvironment control, all of which are involved in tumor progression[24,25]. Considering DLG1's tumor suppressive function in SKCM, the promoter hypermethylation and function-

altering mutations confirm this data. Furthermore, as seen in the STRING protein-protein interaction analysis, DLG1 can interact with other tumor suppressors like PTEN, and is known to regulate cell proliferation in various contexts. This suggests that the regulation of DLG1 during the cell cycle is crucial for tightly controlling cell growth.

In mammalian cell cultures, reducing the levels of PATJ protein has been reported to destabilize the Crb complex and cause defects at tight junction areas[7,26]. In the SKCM cohort, PATJ expression is lower compared to healthy control groups. It contains an L27 domain and ten PDZ domains[26]. The p.A173del mutation, which can alter the reading frame, is located in the second PDZ domain, where it interacts with AMOT and TSC2 proteins. PATJ is also used to interact with the second PDZ domain with tuberous sclerosis complex 2 protein (TSC2), which may link the mTOR pathway to the CRB complex and support the hypothesis that cell polarity proteins play a role in signal transduction. Through this domain, binding to the AMOT binding protein family establishes tight junctions and stabilizes epithelial polarity[27]. Additionally, the carboxyl terminals of Zona occludens-3 (ZO-3) and claudin-1 interact with the sixth and eighth PDZ domains, respectively, suggesting that PATJ plays a significant role in the formation of tight junctions[26,27]. Six different critical oncogenic missense mutations were identified in the SKCM cohort within these domains.

The loss of CRB complex function leads to the displacement and/or disruption of all other core proteins in the Crumbs complex, including those in embryonic and follicular epithelia[5,7,28]. CRB, a Type I transmembrane protein, consists of an extracellular region, a transmembrane domain, a FERM-binding motif (FBM), a PDZ-binding motif (PBM) and several potential aPKC phosphorylation sites within a 37-residue cytoplasmic tail. The FBM plays a role in polarity formation by binding to PALS1 and Epb4.1l5, while the PBM interacts with the PDZ domains of PALS1 and PAR6, also playing a significant role in polarity formation[7,28]. In the SKCM cohort, the p.Q1376* nonsense mutation in the FBM and PDZ domains could lead to CRB function loss. Studies have suggested that CRB genes might serve as potential tumor suppressors and that CRB is an upstream component of the Hippo signaling pathway. As is well known, Hippo signaling critically regulates the cell cycle, proliferation, apoptosis, and contact inhibition[28]. In the SKCM cohort, the loss of CRB3 has been reported to be associated with increased expression of vimentin and decreased expression of E-cadherin, two key features of epithelial-to-mesenchymal transition. Furthermore, the loss of CRB3 enhances TGF-β signaling, making the cells more prone to TGF-β-induced EMT. In support of these findings "tissue invasion and metastasis" ($p=9 \times 10^{-5}$) was found to be a prominent feature in the cancer hallmark analysis, indicating that SKCM is characterized by increased potential for spread to surrounding tissues, in line with its aggressive and heterogeneous nature. CRB proteins interact with HIST1H4F and H2AC2 proteins, which are involved in chromatin architecture formation, genetic information packaging, and regulation of DNA-dependent processes like transcription, repair, replication, and recombination[28].

The adapter PALS1 consists of a PDZ domain, followed by an SH3 domain adjacent to an inactive Guanylate kinase homology region and a COOH-terminal segment. PALS1 regulates cell polarity by binding to the PBM domain of CRB3, and it is known to interact with PATJ through its L27 domain[29]. In the SKCM cohort, pathogenic mutations, such as the p.Q218H missense mutation in the PATJ binding region and the p.X193_splice region mutation located before the L27 domain, are likely to cause dysfunctional, shorter transcripts, leading to differences in mRNA expression. Loss of PALS1 leads to the disruption of tight and adherens junctions, which destabilizes cell polarity.

The scaffold protein PAR3, along with PAR6 and the aPKC, forms the PAR complex, responsible for proper apical polarity and the formation and maintenance of tight junctions in epithelial cells. In metastatic breast cancer tissues, decreased expression of membrane PAR3 has been studied to reduce cell-cell cohesion through the Tiam1/Rac-GTP-dependent pathway, promoting ErbB2-mediated metastasis[3,8,18,30]. In the SKCM cohort, decreased PAR3 expression was identified, and all patients with detected oncogenic mutations were metastatic, in line with the literature. Specifically, PARD3 controls multiple intracellular signaling pathways through its PDZ domains, aPKC binding site, and coiled-coil region[18,19,30]. Critical mutations were identified in these domains within the SKCM cohort. For example, the PDZ domain interacts with adhesion molecules, Nectin, Par6, the adaptor protein GAB1,

phosphoinositides (PIPs), lipid phosphatase PTEN, and the Hippo pathway transcription factor YAP[8,18,19,30]. In the SKCM cohort, oncogenic mutations such as p.G285E, p.A499V, p.G521C and p.D595N were found in the PDZ domain, which may affect these interactions. The p.D595N mutation in the PDZ3 domain, located in the YAP binding region, could disrupt interactions with Hippo pathway members, which may alter the transcription of genes regulating proliferation and apoptosis, depending on the physiological and cellular context. Moreover, missense mutations and nonsense mutations that result in early transcript termination were identified in the coiled-coil domain of PAR3, which may lead to a scattered distribution of PARD3 in the cytosol. The PB1 domain of PAR3 facilitates the formation of large PARD3 oligomeric complexes through self-association, which is critical for membrane targeting. In the SKCM patients, the p.X135_splice region mutation detected in this domain was found in a 64-year-old male patient with metastasis. PAR3 is also known to act as a tumor suppressor, and loss of PAR3 in tumor cells is associated with abnormal expression of critical genes like P-KADHERIN, SNAIL1 and MMP9, as well as abnormal regulation of signaling pathways such as STAT3, TIAM1/RAC1, and NOTCH [5,8,18,19,30]. Homozygous deletions are a common mechanism for inactivating tumor suppressor genes, and deletions were detected in metastatic patients in the SKCM cohort. Additionally, PAR3 expression was downregulated in the SKCM cohort compared to healthy controls and was found to behave as a tumor suppressor. The cancer hallmark analysis revealed significant indicators for important biological capabilities such as *Sustaining Proliferative Signaling, Tumor-Promoting Inflammation, Evading Growth Suppressors, and Evading Immune Destruction*. PAR3 is reported to act as a tumor suppressor in various cancers[8,18,19,30]. Based on the findings, it can be concluded that PAR3 functions as a tumor suppressor in SKCM, similar to other solid tumors. aPKCs interact with PAR6 and its binding partner PAR3 to form the "PAR complex," which regulates apical-basal polarity and asymmetric cell division and differentiation. The role of the kinase aPKC in regulating cell polarity is primarily achieved through the phosphorylation of various targets[19,30]. Missense mutations have been identified in the kinase domain that could show oncogenic/pathogenic effects. Additionally, the PB1 domain is responsible for protein-protein interactions of PKCι with MEK5/ERK (MAPK) and other proteins with PB1 domains, such as PAR-6.

Conclusion

Despite comprehensive genetic profiling analyses of polarity complex genes that may be responsible for SKCM pathogenesis, we acknowledge some limiting factors in this study. This work was carried out using bioinformatics tools and limited experimental design. Therefore, to clarify the impact of polarity complex genes on SKCM pathogenesis, wet-lab studies with a larger sample group are required. A detailed molecular understanding of how polarity is established and how functional disruption contributes to skin diseases awaits further research.

Multiple polarity aspects are known to be important for the shape and function of the epidermis. There is substantial cross-talk between the polarity mechanism and tissue physiology. Extending our understanding of the molecular mechanisms and interactions underlying cell polarity processes will help us to use the possibilities of therapeutic intervention of cell polarity signaling for the diagnosis and treatment of skin cutaneous melanoma.

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Ethics

Ethical approval and ethical standards

The data used in our study were obtained from public database TCGA, therefore, ethical approval was not required.

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Conflict of Interest

The authors declared that they have no conflict of interest.

Financial Disclosure

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