

## **SUPPORTING INFORMATION**

### **“Heterogeneous Data Sources Integration for Gene Expression Analysis and Multiclass Classification for Skin Cancer Profiling”,**

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### **PART 3: ABOUT THE BIOLOGICAL INTERPRETATION OF 17 SELECTED GENES**

There are different types of skin cancer. Basal cell carcinoma (BCC) is the most common form of skin cancer while squamous cell carcinoma (SCC) is the second most common form of skin cancer [1-3]. Both squamous cell and basal cell skin carcinomas are sometimes called non-melanoma skin cancers [4]. Melanoma is the third most common form of skin cancer and is one of the most aggressive [5]. There are others less common types of skin cancer including Merkel cell carcinoma, sebaceous carcinoma, microcystic adnexal carcinoma, cutaneous lymphomas, lentigo maligna, and actinic keratosis (a pre-cancerous skin condition) [6-8].

In order to assess the relationship of the selected genes with skin cancer or their relationship with other types of cancer, we have made an analysis of published scientific literature related to these genes. Examining the literature related to these 17 genes gave insight into how these genes might be related to different types of cancer. All these selected genes are protein-coding genes. Supplementary Table S3 shows symbols and names of these genes, their function class, and the types of cancer related to these genes.

Analysis of the literature revealed that all these genes are involved in human cancer development. Furthermore, for DSC3, BNC2, TYRP1, ISL1, DSC1, MLANA, LGR5, CLDN1, POU4F1, KRT20, and TGM3 genes, we also found articles in the literature that support their association with any type of skin cancer.

In the case of desmocollins 1 and 3 (DSC3 and DSC1), a type-1 transmembrane glycoproteins localized in desmosomes, both types of proteins seem to be implicated in the etiology of melanoma. However, their role in cancer development and progression is not completely understood. These two desmosomal proteins have been performed both tumor suppressive and tumor promoting functions.

**Supplementary Table S3.** Summary of the 17 selected genes using this method.

Gene symbol	Gene name	Function class	Types of cancer related to the gene
<i>DSC3</i>	Desmocollin 3	Cell adhesion junctions	<b>Skin cancer</b> [10, 13] Ovarian cancer [9] Breast cancer [14, 15]
<i>SCGB2A1</i>	Secretoglobulin family 2A member 1	Secreted protein	Epithelial ovarian cancer [16-19] Breast cancer [20, 21] Colorectal cancer [22]
<i>BNC2</i>	Basonuclin 2	DNA-binding zinc-finger protein	<b>Skin cancer</b> [1, 23, 24] Epithelial ovarian cancer [25-28] Hepatocellular carcinoma [29] Urothelial carcinomas [30] Esophageal cancer [31] Prostate cancer [32]
<i>TYRP1</i>	Tyrosinase related protein 1	Melanin synthesis	<b>Skin cancer</b> [33-41]
<i>ISL1</i>	ISL LIM homeobox 1	Transcription factor	<b>Skin cancer</b> [42, 43] Neuroblastoma [44] Gastric cancer [45] Bladder cancer [46] Ameloblastoma [47] Soft tissue sarcomas [48]
<i>DSC1</i>	Desmocollin 1	Cell adhesion junctions	<b>Skin cancer</b> [49, 50]
<i>MLANA</i>	Melan-A	Involved in T-cell responses	<b>Skin cancer</b> [8, 51-57]
<i>CRYBA2</i>	Crystalline $\beta$ A2	Structural components	Neuroblastoma [58]
<i>ANXA3</i>	Annexin A3	Ca <sup>2+</sup> -regulated phospholipid- and membrane-binding proteins	Lang cancer [59] Gastric cancer [60] Prostate cancer [61, 62] Colorectal cancer [63-65] Liver cancer [66, 67] Breast cancer[68]
<i>PCP4</i>	Purkinje cell protein 4	Regulation protein	Breast cancer [69, 70] Esophageal cancer [71]
<i>LGR5</i>	Leucine rich repeat containing G protein-coupled receptor 5	Stem cell marker	<b>Skin cancer</b> [72-77] Brain cancer [78] Colon and rectum cancer [79]
<i>CLDN1</i>	Claudin 1	Intercellular junction	<b>Skin cancer</b> [80-86]
<i>POU4F1</i>	POU class homeobox 1	Transcription factor	<b>Skin cancer</b> [87-89] Breast cancer [90] Leukemia [91-93] Cervical cancer BRN3A [94]
<i>SOSTDC1</i>	Sclerostin domain containing 1	Cell signaling	Lung cancer [95] Thyroid cancer [96] Breast cancer[97, 98] Gastric cancer [99, 100] Renal cancer [101, 102] Epithelial ovarian cancer [103] Prostate cancer [104]
<i>KRT20</i>	Keratin 20	Structural protein	<b>Skin cancer</b> [105-109]
<i>TGM3</i>	Transglutaminase 3	Enzyme	<b>Skin cancer</b> [110] Oral cancer [111] Esophageal cancer [112, 113] Laryngeal cancer [114]
<i>MYO15A</i>	Myosin XVA	Myosin protein	Endocrine tumors [115, 116]

On one hand, elevated levels of DSC3, a desmosomal cadherin that is required for maintaining cell adhesions, were associated with a worse survival for melanoma [9] while Riker et al., considered DCS3 as a tumor suppressor gene due to present low level of protein expression in primary and metastatic cutaneous melanoma cell lines [10]. On the other hand, although the significance of DSC1 mutations in melanoma is unclear due to the fact that melanocytic cells do not have desmosomes [11], missense and nonsense somatic mutations were frequently found in this candidate melanoma gene [12]. Furthermore, DSC3 expression has been observed in several solid tumors. An increase of DSC3 expression has been observed in lung cancer while in other types of cancer, such as breast cancer, its expression has been reduced [13-15].

Basonuclin 2 (BNC2), a DNA-binding zinc-finger protein, is considered as a skin color gene and has been associated with SCC risk. BNC2 is expressed in melanocytes and keratinocytes, and it is thought to act both as a messenger RNA-processing enzyme and as a transcription factor [1, 23, 24]. There are many studies related to the role of BNC2 in different kinds of cancer such as epithelial ovarian cancer [25, 27, 28], hepatocellular carcinoma [29], bladder cancer [25], esophageal cancer [25, 31], urothelial carcinoma [30], and prostate cancer [32]. BNC2 expression was decreased in cancer cells, and stable expression caused cancer growth arrest. Thus, all these works suggested a putative tumor suppressor function of BNC2 during cancer development [25-32].

Tyrosinase-related protein 1 (TYRP1) is exclusively expressed in melanocytes and melanoma cells, and it is considered a pigmentation-associated gene. TYRP1 is involved in the production of eumelanin which is associated with skin fair pigmentation, being responsible for increasing skin sensitivity to sun. TYRP1 is being considered as a risk factor for the development of melanoma and a prognostic marker for metastatic skin melanoma [33-40]. Furthermore, Kosiniak-Kamysz et al. related the influence of pigmentation genes such as TYRP1 in the development of BCC [41].

The human insulin gene enhancer-binding protein islet-1 (ISL1) is a LIM-homeodomain transcription factor that promotes the proliferation of adult pancreatic islet cells. Although it is related to pancreatic neuroendocrine neoplasms, it is also related to certain groups of non-pancreatic neuroendocrine carcinomas including Merkel cell carcinoma, also called neuroendocrine carcinoma of the skin, neuroendocrine carcinomas of the lung [42, 43], and bladder cancer [46]. However, the role of ISL1 in the development of these tumors is still unclear. Furthermore, ISL1 promotes the proliferation of and gastric cancer and lymphoma cells [45] and is overexpressed in Skeletal muscle cancer [48] and ameloblastoma [47]. Besides being considered as a useful marker for metastatic pancreatic neuroendocrine neoplasms, ISL1 is also considered as a marker of neuroblastoma [44].

Protein Melan-A also known as melanoma antigen recognized by T cells 1 (MART-1)/MLANA is considered as a melanocyte marker and is important in melanoma diagnostics. Some tumors are associated with reduced expression of MLANA [51, 53]. Since its discovery in 1994, MART-1 has been the focus in the development of strategies in order to target melanoma through the immune system. In fact, it currently seems to be the most useful histological biomarker for the diagnosis of melanoma due to its nature as an specific and sensitive gene for distinguishing both primary and metastatic melanoma [52, 54, 55, 57]. MLANA is also considered to be a useful marker for identifying melanocytes in vitiligo patients' skin [56], and to confirm the diagnosis of lentigo maligna in early lesions and in the differential diagnosis from melanocytic hyperplasia in chronically sun-damaged skin [8].

Leucine-rich G-protein-coupled receptor 5 (LGR5), also known as G-protein-coupled receptor GPR49, functions as a marker of stem cells in the hair follicle in the skin, and stem cells in the small intestine and colon [72, 74-78]. LGR5 protein is involved in both SCCs [72, 73] and BCCs carcinogenesis in epidermis [74, 77], playing a significant role in tumor formation and cell proliferation. Furthermore, LGR5 is overexpressed in other types of cancer such as colorectal cancer promoting the growth of colon tumor cells [77, 79]. As expression of LGR5 is associated with activation of Wnt signaling pathway [78, 79], and Wnt signaling pathway is also involved in brain development, it is also suggested that LGR5 plays a role in maintenance and/or survival of brain cancer stem cells [78]. Thus, the overexpression of LGR5 revealed that LGR5 functions as an oncogene [77].

Claudin-1 (CLDN1) is a transmembrane protein involved in the formation of multiprotein complexes at the tight junctions in the epithelium of the skin [80, 84, 85]. Claudins regulate skin permeability, and specifically CLDN1 is suggested to be involved in proliferation and differentiation of keratinocytes. It is related to cutaneous SCC development [85, 86]. It is suggested to be downregulated by Snail and Slug (two transcription factors which promote epithelial-mesenchymal transition in malignant tumors) in cutaneous SCC [81, 85]. On the other hand, Morita et al. described a restriction of strong expression of CLDN1 to keratinized areas in 5 SCC [83]. Furthermore, CLDN1 downregulation is also implicated in the acquisition of metastatic phenotype in cutaneous melanoma [80] and in the formation of melanoma brain metastasis in brain endothelial cells. Thus, Izraely et al. suggested CLDN1 as a useful predictor for melanoma patients with a high risk of brain metastasis [82].

POU4F1 (POU class homeobox 1) is a transcription factor member of the Pit-Oct-Unc (POU) domain family, and its expression has been considered essential for melanoma cell proliferation and survival. POU4F1 has been suggested as a useful biomarker to distinguish early stage melanomas from benign lesions. 55% of human melanoma cell lines express increase levels of POU4F1, and inhibition of POU4F1 expression is involved in reducing melanoma cell viability and tumor growth. In melanoma cells, loss of POU4F1

is associated with apoptosis [87, 88]. POU4F1 has been also linked with MCC risk [89]. Furthermore, POU4F1 has been related to other cancer development such as cervical cancer [94], myeloid leukaemia [91-93], and breast cancer [90].

Cytokeratin-20 (KRT20, CK20) is an epithelial antigen that is expressed in approximately 95% of MCC thus being considered as a marker for this type of tumor [105, 107, 109]. Consequently, KRT20 expression is used as a diagnostic tool for detecting MCC [108]. However, a small amount of tumors lack KRT20 expression. This loss of KRT20 expression in cutaneous MCC has been related with decreased expression of other lineage markers such as cytokeratin 8 and chromogranin A [106].

Transglutaminase 3 (TGM3) is an enzyme with Ca<sup>2+</sup>-dependent transamidation activity in the non-proliferating layers of the epidermis. TGM3 is indispensable for normal formation of epidermis. Its principal function is catalyzing the crosslinks of proteins through the formation of isopeptide bonds between peptidyl glutamine and lysine residues. It is suggested that a genetic variant in TGM3 may disrupt the normal differentiation of corneocytes and this could increase susceptibility to BCC risk [110]. TGM3 is also down regulated in other types of cancer of head and neck [117, 118] such as oral squamous cell carcinoma [111], esophageal squamous cell carcinoma [112, 113], and laryngeal carcinoma [114].

Secretoglobin, family 2A, member 1 (SCGB2A1), also known as mammaglobin 2, is a small secreted protein of the uteroglobin superfamily. Normal expression of SCGB2A1 has been described in human ocular tissues, prostate, pituitary, and in secretory mucosal epithelia of breast, uterus and lacrimal glands [19]. SCGB2A1 overexpression has been observed in epithelial ovarian cancer [17, 18], primary epithelial breast cancer and in occult breast metastasis [17, 20, 21], liver cancer, and colorectal cancer [22]. Thus, SCGB2A1 has been reported as a predicting biomarker in several types of cancer such as epithelial ovarian cancer [16, 19], breast [17, 20], and colorectal cancer [22]. *Tassi et al.* observed that SCGB2A1 expression correlated with reduce recurrence, disease progression and death associated to cancer [19].

Sclerostin domain containing protein 1 (SOSTDC1) is an important regulator of cell signaling [101, 103]. SOSTDC1 participates in the development of various cancers acting as a tumor suppressor in several types of cancer such as gastric cancer [96, 99, 100] and non-small cell lung cancer [95]. SOSTDC1 is down regulated in epithelial ovarian cancer [103], breast cancer [95, 97, 98], gastric cancer [99, 100], renal cancer [101], prostate cancer [104], thyroid cancer [96], and non-small cell lung cancer [95]. SOSTDC1 expression is considered as a potential prognostic factor in gastric cancer [99]. SOSTDC1 down regulation has been associated with poor clinical outcome in breast cancer and high expression of SOSTDC1 has been associated with better prognosis in breast cancer [95, 97]. One way by which SOSTDC1 exert its function is by regulating both bone morphogenetic proteins (BMP) signaling pathway which are involved in activation of cell

proliferation and differentiation, and wingless/int (Wnt) signaling pathways [97, 101]. This dual regulation of BMP and Wnt signaling pathways plays a role in breast cancer [97], renal cancer [95], prostate cells [104] and kidney cells [102]. On the other hand, the tumor suppressive function of SOSTDC1 in lung cancer and thyroid cancer has been associated with the pathway that controls the activity of the retinoblastoma tumor suppressor protein (Rb), which in turn regulates the E2F transcription factor [95, 96].

Although SCGB2A1 and SOSTDC1 have not been yet linked to skin cancer, they are related to development of epithelial cancers such as ovarian and breast cancer. It is known that there are many types of epithelial cells which are cells that cover the inside and outside surfaces of the body. We may speculate that genes involved in epithelial ovarian cancer and/or epithelial breast cancer could be also involved in skin cancer development. However, the future researches will ultimately determine the validity of this approach.

Annexin 3 (ANXA3), purkinje cell protein 4 (PCP4), and myosin 15A (MYO15A) have not been related to skin cancer either. Nevertheless, all of them have been linked with certain kinds of cancer.

ANXA3 is an intracellular protein with calcium dependent phospholipid binding activity that plays a role in cellular growth and signal transduction [59, 61]. ANXA3 is considered a prognostic biomarker of lung carcinoma [59] and gastric cancer [60]. ANXA3 downregulation has been involved in prostate cancer [61, 62] and renal cancer. On the other hand, ANXA3 expression has been observed upregulated in colorectal cancer [63, 65], liver cancer [66, 67], and gastric cancer [59]. Furthermore, ANXA3 expression has been involved in proliferation, invasion and migration of breast cancer cells [68].

PCP4, also known as PEP19, is a calmodulin (CaM) binding protein that accelerates both the association and dissociation of calcium with calmodulin, regulating CaM-dependent signaling [69, 70]. PCP4 modulates calcium/CaM-dependent kinase (CaMK) activity influencing apoptosis. However, relationship between PCP4 and apoptosis has not been fully investigated yet [69]. PCP4 has been identified in studies investigating one type of esophageal cancer, squamous cell carcinoma [71]. High PCP4 expression levels have been observed in breast cancer cells where PCP4 inhibits apoptosis via CaMKK and Akt signaling pathways and increases motility [69, 70].

MYO15A is a protein that hydrolyzed adenosine triphosphate (ATP) and it is suggested to be involved in cytoplasmic organelle movement and/or hormone secretion. MYO15A is considered as a useful marker for endocrine cancers [115, 116].

Despite ANXA3, PCP4 and MYO15A have not been related to skin cancer so far, it cannot be ruled out that they will be related in the future. In fact, *Wu et al.* suggested that ANXA3 might be considered as a biological indicator for the prognosis and tumor development, invasion and metastasis [119].

## Summary

Summarizing information collected from the literature, most genes identified by our approach showed association with some type of skin cancer. These results reveal the potential of our technique in selecting genes that may be considered as biomarkers for skin cancer. Further studies are necessary in order to validate these results.

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