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Candidate Biomarker Identification for the Cancers of Mouth Cavity Using Gene Expression Data

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ABSTRACT:Gene expression indicates the present state of the cell. Samples associated with the normal and oral tissue in *Homo sapiens* are collected by providing different oral tissue query terms from GEO and ArrayExpress database. Manual curation is carried using Standard Operating Procedure (SOP) provided by IBAB for both normal and cancerous condition. These samples are submitted to the novel algorithm developed at IBAB, Bangalore, to validate samples and identify oral cancer specific genes. The study retrieved 2065 samples for oral cancer condition in *Homo sapiens*. Out of 2065 samples, genes expressed in oral cancer were 12062; genes not expressed in oral cancer were 7811. The study also retrieved 838 samples for normal oral condition, out of which genes expressed in Normal oral, were 12112 and genes not expressed in Normal oral were 7812. By comparison, 518 genes were identified which were expressed in oral cancer and not detected in Normal oral tissue.

KEYWORDS:Gene expression, Meta analysis, oral cancer, biocuration (manual curation), biomarker

I. INTRODUCTION

Meta analysis is a method that focuses on contrasting and combining results from different studies, in the hope of identifying patterns among study results, sources of disagreement among those results, or other interesting relationships that may come to light in the context of multiple studies. It can help to investigate the relationship between study features and study outcomes. Oral cancer is the second most common cancer in the world.

Paper is organized as follows. Section II describes materials and methods, Section III displays the obtained results. Finally, Section IV presents conclusion.

II. MATERIALS AND METHODS

1. **Identification of tissue of interest:**
   Oral tissue of species Homo sapiens is selected for the study. The study is carried out for cancerous and normal condition.
2. **Identification of data sets from repositories:**
   The results of microarray experiments are deposited in public repositories. GEO (Gene Expression Omnibus) and ArrayExpress are two such public repositories. The data sets are collected from these databases using different specific query terms. Fig 1 gives the list of Oral cancer tissue synonyms and oral related terms used to query public repositories (GEO and ArrayExpress). Similarly Fig 2 gives the list of Normal oral tissue synonyms and oral related terms used to query public repositories (GEO and ArrayExpress).

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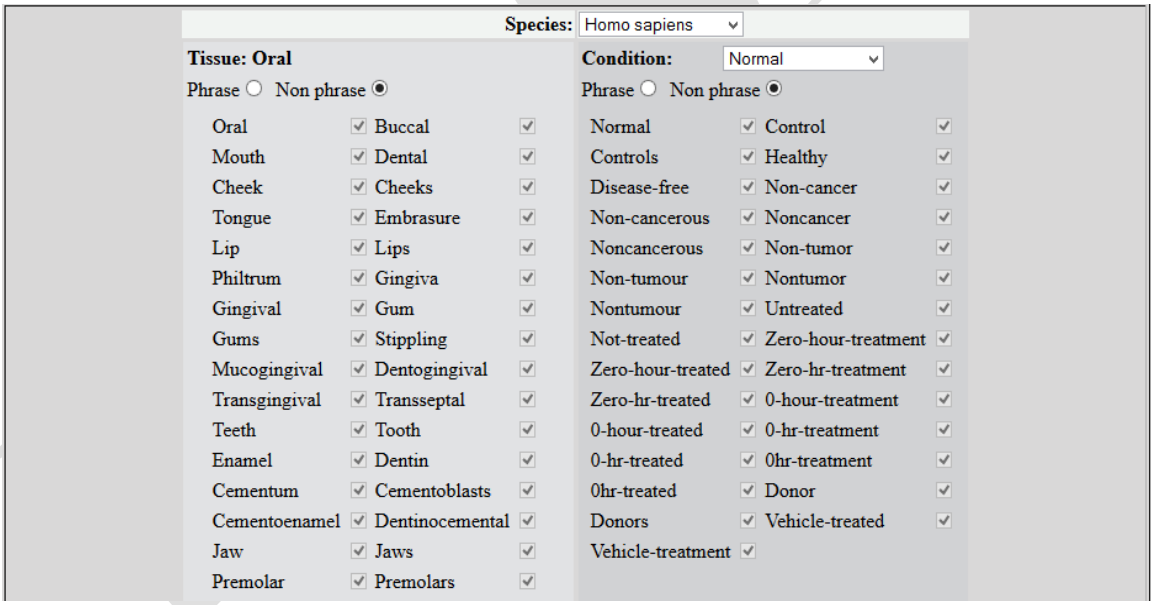
Tissue: Oral				Condition: Cancer			
Phrase ○ Non phrase ●				Phrase ○ Non phrase ●			
Oral	✓	Buccal	✓	Cancer	✓	Cancers	✓
Mouth	✓	Dental	✓	Cancerous	✓	Precancerous	✓
Cheek	✓	Cheeks	✓	Carcinoma	✓	Carcinomas	✓
Tongue	✓	Embrasure	✓	Sarcoma	✓	Sarcomas	✓
Lip	✓	Lips	✓	Carcinosarcoma	✓	Carcinosarcomas	✓
Philtrum	✓	Gingiva	✓	Tumor	✓	Tumors	✓
Gingival	✓	Gum	✓	Tumour	✓	Tumours	✓
Gums	✓	Stippling	✓	Neoplasm	✓	Neoplasms	✓
Mucogingival	✓	Dentogingival	✓	Neoplastic	✓	Neoplasia	✓
Transgingival	✓	Transseptal	✓	Metastasis	✓	Metastases	✓
Teeth	✓	Tooth	✓	Metastatic	✓	Metastasize	✓
Enamel	✓	Dentin	✓	Metastasized	✓	Metastasise	✓
Cementum	✓	Cementoblasts	✓	Metastasised	✓	Malignant	✓
Cementoenamel	✓	Dentinocemental	✓	Malignancy	✓	Malignancies	✓
Jaw	✓	Jaws	✓	Adenocarcinoma	✓	Adenocarcinomas	✓
Premolar	✓	Premolars	✓	Carcinogenic	✓	Carcinogenesis	✓
Molar	✓	Molars	✓	Tumorigenic	✓	Tumourigenic	✓
Canine	✓	Canines	✓	Lesion	✓	Lesions	✓
Incisor	✓	Incisors	✓	Blastoma	✓	Blastomas	✓
Cuspid	✓	Cuspids	✓	Lymphoepithelioma-like	✓	Hemangioendothelioma	✓
Bicuspid	✓	Bicuspids	✓	Hemangioendotheliomas	✓	Mesothelioma	✓
Periodontial	✓	Retromolar	✓	Angiosarcomas	✓	Hemangiosarcoma	✓
Odontoblast	✓	Odontoblasts	✓	Hemangiosarcomas	✓	Lymphangiosarcoma	✓
Cusp	✓	Cusps	✓	Lymphangiosarcomas	✓	Glomangiosarcoma	✓
Cingulum	✓	Mammelons	✓	Glomangiosarcomas	✓	Fibrosarcoma	✓
Mammelon	✓	Genioglossus	✓	Fibrosarcomas	✓	SCC	✓
Hyoglossus	✓	Styloglossus	✓	SCCs	✓	ADC	✓
Palatoglossus	✓	Verticalis	✓	ADCs	✓	SqCC	✓
Transversus	✓	Vermilion	✓	SqCCs	✓	Adenoid-cystic	✓
Cupid's	✓	Cupids	✓	AdCC	✓	AdCCs	✓
Cupid	✓	Procheilon	✓	Adenocyst	✓	Adenocysts	✓
Labial	✓	Labium	✓	Adenocystic	✓	Adenoidcystic	✓
Labii	✓	Orifice	✓	ACC	✓	ACCs	✓
				Mucoepidermoid	✓	Signet	✓

Fig.1: Oral cancer tissue synonyms and oral related terms used to query public repositories (GEO and ArrayExpress)



Species: Homo sapiens							
Tissue: Oral				Condition: Normal			
Phrase ○ Non phrase ●				Phrase ○ Non phrase ●			
Oral	✓	Buccal	✓	Normal	✓	Control	✓
Mouth	✓	Dental	✓	Controls	✓	Healthy	✓
Cheek	✓	Cheeks	✓	Disease-free	✓	Non-cancer	✓
Tongue	✓	Embrasure	✓	Non-cancerous	✓	Noncancer	✓
Lip	✓	Lips	✓	Noncancerous	✓	Non-tumor	✓
Philtrum	✓	Gingiva	✓	Non-tumour	✓	Nontumor	✓
Gingival	✓	Gum	✓	Nontumour	✓	Untreated	✓
Gums	✓	Stippling	✓	Not-treated	✓	Zero-hour-treatment	✓
Mucogingival	✓	Dentogingival	✓	Zero-hour-treated	✓	Zero-hr-treatment	✓
Transgingival	✓	Transseptal	✓	Zero-hr-treated	✓	0-hour-treatment	✓
Teeth	✓	Tooth	✓	0-hour-treated	✓	0-hr-treatment	✓
Enamel	✓	Dentin	✓	0-hr-treated	✓	0hr-treatment	✓
Cementum	✓	Cementoblasts	✓	0hr-treated	✓	Donor	✓
Cementoenamel	✓	Dentinocemental	✓	Donors	✓	Vehicle-treated	✓
Jaw	✓	Jaws	✓	Vehicle-treatment	✓		
Premolar	✓	Premolars	✓				

Fig. 2: Normal oral tissue synonyms and oral related terms used to query public repositories (GEO and ArrayExpress)

3. Manual curation:

Data validation demands precision. Validation of samples requires a set of rules and regulations to be framed and followed strictly, to avoid unhealthy data which might bias the results. For the current study SOP (Standard Operating Procedure) was provided, carefully framed by a team of researchers at IBAB, Bangalore to validate the samples. The SOP describes the different conditions for selection of valid datasets for stomach tissue and also

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categorizing samples into different categories for normal and cancer condition as shown in the Table 1. Normal condition is further categorized into normal, maybe normal and maybe adult.

Sl.No	Condition	Description
1	**Normal**	Tissue/cells/commercial-sample/cell line/cultured cells, from an adult subject with no evidence of abnormality. **It should NOT BE:** tissue/cells/commercial-sample/cell line/cultured cells, with no age specification; any treated tissue/cells/commercial-sample/cell line/cultured cells [e.g., hormone, chemical, radiation, knockout, surgical (not the surgery done for collection of sample itself), vehicle, placebo, alterations in diet/ habits/ environment/ lifestyle/ experiment]; normal cells/tissue adjacent to tumor; pooled sample/RNA with multiple tissues including the tissue of interest (e.g., "a pool of 10 tissues including lung" should not be included under lung or any other single tissue).
2	**Maybe adult**	Tissue/cells/commercial-sample/ cell line/cultured cells, from a subject with no age specification, and no evidence of abnormality. **It should NOT BE:** any treated tissue/cells/commercial-sample/cell line/cultured cells [e.g., hormone, chemical, radiation, knockout, surgical (not the surgery done for collection of sample itself), vehicle, placebo, alterations in diet/ habits/ environment/ lifestyle/ experiment], normal cells/tissue adjacent to tumor; tissue with known developmental stages; pooled sample/RNA with multiple tissues including the tissue of interest (e.g., "a pool of 10 tissues including lung" should not be included under lung or any other single tissue).
3	**Maybe normal**	Tissue/cells/commercial-sample/cells/cell line/cultured cells, from an adult subject with an evidence of suspicion of variation to normal state [vehicle/placebo/surgical (not the surgery done for collection of sample itself) treatment, normal tissue adjacent to tumor tissue/cells, subject with other tissue disorders (e.g., normal lung tissue from subject with prostate cancer)]. **It should NOT BE:** tissue/cells/commercial-sample/cell line/cultured cells, with no age specification; any treated tissue/commercial-sample/cell line/cultured cells [e.g., hormone, chemical, radiation, knockout, alterations in diet/ habits/ environment/ lifestyle/ experiment]; pooled sample/RNA with multiple tissues including the tissue of interest (e.g., "a pool of 10 tissues including lung" should not be included under lung or any other single tissue).
4	**Cancer**	Cancer tissue/cells/commercial-sample/cell line/ cultured cells. **It should NOT BE:** benign tumor; tissue/cells/commercial-sample/cell line/ cultured cells with no evidence of malignancy (samples with no indication of either benign or malignant status); any treated tissue [e.g., hormone, chemical, radiation, surgical (not the surgery done for collection of sample itself), vehicle, placebo, alterations in diet/ habitsnote3/ environment/ lifestyle/ experiment]; metastatic tissue/cells from a different origin, other than tissue of interest (e.g., metastasized tissue/cells originating from breast cancer/prostate cancer); cancer tissue/cells metastasized to any other tissue (e.g., metastasized lung cancer tissue/cells taken from prostate); pooled sample/RNA with multiple tissues including the tissue of interest (e.g., "a pool of 10 cancer/normal/cancer & normal tissues including lung cancer" should not be included under lung cancer or any other cancer or normal tissue).

Table 1: Conditions in SOP (Standard operating procedure) used for validating the datasets

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4. Identification of crucial genes:

A tool with novel algorithm [2] at IBAB, accepts the tissue name, condition for which the datasets are to be Meta analysed, and the species for which the proposed work should be carried out. The crucial genes associated with the cancer and normal condition of the oral tissue are derived using this algorithm. Based on the scoring method, the algorithm gives reliability scores for all the genes transcribed, and not transcribed during the study. The algorithm also gives the number of samples, number of studies, EST count, from which the score has been derived. The algorithm gives two sets of genes, first a list of transcribed genes, with reliability score and second list of dormant genes, which are basically not expressed in the tissue along with the condition (Normal and cancerous).

III. RESULTS

1. Identification of data sets from public repositories (GEO and ArrayExpress):

The query set prepared from oral cancer synonyms and related terms using relational expression, was used to query GEO and ArrayExpress. Fig 3 gives the list of datasets obtained for oral cancer. This yielded 1164 samples (hits), from 44 studies in GEO and 901 samples (hits) from 18 studies in ArrayExpress, with Affymetrix platform. The same procedure was followed for normal oral tissue. This yielded 511 samples (hits) from 46 studies in GEO and 327 samples (hits) from 10 studies in ArrayExpress, with Affymetrix platform.

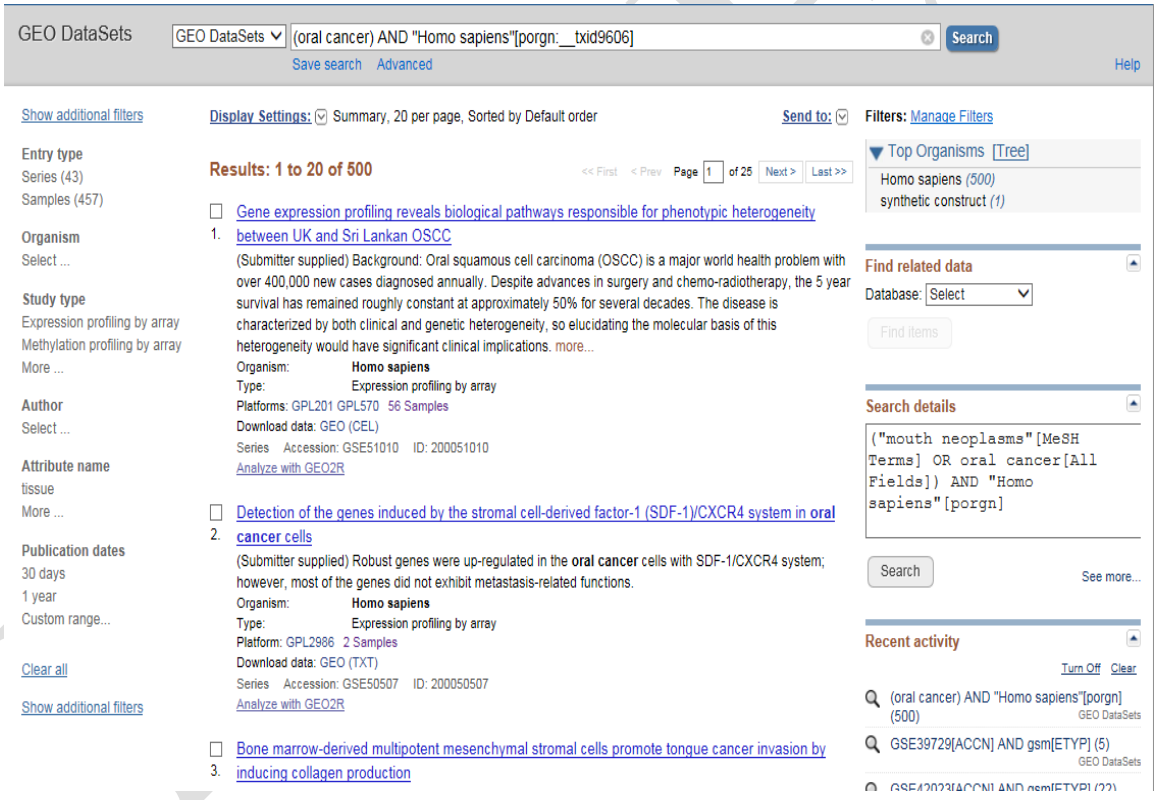

Fig 3: List of data sets obtained for oral cancer

2. Manual curation:

The validation of microarray data is carried out manually following the SOP. The data is recorded. Fig 4 gives the framework of manual curation in excel format.

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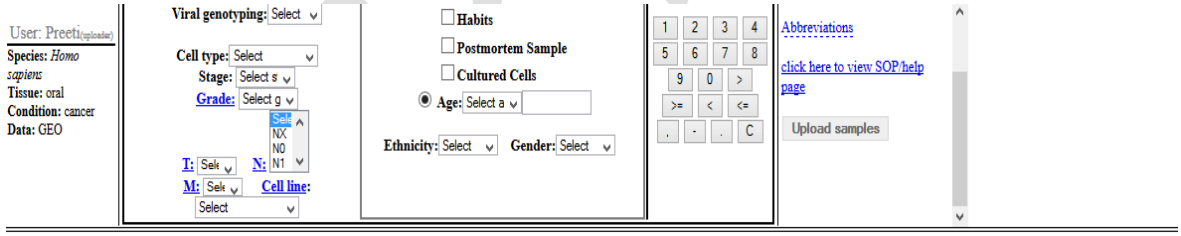
Name of the uploader			Preeti				
Tissue/Condition			Oral cancer				
Date started			17/01/2014				
S.No	GSMs screened	GSMs uploaded	Condition(s) to be marked for uploading	Screening status: Releveant; Completely irrelevant (1 reason); Not for current priority: Secondary tumor; Treatment; Others (keywords: e.g., pooled sample)	Uploaded condition(s) [copy from the uploading form]	Any additional comments	
15	GSM1049164	GSM1049164	Oral:Oral cancer:--:Tstage:2:--:male:--:65years:--	Releveant			
16	GSM1049169			Not for current priority: Treatment			
17	GSM1049171			Not for current priority: Treatment			
18	GSM1049181			Not for current priority: Treatment			
19	GSM1068066	GSM1068066	Oral:Oral cancer- sproadic Burkitt lymphoma - nc	Releveant			
20	GSM1068068	GSM1068068	Oral:Oral cancer- sproadic Burkitt lymphoma- no	Releveant			
21	GSM1072427			Not for current priority: Treatment			
22	GSM125132			Completely irrelevant: Breast cancer			
23	GSM125136			Completely irrelevant: Breast cancer			
24	GSM151693	GSM151693	Oral:Oral cancer- OSCC:--:CAL 27:--:G3:--	Releveant			
25	GSM155673	GSM155673	Oral:Head and neck cancer:--:T stage-IV:--:Male:	Releveant			
26	GSM155701	GSM155701	Oral:Head and neck cancer:--:--:Male:--:67 years	Releveant			
27	GSM155704	GSM155704	Oral:Head and neck cancer:--:--:Male:--:55 years	Releveant			
28	GSM190622	GSM190622	Oral:Buccal carcinoma:--:SqCC/Y1:--	Releveant			
29	GSM198891			Completely irrelevant: ovarian carcinoma			
30	GSM198900			Completely irrelevant: ovarian carcinoma			
31	GSM198902			Completely irrelevant: ovarian carcinoma			
32	GSM248662	GSM248662	Oral:Oral cancer- OTSCC:--:pN0:--:Male:--:67 yea	Releveant			
33	GSM248663	GSM248663	Oral:Oral cancer- OTSCC:--:pN0:--:Male:--:41 yea	Releveant			
34	GSM250938			Completely irrelevant: Acute Monocytic Leukemia			
35	GSM250939			Completely irrelevant: Acute Monocytic Leukemia			

Fig 4: Framework of manual curation

After manual curation, sample description is entered into the pipeline. After registration and login process is completed, a query interface page is displayed wherein the type of condition is selected (cancer or normal). Next, sample interface page is displayed. Here, their respective characteristics are selected from the drop down menu provided in the interface. Then these samples are uploaded by clicking the upload samples button as shown in the Fig. 5



Most relevant samples

SI	GSM accn	Characteristics	Source name	Title	Description	Uploaded
1	GSM1020099	tissue type: HPV-negative Oral squamous cell Carcinoma (OSCC) Tumor stage: I/II age: 40-49 Sex: F vital: Alive fu time: 62.85 treatment: uni-modality	HPV-negative OSCC patient		HPV-negative OSCC #1	Uploaded by Preeti. Condition : Oral:Oral cancer - Carcinoma - Squamous cell: --:HPV-: --:I/II: --: --: --: --: --:Female: --:40-49Years
2	GSM1020100	tissue type: HPV-negative Oral squamous cell Carcinoma (OSCC) Tumor stage: I/II age: 50-59 Sex: M vital: Dead-Oral ca fu time: 55.66 treatment: uni-modality	HPV-negative OSCC patient		HPV-negative OSCC #3	Uploaded by Preeti. Condition : Oral:Oral cancer - Carcinoma - Squamous cell: --:HPV-: --:I/II: --: --: --: --: --:Male: --:50-59Years

Fig. 5: Sample uploading page for oral cancer

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3. Identification of crucial genes and candidate biomarker:

Fig 6 shows the genes which are transcribed with high reliability score (RS) in oral cancer condition and Fig 7 shows the genes which are transcribed with high reliability score (RS) in normal oral condition.

Gene	RS	Gene	RS
CRIP2	259.76	TLR10	246.41
FXYD6	259.64	EQTN	245.66
POFUT1	259.51	730034	245.5
KIAA1984	259.23	TMEM178A	245.19
TMEM98	258.88	SYCP3	245.07
DNAJC18	258.34	DPF1	245.07
ZNF808	257.88	PAX3	244.7
EIF3LP3	257.79	LINC00523	244.6
PGBD1	257.23	GCSAM	244.56
LINC00165	256.93	PTCRA	244.4
SMIM4	256.86	PADI2	244.38
TBC1D17	256.59	PF4V1	244.12
POP1	256.08	TMEM156	243.97
ZNF141	255.76	BPIFA1	243.67
BCL7A	255.37	ETV4	243.45
KIAA1324	255.12	DUSP13	242.94
CCDC121	254.88	CDH8	242.22
UTP20	254.56	WNT3	241.94
SUSD4	254.54	NLRP7	240.61
SLC4A5	254.00	RELL2	239.91

Fig 6: Screen shot of the genes involved in the oral cancer with their reliability score (RS).

Gene	RS	Gene	RS
CYP24A1	504.49	GPR82	468.91
LRRN3	504.48	NOC4L	468.77
PLA2G15	504.33	POFUT1	468.06
ALG1	504.05	SEPT3	467.96
ALKBH4	503.96	C9orf135	467.92
CNTRL	503.95	CUZD1	467.79
KLHL3	503.62	C1orf168	467.75
LOC145474	503.48	ATP1B4	467.69
CASP10	503.18	BMP5	467.62
ATP6V0A4	502.86	LOC339468	467.47
SIGLEC6	502.44	RAB43	466.96
ANK1	502.23	CCDC136	466.52
PRDM15	501.92	SCN9A	466.17
KLHDC7B	501.90	ZNF385C	466.1
TBL3	501.70	ZNF609	465.86
PTTG3P	501.30	MRAP	465.76
DPH7	501.18	THEM6	465.76
TMPRSS15	500.84	SLC26A10	465.02

Fig 7: Screen shot of the genes involved in the normal oral with their reliability score (RS).

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Once the exclusive genes involved in both normal oral and oral cancer are obtained comparison of these two list is done to identify the candidate biomarker. Identify the genes that are expressed only in cancer condition and not in normal condition. Such genes are identified and listed. The study has identified top 100 candidate biomarkers which are listed in Fig 8 with GeneID and symbol.

Geneid	Symbol	Geneid	Symbol	Geneid	Symbol	Geneid	Symbol
23509	POFUT1	9056	SLC7A7	403314	APOBEC4	2921	CXCL3
162417	NAGS	2671	GFER	169714	QSOX2	7472	WNT2
3204	HOXA7	23555	TSPAN15	9260	PDLIM7	221336	BEND6
3202	HOXA5	338324	S100A7A	221150	SKA3	113278	SLC52A3
6857	SYT1	54972	TMEM132A	1993	ELAVL2	113130	CDCA5
2627	GATA6	93444	LOC93444	401237	LINC00340	389792	IER5L
169792	GLIS3	8564	KMO	64108	RTP4	220441	RNF152
25907	TMEM158	55210	ATAD3A	5155	PDGFB	128872	HMGB3P1
10609	LEPREL4	64078	SLC28A3	10460	TACC3	30850	CDR2L
1265	CNN2	8530	CST7	1889	ECE1	80117	ARL14
79783	C7orf10	2026	ENO2	81570	CLPB	93109	TMEM44
9119	KRT75	8216	LZTR1	3604	TNFRSF9	29985	SLC39A3
54821	ERCC6L	5918	RARRES1	84740	AFAP1-AS1	84296	GINS4
578	BAK1	51339	DACT1	112869	CCDC101	115362	GBP5
9047	SH2D2A	11247	NXPH4	26164	MTG2	23245	ASTN2
84517	ACTRT3	26	AOC1	646903	LOC646903	9156	EXO1
51804	SIX4	6351	CCL4	26256	CABYR	80301	PLEKHO2
1852	DUSP9	995	CDC25C	2185	PTK2B	6336	SCN10A
79649	MAP7D3	7857	SCG2	80304	C2orf44	8463	TEAD2
7138	TNNT1	80210	ARMC9	121355	GTSF1	649446	DLGAP1-AS1
150726	FBXO41	705	BYSL	85352	KIAA1644	84989	JMJD1C-AS1
10195	ALG3	84868	HAVCR2	101	ADAM8	144097	C11orf84
150468	CKAP2L	29886	SNX8	55143	CDCA8	91523	PCED1B
6530	SLC6A2	256227	STEAP1B	29065	ASAP1-IT1	338620	LOC338620
3200	HOXA3	9489	PGS1	7226	TRPM2	875	CBS

Fig 8: List of top 100 candidate biomarkers

IV. CONCLUSION

Gene expression data from public repositories (GEO and ArrayExpress) was compiled to apply a meta-analysis algorithm to compare expression of the genes across studies, identify differentially expressed genes across normal oral tissue and oral cancer. Genes which show differential expression with high reliability score in cancer condition were identified. POFUT1, NAGS, HOXA7etc. are the genes which show high variation in transcription in cancer condition.Comparison of those genes from normal and cancerous oral tissue was done to identify potential candidate Biomarkers.Further insight into these markers will yield the better prognosis, diagnosis and treatment of the disease analysis. Functional analysis like pathways and protein-protein interactions can also be carried out which helps in better understanding of genes at system level.

V. ACKNOWLEDGEMENT

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BIOGRAPHY

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