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Dataset of differential gene expression between total normal human thyroid and histologically normal thyroid adjacent to papillary thyroid carcinoma



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ABSTRACT

This article contains further data and information from our published manuscript [1]. We aim to identify significant transcriptome alterations of total normal human thyroid vs. histologically normal thyroid adjacent to papillary thyroid carcinoma. We performed a systematic meta-analysis of all the available gene expression profiles for the whole organ also collecting gene expression data for the normal thyroid adjacent to papillary thyroid carcinoma. A differential quantitative transcriptome reference map was generated by using TRAM (Transcriptome Mapper) software able to combine, normalize and integrate a total of 35 datasets from total normal thyroid and 40 datasets from histologically normal thyroid adjacent to papillary thyroid carcinoma from different sources. This analysis identified genes and genome segments that significantly discriminated the two groups of samples. Differentially expressed genes were grouped and enrichment function analyses were performed identifying the main features of the differentially expressed genes between total normal thyroid and histologically normal thyroid adjacent to papillary thyroid carcinoma. The search for housekeeping genes retrieved 414 loci.

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Specifications table

Subject area	Biology
More specific subject area	Genomics, bioinformatics
Type of data	Table, figure
How data was acquired	Microarray data repository: Gene Expression Omnibus (GEO) provided by the National Center for Biotechnology Information (NCBI) and Array Express provided by the European Bioinformatics Institute (EBI)
Data format	Raw data
Experimental factors	Database search, dataset selection, TRAM (Transcriptome Mapper) analysis
Experimental features	Analysis of gene expression data by TRAM software; enrichment function analysis
Data source location	Data sources are public database entries and are listed in the Supplementary Table 1 Meta-analysis results have been obtained in Bologna, Italy, DIMES Department at University of Bologna
Data accessibility	Data are with this article
Related research article	[1]

Value of the data

- The meta-analysis performed in this study provides a differential reference expression value for 24,699 known, mapped transcripts, common to total and histologically normal thyroid adjacent to papillary thyroid carcinoma, and a view of the genomic regions with altered expression by a chromosomal segment representation.
- The histologically normal thyroid adjacent to papillary thyroid carcinoma is often used as normal control in thyroid tumor studies. Differentially expressed genes identified in this comparison provide a molecular view of the behavior of normal tissue adjacent to papillary thyroid carcinoma vs. total normal thyroid tissue and might yield biological insight about the biology of thyroid tumors.
- Enrichment function analysis performed for the gene groups classified on their gene expression ratio intervals identified interesting molecular functions of genes which are under-expressed in total normal thyroid and on the contrary have a high expression level in the normal thyroid adjacent to papillary thyroid carcinoma.
- The housekeeping gene search useful for gene expression studies on thyroid tissue retrieved 414 loci, different from those retrieved in the total normal thyroid except for seven genes as *ACTG1*, *BLOC1S2*, *DIABLO*, *OCIAD2*, *GTPBP6*, *EIF2B2*, *AKR1B1*.
- The quantitative reference values of the enzyme mRNAs might be used in metabolic network models for the validation of hypotheses about the relationships among mRNA levels, corresponding enzymatic proteins and the quantities of their substrates or products obtained by metabolome experiments.

1. Data*1.1. Database searching and database building*

The systematic search performed in gene expression data repositories retrieved 35 datasets from 10 microarray experiments on the total normal human thyroid and 40 datasets from 4 microarray experiments on the histologically normal thyroid adjacent to papillary thyroid carcinoma. The 35 datasets of the total thyroid were already used in Ref. [\[1\]](#). Sample identifiers (GEO and EBI ID numbers) and main sample features are listed in the [Supplementary Table 1](#).

1.2. Total normal thyroid vs. histologically normal thyroid adjacent to papillary thyroid carcinoma transcriptome map

The differential transcriptome map was performed integrating 35 datasets from total normal human thyroid [\[1\]](#) and 40 datasets from histologically normal thyroid adjacent to papillary thyroid carcinoma. The 35 datasets included in the Pool A folder provided reference gene expression values for 25,574 loci coming from 947,816 data points (data from Ref. [\[1\]](#) updated after the analysis with TRAM 1.3 software version), the 40 datasets included in the Pool B folder provided reference gene expression values for 24,699 loci ([Supplementary Table 2](#)) coming from 1,917,840 data points, and the differential

transcriptome map obtained provided reference gene expression values for 24,699 loci ([Supplementary Table 3](#)) common to both pools ([Fig. 1](#)).

At single gene level, the known gene *HTN3*, encoding for histatin 3, has the highest gene expression ratio (360.91) followed by *STATH*, encoding for statherin (gene expression ratio=324.27), *HTN1*, encoding for histatin 1 (gene expression ratio=240.67), *SMR3B* encoding for submaxillary gland androgen regulated protein 3B (gene expression ratio=128.73) and *ZG16B* encoding for zymogen granule protein 16B (gene expression ratio=116.25) ([Table 1](#)). These 5 genes are over-expressed in total normal thyroid and have a very low expression value in the histologically normal thyroid adjacent to papillary thyroid carcinoma ([Table 1](#)). Fifty genes have a gene expression ratio between 10 and 100 ([Table 1](#)).

The genome segment that has the highest statistically significant expression value is on chromosome 4 (4q13.3) ([Table 2](#)) including the over-expressed known genes (*STATH*, *HTN1*, *HTN3*, *SMR3A*, *SMR3B*, *MUC7*). There are no significantly under-expressed segments.

1.3. Functional enrichment analysis

The results of functional enrichment analysis, performed by “ToppFun” from the “ToppGene Suite” Gene Ontology tool, of over- and under-expressed genes (with expression ratios between 1.30 and 10.00 and 0.69 and 0, respectively) in the total normal thyroid vs. histologically normal thyroid adjacent to papillary thyroid carcinoma differential transcriptome map, are shown in [Table 3](#) and [Table 4](#). Input gene lists included 5,012 out of 6,686 over-expressed and 4,258 out of 4,854 under-expressed genes resulted following exclusion of all the EST clusters ([Supplementary Table 3](#)).

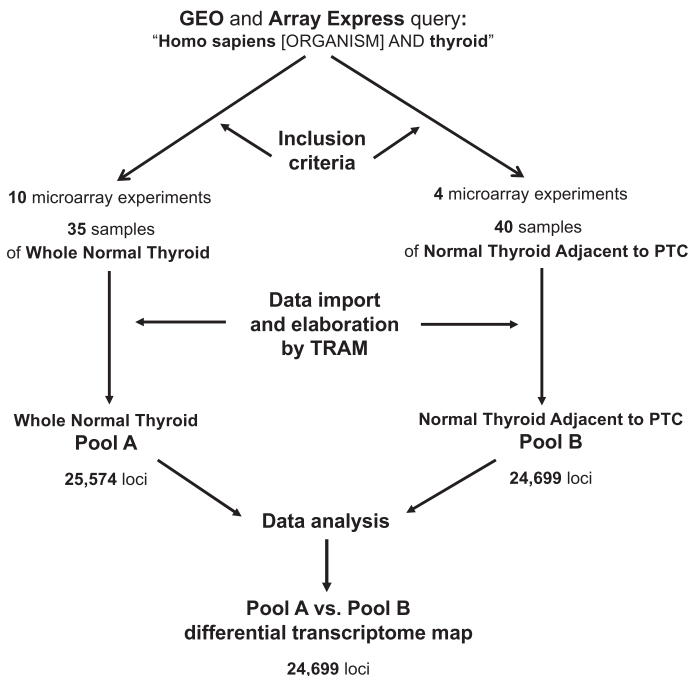


Fig. 1. Meta-analysis study design. A search for thyroid tissue gene expression profiles was performed on the online databases GEO and Array Express. It was followed by the selection of experiments and samples according to the inclusion and exclusion criteria, the import and elaboration of data by TRAM software, and the generation and analysis of the whole normal thyroid, histologically normal thyroid adjacent to papillary thyroid carcinoma as well as of the whole normal thyroid vs. histologically normal thyroid adjacent to papillary thyroid carcinoma transcriptome maps. PTC: papillary thyroid carcinoma.

Table 1

List of loci of the differential transcriptome map between whole normal thyroid (Pool A) and histologically normal thyroid adjacent to papillary thyroid carcinoma (Pool B). Loci are sorted in descending order of expression ratio (Ratio A/B). Chr: chromosome. SD: standard deviation. N/A: not available in the "NCBI Gene" database (<http://www.ncbi.nlm.nih.gov/gene>) when the analysis was performed.

Gene name	Chr	Location	Value A	Value B	Ratio A/B	Data Points A	Data Points B	SD as % of Expression A	SD as % of Expression B
Gene expression ratio >100									
<i>HTN3</i>	chr4	4q13.3	1,876.98	5.20	360.91	25	40	130.02	10.20
<i>STATH</i>	chr4	4q13.3	2,224.34	6.86	324.27	33	40	150.28	30.81
<i>HTN1</i>	chr4	4q13.3	2,039.62	8.47	240.67	31	40	155.53	48.36
<i>SMR3B</i>	chr4	4q13.3	1,444.86	11.22	128.73	28	40	137.51	56.34
<i>ZG16B</i>	chr16	16p13.3	1,779.84	15.31	116.25	16	40	110.20	58.66
Gene expression ratio >10 and <100									
<i>LINC01521</i>	chr22	22q12.2	1,034.91	11.42	90.65	15	40	260.89	77.62
<i>PTH</i>	chr11	11p15.3	343.99	5.10	67.45	38	40	126.93	24.13
<i>MUC7</i>	chr4	4q13.3	495.47	8.58	57.72	53	80	260.31	54.80
<i>NACA2</i>	chr17	17q23.2	544.38	9.80	55.53	29	40	143.02	79.12
<i>PRH1</i>	chr12	12p13.2	1,346.40	26.14	51.51	40	80	183.58	77.46
<i>HBD</i>	chr11	11p15.4	1,016.65	21.48	47.33	49	40	210.97	54.06
<i>SMR3A</i>	chr4	4q13.3	318.57	7.86	40.53	40	80	220.10	33.07
<i>KRT13</i>	chr17	17q21.2	332.61	9.54	34.86	30	40	478.35	40.15
<i>LINC01234</i>	chr12	12q24.13	214.17	6.52	32.85	24	80	325.50	31.97
<i>CST4</i>	chr20	20p11.21	791.16	31.20	25.35	21	40	191.60	29.20
<i>FOXM1</i>	chr12	12p13.33	291.00	13.33	21.82	33	40	395.21	29.83
<i>CST1</i>	chr20	20p11.21	206.18	9.48	21.74	31	40	208.13	30.56
<i>MGC16025</i>	chr2	2q37.3	149.46	7.63	19.59	15	40	245.74	35.23
<i>GBP4</i>	chr1	1p22.2	542.60	28.00	19.38	39	80	408.89	59.18
<i>TAS2R1</i>	chr5	5p15.31	350.21	18.07	19.38	31	40	408.60	21.54
<i>HCAR3</i>	chr12	12q24.31	285.79	15.54	18.39	22	40	309.92	55.06
<i>GABRD</i>	chr1	1p36.33	278.26	15.72	17.70	47	80	475.42	54.59
<i>PPIAL4A</i>	chr1	1p11.2	104.49	6.03	17.34	21	40	231.22	44.18
<i>LINC02078</i>	chr17	17q25.3	170.77	10.00	17.08	13	40	227.57	31.84
<i>BPIFB2</i>	chr20	20q11.21	290.54	17.27	16.82	26	40	275.56	35.69
Hs.649237	chr16	N/A	393.84	24.42	16.13	11	40	41.67	64.68
<i>PIP</i>	chr7	7q34	360.81	22.48	16.05	35	40	187.82	49.66
<i>AKAP6</i>	chr14	14q12	191.95	12.63	15.20	51	80	650.30	48.25
<i>RHOC</i>	chr1	1p13.2	180.95	13.47	13.44	24	40	103.28	35.67
<i>CCDC103</i>	chr17	17q21.31	463.69	34.98	13.26	13	40	231.41	20.32
<i>CRCT1</i>	chr1	1q21.3	92.27	7.04	13.10	31	40	493.70	29.20
<i>SBSN</i>	chr19	19q13.12	187.27	14.41	13.00	22	40	414.04	53.84
<i>NPHS2</i>	chr1	1q25.2	275.83	21.32	12.93	31	40	382.71	63.61
<i>KRT6A</i>	chr12	12q13.13	105.18	8.35	12.60	50	80	576.30	55.43
<i>BPIFA2</i>	chr20	20q11.21	236.54	18.92	12.50	26	40	133.55	48.56
<i>AGXT</i>	chr2	2q37.3	132.65	10.75	12.34	73	120	548.67	44.40
<i>CNFN</i>	chr19	19q13.2	165.81	13.79	12.02	26	40	355.33	18.49
<i>CRISP3</i>	chr6	6p12.3	63.55	5.30	11.98	33	40	158.98	20.82
<i>CEP19</i>	chr3	3q29	277.20	23.20	11.95	45	80	348.49	62.90
<i>KLF8</i>	chrX	Xp11.21	290.06	24.35	11.91	47	80	473.99	83.04
<i>PLA2G1B</i>	chr12	12q24.31	93.86	7.99	11.74	35	40	153.96	38.29
<i>KIR3DX1</i>	chr19	19q13.42	190.23	16.53	11.51	53	80	446.28	61.41
<i>SRSR1C1</i>	chr6	6p21.33	154.59	13.49	11.46	23	40	301.22	22.86
<i>KRT4</i>	chr12	12q13.13	191.37	16.96	11.28	53	80	621.34	64.17
<i>ALPP</i>	chr2	2q37.1	209.50	18.93	11.07	51	80	467.86	70.41
<i>SPRR3</i>	chr1	1q21.3	155.41	14.05	11.06	52	80	455.13	43.64
<i>PRR4</i>	chr12	12p13.2	233.81	21.42	10.92	33	40	169.40	26.73
<i>FOXL2</i>	chr3	3q22.3	99.01	9.25	10.70	33	40	211.90	53.22
<i>DMRTC2</i>	chr19	19q13.2	57.74	5.47	10.56	26	40	174.35	16.37
<i>DNMT3L</i>	chr21	21q22.3	101.54	9.68	10.49	31	40	357.89	28.81
<i>POLE</i>	chr12	12q24.33	328.71	31.44	10.46	49	40	417.34	25.33
<i>GALNT4</i>	chr12	12q21.33	376.31	36.31	10.36	36	80	411.01	74.50
<i>MTPN</i>	chr7	7q33	256.91	24.88	10.33	26	40	127.05	38.70
<i>C9</i>	chr5	5p13.1	49.48	4.82	10.26	33	40	307.49	14.30
<i>GPR88</i>	chr1	1p21.2	53.33	5.25	10.17	33	40	249.83	13.38

Table 2

The genomic segments significantly over-expressed in the total normal thyroid (Pool A) vs. histologically normal thyroid adjacent to papillary thyroid carcinoma (Pool B) differential transcriptome map. Over-expressed genes are in bold, under-expressed genes are with an asterisk and in bold. Under-expressed genomic segments were not found.

Chr and location	Segment start	Segment end	Value A/B	q-value	Genes in the segment
chr4 (4q13.3)	70,000,001	70,500,000	105.52	0.00000017	STATH HTN3 HTN1 MR3A SMR3B MUC7
chr4 (4q13.3)	70,250,001	70,750,000	21.34	0.00201816	SMR3A SMR3B MUC7 UTP3*
chr12 (12p13.2)	11,000,001	11,500,000	9.31	0.00214630	PRH1 PRB3 PRB4
chr20 (20p11.21)	23,500,001	24,000,000	6.99	0.00000413	CST3 CST4 CST1 CST2 CST5
chr12 (12p13.2)	10,750,001	11,250,000	6.05	0.00335694	TAS2R10 PRR4 PRH1
chr16 (16q23.1-q23.2)	78,500,001	79,000,000	4.50	0.00024953	Hs.649237 Hs.648714 Hs.649874
chr17 (17q21.2)	41,250,001	41,750,000	3.61	0.00021980	KRT31 KRT35 KRT13 KRT15 KRT14
chr1 (1q21.3)	152,250,001	152,750,000	3.44	0.00113717	KRNN CRCT1 LCE2B
chr1 (1q21.3)	153,000,001	153,500,000	3.15	0.00004193	SPRR3 SPRR1B PGLYRP3 S100A9 S100A12
chrX (Xq13.2)	74,000,001	74,500,000	2.88	0.00011566	Hs.720466 FTX Hs.607917 Hs.625698
chr17 (17q21.2)	41,000,001	41,500,000	2.51	0.00003900	KRTAP1-5 KRTAP4-6 KRTAP4-4 KRTAP4-1 KRTAP9-3 KRT31 KRT35
chr17 (17q12.2)	40,750,001	41,250,000	2.51	0.00016288	KRTAP3-2 KRTAP1-5 KRTAP4-6 KRTAP4-4 KRTAP4-1 KRTAP9-3
chr11 (11q14.1)	85,750,001	86,250,000	2.15	0.00045054	Hs.658368 Hs.658335 Hs.656225
chr19 (19q13.33)	49,750,001	50,250,000	1.98	0.01225630	AKT1S1 TBC1D17 ATF5

1.4. Housekeeping gene search

In the histologically normal thyroid adjacent to papillary thyroid carcinoma transcriptome map, the search for housekeeping genes with the described criteria (Methods section) retrieved 414 loci, including the known genes *RPL41*, and *TG*, encoding for ribosomal protein L41 and thyroglobulin, respectively, having low standard deviation (SD), the highest expression values and a high number of data points ($n=40$) (Table 5). This search did not give the same results of total normal thyroid transcriptome map (see Table 4 [1]). The two transcriptome maps have in common only seven genes: *ACTG1*, *BLOC1S2*, *DIABLO*, *OCIAD2*, *GTPBP6*, *EIF2B2*, *AKR1B1*.

2. Experimental design, materials and methods

2.1. Database search and selection

Gene expression data repositories were systematically searched for any single human thyroid sample available from subjects explicitly stated as “healthy” or “normal” as previously described [1]. The criteria for inclusion or exclusion in the analysis of each retrieved dataset were as previously described [2]. In addition, datasets from histologically normal thyroid adjacent to papillary thyroid carcinoma were collected when available in the experiments retrieved as described.

2.2. TRAM analysis

TRAM software [3] allows the import, decoding of probe set identifiers to gene symbols via UniGene data parsing [4], integration and normalization of gene expression data recorded in the GEO and ArrayExpress databases or in a custom source in tab-delimited text format for the generation and analysis of transcriptome maps [1,5]. Furthermore, it creates a graphical representation of gene expression profiles along the chromosomes and determines the statistical significance of differential expression of chromosomal segments through hypergeometric distribution [3,6].

The most current version of TRAM has been used (TRAM 1.3, set up on November 11, 2017) [5]. Pool A was composed of whole normal thyroid tissue datasets, while Pool B included histologically normal thyroid adjacent to papillary thyroid carcinoma datasets (Supplementary Table 1), thus allowing the

Table 3

Results of functional enrichment analysis, performed by “ToppFun” from the “ToppGene Suite” Gene Ontology tool, of over-expressed genes (with expression ratios between 1.30 and 10.00) in the total normal thyroid vs. histologically normal thyroid adjacent to papillary thyroid carcinoma differential transcriptome map. The first 10 results of each Gene Ontology categories are listed. Complete results are provided in [Supplementary Table 4](#).

Gene expression ratio 1.30–10.00			
Genes from input	GO: molecular function	Name	p-Value
148	GO:0022838	substrate-specific channel activity	5.76E-09
143	GO:0005216	ion channel activity	1.19E-08
155	GO:0022803	passive transmembrane transporter activity	1.91E-08
154	GO:0015267	channel activity	2.92E-08
294	GO:0022857	transmembrane transporter activity	4.18E-08
114	GO:0022836	gated channel activity	1.02E-07
256	GO:0015075	ion transmembrane transporter activity	1.15E-07
14	GO:0005132	type I interferon receptor binding	2.04E-07
358	GO:0005215	transporter activity	3.17E-07
58	GO:0022834	ligand-gated channel activity	1.52E-06
Genes from input	GO: Biological process	Name	p-Value
15	GO:0033141	positive regulation of peptidyl-serine phosphorylation of STAT protein	1.82E-06
432	GO:0006811	ion transport	2.85E-06
15	GO:0033139	regulation of peptidyl-serine phosphorylation of STAT protein	4.55E-06
19	GO:0002323	natural killer cell activation involved in immune response	9.71E-06
38	GO:0060349	bone morphogenesis	2.38E-05
22	GO:0003009	skeletal muscle contraction	2.51E-05
16	GO:0042501	serine phosphorylation of STAT protein	3.03E-05
21	GO:0033275	actin-myosin filament sliding	3.74E-05
Genes from input	GO: Cellular component	Name	p-Value
422	GO:0005615	extracellular space	1.14E-11
472	GO:0031226	intrinsic component of plasma membrane	4.23E-09
453	GO:0005887	integral component of plasma membrane	1.49E-08
297	GO:0098590	plasma membrane region	1.36E-07
79	GO:0045211	postsynaptic membrane	3.42E-06
97	GO:0097060	synaptic membrane	1.19E-05
339	GO:0098589	membrane region	1.26E-05
91	GO:0034702	ion channel complex	1.15E-04
99	GO:1902495	transmembrane transporter complex	2.26E-04
128	GO:0031012	extracellular matrix	3.14E-04

creation of a differential expression map between the two biological conditions along with the maps for each separate condition. Thresholding of sample expression values equal to or lower than “0” (≤ 0) [2], calculation of the mean expression value for each locus and determination of percentiles of expression for each gene have been previously described [2,3].

The parameters for the “Map” mode graphical representation were chosen based on the gene distribution in human genome [7,8] (window size of 500,000 base pairs or bp and a shift of 250,000 bp). For each segment, its expression value, the over-/under-expression and the statistical significance have been calculated by TRAM as described [3,5].

Apart from gene expression analyses, these data might be used in metabolic network models [9–12] for the validation of hypotheses about the relationships among mRNA levels, corresponding enzymatic proteins and the quantities of their substrates or products obtained by metabolome experiments [13,14].

The data related to the human normal whole thyroid have already been experimentally validated by “Real-Time” reverse transcription polymerase chain reaction obtaining an excellent correlation coefficient ($r=0.93$) between *in vitro* and *in silico* data as previously described [1].

It was not possible to validate the data related to histologically normal thyroid gland adjacent to papillary thyroid carcinoma because commercial RNA of this particular type of tissue is not available,

Table 4

Results of functional enrichment analysis, performed by “ToppFun” from the “ToppGene Suite” Gene Ontology tool, of under-expressed genes (with expression ratios between 0 and 0.69) in the total normal thyroid vs. histologically normal thyroid adjacent to papillary thyroid carcinoma differential transcriptome map.

Gene expression ratio 0.69–0			
Genes from input	GO: molecular function	Name	p-Value
463	GO:0003723	RNA binding	8.64E-16
499	GO:0019899	enzyme binding	8.25E-10
467	GO:0035639	purine ribonucleoside triphosphate binding	6.77E-09
472	GO:0001882	nucleoside binding	7.30E-09
480	GO:0017076	purine nucleotide binding	1.13E-08
469	GO:0001883	purine nucleoside binding	1.17E-08
469	GO:0032549	ribonucleoside binding	1.17E-08
468	GO:0032550	purine ribonucleoside binding	1.31E-08
475	GO:0032555	purine ribonucleotide binding	1.91E-08
478	GO:0032553	ribonucleotide binding	2.33E-08
Genes from input	GO: Biological process	Name	p-Value
274	GO:0032446	protein modification by small protein conjugation	6.27E-13
294	GO:0070647	protein modification by small protein conjugation or removal	1.24E-10
233	GO:0016567	protein ubiquitination	2.16E-10
478	GO:0065003	protein-containing complex assembly	5.47E-10
38	GO:1904667	negative regulation of ubiquitin protein ligase activity	2.40E-09
264	GO:1903047	mitotic cell cycle process	3.45E-09
284	GO:0000278	mitotic cell cycle	4.09E-09
39	GO:0031145	anaphase-promoting complex-dependent catabolic process	4.13E-09
259	GO:0006396	RNA processing	4.70E-09
163	GO:0044772	mitotic cell cycle phase transition	1.06E-08
Genes from input	GO: cellular component	Name	p-Value
483	GO:0005739	mitochondrion	4.47E-14
270	GO:0005730	nucleolus	2.18E-13
225	GO:1990904	ribonucleoprotein complex	3.42E-11
116	GO:0016604	nuclear body	9.51E-08
261	GO:0044429	mitochondrial part	8.96E-07
16	GO:0022624	proteasome accessory complex	1.08E-06
50	GO:0000784	nuclear chromosome, telomeric region	2.84E-06
220	GO:0005768	endosome	3.85E-06
310	GO:0005773	vacuole	4.78E-06
10	GO:0008540	proteasome regulatory particle, base subcomplex	5.08E-06

however experimental validations of the results obtained in several previous studies [1,2] show that the results provided by the TRAM tool were highly reliable [15].

2.3. Functional enrichment analysis

An enrichment function analysis was performed for three arbitrarily chosen intervals of ratio of the mean gene expression values: expression ratio close to one (0.70–1.29) implying that the genes are not differentially expressed between histologically normal thyroid adjacent to papillary thyroid carcinoma and total thyroid, expression ratio ≥ 1.30 (1.30–10.00) and expression ratio < 0.7 (0.69–0). The first interval includes 13,104 loci, the second 6,686, the third 4,854, respectively (Supplementary Table 3). The analysis was performed using “ToppFun” from the “ToppGene Suite” Gene Ontology tool [16]. We submitted the list of genes with expression ratio ≥ 1.30 and a list of genes of all the chromosomes with expression ratio < 0.7 , excluding EST clusters. The selected genes were categorized according to GO classification based on their hypothetical molecular functions and biological processes. The analysis was assessed for Molecular Function and Biological Process and Cellular Component categories.

Table 5

List of the first 20 (out of 414) predicted housekeeping genes for the histologically normal thyroid adjacent to papillary thyroid carcinoma transcriptome map.

Gene name	Chromosome	Location	Expression value B	Data points B	SD as % of expression B
RPL41	chr12	12q13.2	7,559.25	40	7.67
RPL39	chrX	Xq24	4,195.49	40	8.47
RPL9	chr4	4p14	4,586.08	40	10.91
TG	chr8	8q24.22	7,619.57	40	11.06
ACTG1	chr17	17q25.3	3,836.40	80	11.55
RPL27	chr17	17q21.31	2,928.50	40	13.95
TOMM6	chr6	6p21.1	368.69	40	14.09
WASHC5	chr8	8q24.13	118.48	40	14.34
RRAGA	chr9	9p22.1	594.55	40	14.51
NDUFA4	chr7	7p21.3	1,563.68	40	14.70
PTDSS1	chr8	8q22.1	493.86	40	14.98
RPS13	chr11	11p15.1	2,900.71	40	15.08
KIAA1191	chr5	5q35.2	496.47	40	15.33
CTR9	chr11	11p15.4	254.23	40	15.58
DUSP11	chr2	2p13.1	180.36	40	15.78
RPS4X	chrX	Xq13.1	4,512.67	80	16.15
SLTM	chr15	15q22.1	558.06	40	16.18
MRPS35	chr12	12p11.22	275.88	40	16.37
UNC50	chr2	2q11.2	435.55	40	16.45
FAM96A	chr15	15q22.31	499.93	40	16.80

Genes are sorted in ascending order of SD as percentage of the mean value. In bold, the two best genes at behaving like housekeeping genes due to a combination of a low SD, a high expression value and a high number of data points. Following checking in the "Values B" TRAM table, the 40 (TG), and the 40 (RPLP41) data points are derived from all the 40 samples of the histologically normal thyroid adjacent to papillary thyroid carcinoma dataset analyzed.

2.4. Housekeeping gene search

A search of housekeeping genes best suitable for the study of histologically normal thyroid adjacent to papillary thyroid carcinoma (Pool B) has been performed using an optimal combination of parameters [15,17]: in this case, expression value >100, number of data points ≥ 20 and SD, expressed as a percentage of the mean value, ≤ 30 .

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Transparency document

Transparency document associated with this article can be found in the online version at <https://doi.org/10.1016/j.dib.2019.103835>.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.dib.2019.103835>.

References

- [1] L. Vitale, A. Piovesan, F. Antonaros, P. Strippoli, M.C. Pelleri, M. Caracausi, A molecular view of the normal human thyroid structure and function reconstructed from its reference transcriptome map, *BMC Genomics* 18 (2017) 739. <https://doi.org/10.1186/s12864-017-4049-z>.
- [2] M. Caracausi, A. Piovesan, L. Vitale, M.C. Pelleri, Integrated transcriptome map highlights structural and functional aspects of the normal human heart, *J. Cell. Physiol.* 232 (2017) 759–770. <https://doi.org/10.1002/jcp.25471>.
- [3] L. Lenzi, F. Facchin, F. Piva, M. Giulietti, M.C. Pelleri, F. Frabetti, L. Vitale, R. Casadei, S. Canaider, S. Bortoluzzi, et al., TRAM (Transcriptome Mapper): database-driven creation and analysis of transcriptome maps from multiple sources, *BMC Genomics* 12 (2011) 121. <https://doi.org/10.1186/1471-2164-12-121>.

- [4] L. Lenzi, F. Frabetti, F. Facchin, R. Casadei, L. Vitale, S. Canaider, P. Carinci, M. Zannotti, P. Strippoli, UniGene Tabulator: a full parser for the UniGene format, *Bioinformatics* 22 (2006) 2570–2571. <https://doi.org/10.1093/bioinformatics/btl425>.
- [5] M.C. Pelleri, C. Cattani, L. Vitale, F. Antonaros, P. Strippoli, C. Locatelli, G. Cocchi, A. Piovesan, M. Caracausi, Integrated quantitative transcriptome maps of human trisomy 21 tissues and cells, *Front. Genet.* 9 (2018) 125. <https://doi.org/10.3389/fgene.2018.00125>.
- [6] A. Coppe, G.A. Danieli, S. Bortoluzzi, REEF: searching REgionally Enriched Features in genomes, *BMC Bioinf.* 7 (2006) 453. <https://doi.org/10.1186/1471-2105-7-453>.
- [7] A. Piovesan, M. Caracausi, F. Antonaros, M.C. Pelleri, L. Vitale, GeneBase 1.1: a tool to summarize data from NCBI Gene datasets and its application to an update of human gene statistics, *Database (Oxford)* 2016 (2016). <https://doi.org/10.1093/database/baw153>.
- [8] A. Piovesan, M. Caracausi, M. Ricci, P. Strippoli, L. Vitale, M.C. Pelleri, Identification of minimal eukaryotic introns through GeneBase, a user-friendly tool for parsing the NCBI Gene databank, *DNA Res.* 22 (2015) 495–503. <https://doi.org/10.1093/dnares/dsv028>.
- [9] J. Schellenberger, R. Que, R.M. Fleming, I. Thiele, J.D. Orth, A.M. Feist, D.C. Zielinski, A. Bordbar, N.E. Lewis, S. Rahmanian, et al., Quantitative prediction of cellular metabolism with constraint-based models: the COBRA Toolbox v2.0, *Nat. Protoc.* 6 (2011) 1290–1307. <https://doi.org/10.1038/nprot.2011.308>.
- [10] A. Ebrahim, J.A. Lerman, B.O. Palsson, D.R. Hyduke, COBRApy: constraints-based reconstruction and analysis for Python, *BMC Syst. Biol.* 7 (2013) 74. <https://doi.org/10.1186/1752-0509-7-74>.
- [11] C. Frainay, S. Aros, M. Chazalviel, T. Garcia, F. Vinson, N. Weiss, B. Colsch, F. Sedel, D. Thabut, C. Junot, et al., MetaboRank: network-based recommendation system to interpret and enrich metabolomics results, *Bioinformatics* 35 (2019) 274–283. <https://doi.org/10.1093/bioinformatics/bty577>.
- [12] A.E. Cicek, X. Qi, A. Cakmak, S.R. Johnson, X. Han, S. Alshalwi, Z.M. Ozsoyoglu, G. Ozsoyoglu, An online system for metabolic network analysis, *Database (Oxford)* 2014 (2014). <https://doi.org/10.1093/database/bau091>.
- [13] M. Caracausi, V. Ghini, C. Locatelli, M. Mericio, A. Piovesan, F. Antonaros, M.C. Pelleri, L. Vitale, R.A. Vacca, F. Bedetti, et al., Plasma and urinary metabolomic profiles of Down syndrome correlate with alteration of mitochondrial metabolism, *Sci. Rep.* 8 (2018) 2977. <https://doi.org/10.1038/s41598-018-20834-y>.
- [14] R. Farrokhi Yekta, M. Rezaie Tavirani, A. Arefi Oskouie, M.R. Mohajeri-Tehrani, A.R. Soroush, The metabolomics and lipidomics window into thyroid cancer research, *Biomarkers* 22 (2017) 595–603. <https://doi.org/10.1080/1354750x.2016.1256429>.
- [15] M. Caracausi, A. Piovesan, F. Antonaros, P. Strippoli, L. Vitale, M.C. Pelleri, Systematic identification of human housekeeping genes possibly useful as references in gene expression studies, *Mol. Med. Rep.* 16 (2017) 2397–2410. <https://doi.org/10.3892/mmr.2017.6944>.
- [16] J. Chen, E.E. Bardes, B.J. Aronow, A.G. Jegga, ToppGene Suite for gene list enrichment analysis and candidate gene prioritization, *Nucleic Acids Res.* 37 (2009) W305–W311. <https://doi.org/10.1093/nar/gkp427>.
- [17] Z. Tu, L. Wang, M. Xu, X. Zhou, T. Chen, F. Sun, Further understanding human disease genes by comparing with housekeeping genes and other genes, *BMC Genomics* 7 (2006) 31. <https://doi.org/10.1186/1471-2164-7-31>.