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Differential expression of genes coding for ribosomal proteins in different human tissues

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ABSTRACT

Motivation: To perform a computational and statistical study on a large set of gene expression data pertaining six adult human tissues (brain, liver, skeletal muscle, ovary, retina and uterus) for analyzing the expression of ribosomal protein genes.

Results: Unexpectedly, in each of the considered tissues large variations in the expression of ribosomal protein genes were observed. Moreover, when comparing the expression levels of 89 ribosomal protein genes in six different tissues, 13 genes appeared differentially expressed among tissues.

Avalilability: The expression data of the ribosomal protein genes together with supplementary material (complete transcriptional profiles of the considered human tissues) are freely available at the site GETProfiles (http://telethon.bio.unipd.it/GETProfiles/).

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INTRODUCTION

The ribosome, the oldest molecular machinery to have evolved in biological systems (Warner and Nierras, 1998), is a large template-directed enzyme decoding mRNA into proteins (Wimberly *et al.*, 2000).

Recently we successfully applied a computational approach to large-scale analysis of gene expression in different human adult tissues (Bortoluzzi *et al.*, 1998, 2000a,b,c). The basic assumption of the method (Okubo *et al.*, 1992) is that the level of activity and the tissue expression pattern of a given gene may be inferred from the number of corresponding ESTs obtained from unbiased cDNA library(ies) from the considered tissue. The validity of this 'in-silico' approach was proved by a comparison with SAGE results (Bortoluzzi *et al.*, 2000a).

In the course of a computational reconstruction of transcriptional profiles of specific human tissues, we observed that some Ribosomal Protein (RP) genes appear highly expressed in some tissues, but not in others.

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Table 1. UniGene ID of the selected cDNA libraries considered by the present study and total number of EST sequences and of UniGene clusters retrieved per tissue

Tissue	UniGene cDNA libraries (Lib. #)	ESTs	UniGene clusters
Uterus	119, 312, 732, 733, 3600	95 776	11 688
Ovary	576, 652, 935, 1369, 1380, 3223, 3225	30 256	2 741
Brain	128, 859, 857, 15, 255	66 286	2 473
Liver	155	8 257	1 351
Skeletal muscle	24, 272, 500	30 231	3 688
Retina	177, 178, 228, 313	21 054	4 631

Because no systematic studies on the RP genes expression in tissues were produced so far, we attempted to evaluate the expression of these genes in different human adult tissues, by an 'in-silico' approach on a very large set of data, obtained from UniGene (Bogusky and Schuler, 1995).

RESULTS AND DISCUSSION

UniGene (http://www.ncbi.nlm.nih.gov/UniGene/Hs.Home.html) is a collection of entries corresponding to human transcripts. Data were mined by using dedicated software developed in our laboratory (Bortoluzzi *et al.*, 1998, 2000a).

The analysis involved six human tissues (uterus, ovary, brain, liver, skeletal muscle and retina) for which a sufficient number of ESTs, obtained from unbiased cDNA libraries, was available in UniGene. The total number of UniGene clusters and EST sequences retrieved per tissue are reported in Table 1.

Catalogues of genes expressed in the different tissues were produced, following previously established procedures (Bortoluzzi *et al.*, 2000a). They are available at a dedicated website (http://telethon.bio.unipd.it/GETProfiles/). For each gene, the number of ESTs obtained from a specific tissue was used for estimating the expression level of the given gene in the tissue, as per thousand of the total detected transcriptional activity.

For each tissue, catalogued entries were classified into three groups: highly expressed genes (more than 0.05% of the total detected transcriptional activity in the tissue), moderately expressed (from 0.05 to 0.012% of the total), or weakly expressed (less than 0.012% of the total). The number and the percentage of genes falling in each expression category, for each considered tissue, are shown in Table 2.

The entries corresponding to 89 RP genes were identified in each catalogue. The number of detected RP genes differed from tissue to tissue, as shown in Table 2. The expression information for all the 'nucleolar' ribosomal proteins (85 in total, allelic copies and isoforms included) and for four mitochondrial ribosomal proteins was obtained. The expression of RP genes represented on average the 10.3% of the total detected transcriptional activity (from 5.2 to 19.9%, according to the tissue).

RP genes seemed to be more expressed in skeletal muscle and in ovary than in other tissues. No linear correlation was found between the number of the expressed RP genes per tissue and the total number of detected genes, nor with the total number of ESTs per tissue ($r^2 = 0.26$ and $r^2 = 0.02$, respectively). More than 50% of the RP genes appeared to be highly expressed in all the considered tissues, except uterus. In each considered tissue, the percentages of highly expressed genes among RP genes, was always significantly higher than the percentages of highly expressed genes among the whole set of genes in the tissue.

The number of EST sequences corresponding to each RP gene in each considered tissue was obtained and merged in a matrix of 89 rows (genes) per 6 columns (tissues) (Table 3, columns 3–8). The expression level of each RP gene in each considered human tissue, calculated as per thousand of the total transcriptional activity of the tissue (Table 3, columns 9–14), was pairwise compared with those observed in other tissues.

The level of expression of different RP genes showed considerable variation among tissues. In order to assess the statistical significance of the observed differences, the Audic and Claverie's (1997) probability value, corrected for multiple statistical tests (P^*_{AC} value), was calculated for all the possible comparisons. Audic and Claverie's formula takes into account random fluctuations and differences in sample size. The smaller the P_{AC} value is, the more probable it is that the observed differential expression reflects regulated expression. We calculated a P_{AC} value for each of the pairwise comparisons between tissues for all the considered genes. A correction of the calculated P_{AC} value was applied, in order to overcome the problem of multiple statistical tests on the same data and because of the *a posteriori* focusing on genes exhibiting significant variations. The calculated P values were multiplied by nc (where n is the total number of considered genes and c is the number of comparisons between m tissues: $c = (m(m-1))/2$). Thresholds of statistical significance were established at 0.0001, 0.001 and 0.01.

Genes showing in a given tissue a level of expression significantly higher than in all the other tissues were considered as 'differentially expressed'. RP genes significantly more expressed in a specific tissue than in others were identified. These genes are reported in Table 3, marked with asterisks, according to the established levels of significance (one, two or three asterisks indicates that all of the calculated P^*_{AC} values for the comparisons of the level of expression in the considered tissue with the expression levels in all the other tissues were below 0.01, 0.001 or 0.0001, respectively).

In addition, the R statistic, which has been recently proposed as a score of differential expression (Stekel *et al.*, 2000), was calculated for all the considered RP genes in order to identify those genes whose expression most varied across different tissues. R scores have a χ^2 distribution with c degree of freedom, where c is the number of comparisons between tissues. When applied to present data, any value of R greater than 35.61 is associated to a P_R value of less than 0.0001. All genes resulting differentially expressed according to the calculated P^*_{AC} value show a considerably high R score, ranging from 2178.5 and 72.8 (P_R value from 0 to 2.43E − 12).

Thirteen RP genes were found to be differentially expressed in specific human tissues. Five of them were mostly expressed in ovary (RPL14, RPL38, RPS9, RPS10 and RPS19, with very high statistical significance, P^*_{AC} value < 0.0001). Eight were mostly expressed in the skeletal muscle: RPL37, RPL37a, RPL41, RPS17 and RPS25 (P^*_{AC}value < 0.0001); RPS23 (P^*_{AC}value < 0.001); RPL44 and RPS13 (P^*_{AC}value < 0.01).

The histogram in Figure 1 shows the expression levels per tissue of the thirteen differentially expressed RP genes.

Statistical analysis was carried out under very conservative conditions. Moreover, the significance thresholds were kept very stringent. In these conditions, ten out of thirteen differentially expressed RP genes showed a P^*_{AC} value less than 0.0001: all of them resulted associated to a P_R value less than 2.43E − 12.

The hypothesis tested by the Audic and Claverie and by the R statistics are quite different. The P_{AC} value refers to the statistical significance of each observed difference in all the pairwise comparisons. On the other hand, R statistic tests the hypothesis that each value is consistent with the others, i.e. with the mean of the means. The P_R value will reach statistical significance when at least two observed values are different from one another.

We decided to consider as differentially expressed only the RP genes for which expression levels resulted statistically different according to both R and AC tests.

Table 2. Percentages of genes falling in each expression category (highly, moderately and weakly expressed genes). In the last column, the estimated percentage of the total transcriptional activity due to the expression of RP genes is shown

Tissue	Catalogued genes						Ribosomal protein genes							Total transcription(%)
	H	M	W	H(%)	M(%)	W(%)	Tot. no.	H	M	W	H(%)	M(%)	W(%)	
Uterus	213	1907	9568	1.8	16.3	81.9	85	32	39	14	37.2	45.3	17.4	5.5
Ovary	380	1052	1309	13.9	38.4	47.8	76	69	6	1	90.8	7.9	1.3	19.9
Brain	566	1374	533	22.9	55.6	21.6	46	39	6	1	84.8	13	2.2	6.1
Liver	224	1127	0	16.6	83.4	0	59	40	19	0	67.8	32.2	0	5.2
Skeletal muscle	312	1067	2309	8.5	28.9	62.6	83	79	4	0	95.2	4.8	0	18.1
Retina	362	1609	2660	7.8	34.7	57.4	70	38	26	6	54.3	37.1	8.6	7.1

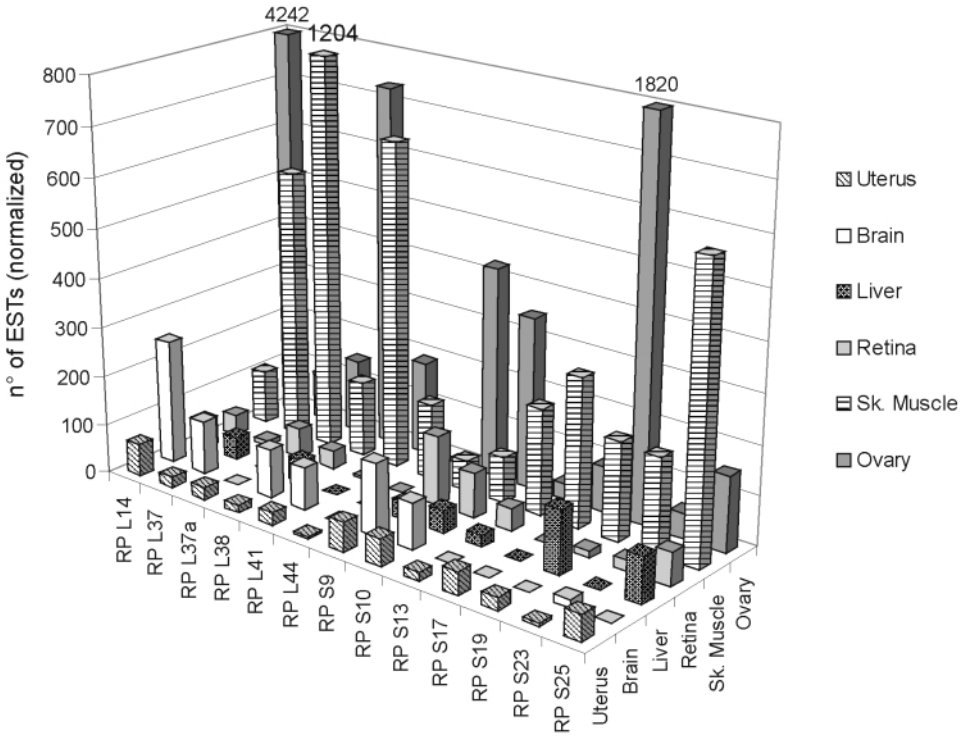

Fig. 1. Expression levels per tissue of the thirteen differentially expressed RP genes. The numbers of ESTs are normalized according to the total numbers of ESTs per tissue.

Ribosome biogenesis in eukaryotes is believed to depend on the co-ordinate production and assembly of four rRNA molecules and at least 79 Ribosomal Proteins (RPs), most of which are synthesized in equimolar amounts (Naora and Naora, 1999), in a series of concerted reactions (Warner and Nierras, 1998). Under normal conditions, ribosomal biogenesis is accurately tuned to the cellular need for protein synthesis. An increased ribosomal biogenesis is, in general, associated with increased proliferative activity, whereas cells in stationary state normally reduce the synthesis of RPs, with a highly coordinated regulation (Tushinski and Warner, 1982; Naora and Naora, 1999).

However, a differential expression of specific RP genes was reported in several pathological conditions, mostly in cancers (Kondoh *et al.*, 1992; Espinosa *et al.*, 1997; Go and Taniguchi, 1998; Shriver *et al.*, 1998; Vaarala *et al.*, 1998; Matsson *et al.*, 1999; Preiherr *et al.*, 2000; Shuda *et al.*, 2000). It is difficult to discuss the above findings in the light of our observations, since previous studies documented the overexpression of single RP genes in specific conditions, whereas we investigated the possible differences in expression within the entire set of RP genes, in different *normal* adult human tissues.

Table 3. Expression of the considered RP genes, identified by UniGene ID and gene description. The number of EST sequences and the estimated expression level (per thousand of the total detected transcriptional activity) corresponding to each RP gene per tissue are reported. Significant R scores (P_R values below 0.0001) are reported. The differentially expressed RP genes, are marked with one, two or three asterisks (P_{AC} value below 0.01, 0.001 or 0.0001, respectively)

UniGene ID	Gene description	Uterus	Ovary	Brain	Liver	Muscle	Retina	Uterus	Ovary	Brain	Liver	Muscle	Retina	R	AC
Hs.119598	RPL3	389	110	238	13	133	117	4.06	3.64	3.59	1.57	4.40	5.56		
Hs.159191	RPL3-like	0	0	0	0	11	0	0.00	0.00	0.00	0.00	0.36	0.00		
Hs.286	RPL4	149	76	106	6	96	57	1.56	2.51	1.60	0.73	3.18	2.71		
Hs.180946	RPL5	93	61	48	0	42	14	0.97	2.02	0.72	0.00	1.39	0.66	26.4	
Hs.174131	RPL6	118	83	147	3	46	0	1.23	2.74	2.22	0.36	1.52	0.00	61.1	
Hs.153	RPL7	87	72	0	12	59	16	0.91	2.38	0.00	1.45	1.95	0.76	99.3	
Hs.99858	RPL7a	129	63	0	5	100	48	1.35	2.08	0.00	0.61	3.31	2.28	132.7	
Hs.178551	RPL8	59	50	60	0	55	23	0.62	1.65	0.91	0.00	1.82	1.09	30.3	
Hs.157850	RPL9	75	83	0	13	94	58	0.78	2.74	0.00	1.57	3.11	2.75	156.3	
Hs.29797	RPL10	100	75	0	11	111	40	1.04	2.48	0.00	1.33	3.67	1.90	147.5	
Hs.252574	RPL10a	77	37	70	5	53	53	0.80	1.22	1.06	0.61	1.75	2.52		
Hs.179943	RPL11	39	32	0	5	26	8	0.41	1.06	0.00	0.61	0.86	0.38		
Hs.182979	RPL12	46	37	38	5	46	18	0.48	1.22	0.57	0.61	1.52	0.85		
Hs.180842	RPL13	117	53	188	9	85	32	1.22	1.75	2.84	1.09	2.81	1.52	35.0	
Hs.119122	RPL13a	124	114	303	15	103	63	1.29	3.77	4.57	1.82	3.41	2.99	87.6	
Hs.158675	RPL14	66	1 340	174	5	34	9	0.69	44.29	2.62	0.61	1.12	0.43	2178.5	Ovary***
Hs.74267	RPL15	136	40	184	8	41	18	1.42	1.32	2.78	0.97	1.36	0.85	30.7	
Hs.82202	RPL17	67	40	0	4	52	24	0.70	1.32	0.00	0.48	1.72	1.14	71.4	
Hs.75458	RPL18	68	31	99	0	29	0	0.71	1.02	1.49	0.00	0.96	0.00	39.6	
Hs.163593	RPL18a	46	48	104	3	41	16	0.48	1.59	1.57	0.36	1.36	0.76	34.1	
Hs.75879	RPL19	28	26	0	3	56	16	0.29	0.86	0.00	0.36	1.85	0.76	75.0	
Hs.184108	RPL21	23	40	0	4	66	21	0.24	1.32	0.00	0.48	2.18	1.00	102.7	
Hs.99914	RPL22	46	20	52	0	28	0	0.48	0.66	0.78	0.00	0.93	0.00		
Hs.234518	RPL23	23	37	0	0	75	15	0.24	1.22	0.00	0.00	2.48	0.71	115.4	
Hs.3254	RPL23-like	11	0	0	0	0	0	0.11	0.00	0.00	0.00	0.00	0.00		
Hs.184776	RPL23a	64	38	0	7	75	41	0.67	1.26	0.00	0.85	2.48	1.95	102.6	
Hs.184582	RPL24	26	50	43	4	45	8	0.27	1.65	0.65	0.48	1.49	0.38		
Hs.91379	RPL26	39	19	46	7	65	0	0.41	0.63	0.69	0.85	2.15	0.00	51.0	
Hs.111611	RPL27	39	14	36	0	36	5	0.41	0.46	0.54	0.00	1.19	0.24		
Hs.76064	RPL27a	49	39	66	7	30	12	0.51	1.29	1.00	0.85	0.99	0.57		
Hs.4437	RPL28	47	71	89	0	32	11	0.49	2.35	1.34	0.00	1.06	0.52	49.9	
Hs.183698	RPL29	68	27	58	0	56	10	0.71	0.89	0.87	0.00	1.85	0.47		
Hs.111222	RPL30	27	28	0	15	76	2	0.28	0.93	0.00	1.82	2.51	0.09	116.6	
Hs.184014	RPL31	30	36	31	12	133	6	0.31	1.19	0.47	1.45	4.40	0.28	145.69	
Hs.169793	RPL32	28	18	46	8	81	13	0.29	0.59	0.69	0.97	2.68	0.62	63.4	
Hs.250895	RPL34	26	16	25	6	47	7	0.27	0.53	0.38	0.73	1.55	0.33	29.5	
Hs.182825	RPL35	10	20	34	0	36	3	0.10	0.66	0.51	0.00	1.19	0.14	39.0	
Hs.179666	RPL35a	47	36	42	5	61	24	0.49	1.19	0.63	0.61	2.02	1.14	31.1	
Hs.76437	RPL36	4	0	0	2	24	2	0.04	0.00	0.00	0.24	0.79	0.09		
Hs.118857	RPL36a	6	0	0	0	17	1	0.06	0.00	0.00	0.00	0.56	0.05	27.0	
Hs.179779	RPL37	22	31	75	4	173	2	0.23	1.02	1.13	0.48	5.72	0.09	211.1	Skeletal muscle***
Hs.184109	RPL37a	26	47	0	0	380	13	0.27	1.55	0.00	0.00	12.57	0.62	655.7	Skeletal muscle***
Hs.2017	RL38	15	232	68	4	48	8	0.16	7.67	1.03	0.48	1.59	0.38	308.8	Ovary***
Hs.177461	RPL39	25	18	0	0	58	0	0.26	0.59	0.00	0.00	1.92	0.00	87.2	
Hs.108124	RPL41	26	60	60	0	209	1	0.27	1.98	0.91	0.00	6.91	0.05	279.4	Skeletal muscle***
Hs.178391	RPL44	5	0	0	0	48	0	0.05	0.00	0.00	0.00	1.59	0.00	90.0	Skeletal muscle*
Hs.182426	RPS2	297	155	216	12	162	0	3.10	5.12	3.26	1.45	5.36	0.00	104.7	
Hs.252259	RPS3	144	150	0	16	59	0	1.50	4.96	0.00	1.94	1.95	0.00	207.97	
Hs.77039	RPS3a	275	207	164	4	141	129	2.87	6.84	2.47	0.48	4.66	6.13	92.8	
Hs.75344	RPS4, X-linked	133	94	0	0	51	22	1.39	3.11	0.00	0.00	1.69	1.04	125.39	
Hs.180911	RPS4, Y-linked	0	0	6	2	0	3	0.00	0.00	0.09	0.24	0.00	0.14		
Hs.76194	RPS5	42	23	0	4	33	20	0.44	0.76	0.00	0.48	1.09	0.95		
Hs.241507	RPS6	172	61	0	6	44	38	1.80	2.02	0.00	0.73	1.46	1.80	102.7	
Hs.75538	RPS7	39	24	0	0	36	9	0.41	0.79	0.00	0.00	1.19	0.43	49.5	
Hs.151604	RPS8	101	98	0	9	41	0	1.05	3.24	0.00	1.09	1.36	0.00	136.6	
Hs.180920	RPS9	60	135	101	3	19	31	0.63	4.46	1.52	0.36	0.63	1.47	102.7	Ovary***

Table 3. *Continued*

UniGene ID	Gene description	Uterus	Ovary	Brain	Liver	Muscle	Retina	Uterus	Ovary	Brain	Liver	Muscle	Retina	R	AC
Hs.71787	30S RPS7 homolog	9	0	21	0	7	8	0.09	0.00	0.32	0.00	0.23	0.38		
Hs.76230	RPS10	54	110	65	4	29	20	0.56	3.64	0.98	0.48	0.96	0.95	72.8	Ovary***
Hs.182740	RPS11	68	87	146	20	71	34	0.71	2.88	2.20	2.42	2.35	1.61	54.6	
Hs.82148	RPS12	19	31	0	9	60	4	0.20	1.02	0.00	1.09	1.98	0.19	93.4	
Hs.165590	RPS13	17	10	0	2	68	10	0.18	0.33	0.00	0.24	2.25	0.47	95.9	Skeletal muscle*
Hs.3491	RPS14	41	51	0	13	56	15	0.43	1.69	0.00	1.57	1.85	0.71	90.3	
Hs.133230	RPS15	19	32	55	0	67	10	0.20	1.06	0.83	0.00	2.22	0.47	65.1	
Hs.2953	RPS15a	18	85	0	3	46	10	0.19	2.81	0.00	0.36	1.52	0.47	138.0	
Hs.80617	RPS16	138	28	46	0	60	0	1.44	0.93	0.69	0.00	1.98	0.00	51.6	
Hs.5174	RPS17	46	29	0	0	95	0	0.48	0.96	0.00	0.00	3.14	0.00	140.6	Skeletal muscle***
Hs.275865	RPS18	39	60	108	9	90	15	0.41	1.98	1.63	1.09	2.98	0.71	74.8	
Hs.126701	RPS19	26	575	0	11	63	3	0.27	19.00	0.00	1.33	2.08	0.14	1031.4	Ovary***
Hs.8102	RPS20	43	122	59	9	94	24	0.45	4.03	0.89	1.09	3.11	1.14	122.86	
Hs.1948	RPS21	10	10	56	1	35	7	0.10	0.33	0.84	0.12	1.16	0.33		
Hs.3463	RPS23	6	16	11	0	61	5	0.06	0.53	0.17	0.00	2.02	0.24	81.5	Skeletal muscle**
Hs.180450	RPS24	38	36	0	6	59	0	0.40	1.19	0.00	0.73	1.95	0.00	91.3	
Hs.113029	RPS25	52	48	0	8	187	15	0.54	1.59	0.00	0.97	6.19	0.71	261.4	Skeletal muscle***
Hs.77904	RPS26	9	9	0	2	26	0	0.09	0.30	0.00	0.24	0.86	0.00	39.3	
Hs.195453	RPS27 (metallopanstimulin 1)	11	24	26	5	41	6	0.11	0.79	0.39	0.61	1.36	0.28	39.3	
Hs.3297	RPS27a	25	64	0	8	40	8	0.26	2.12	0.00	0.97	1.32	0.38	97.6	
Hs.108957	40S RPS27 isoform	0	0	0	0	4	0	0.00	0.00	0.00	0.00	0.13	0.00		
Hs.153177	RPS28	0	14	0	0	33	8	0.00	0.46	0.00	0.00	1.09	0.38	68.1	
Hs.539	RPS29	8	0	62	7	21	7	0.08	0.00	0.94	0.85	0.69	0.33	51.4	
Hs.177415	RPS30	22	48	0	5	40	3	0.23	1.59	0.00	0.61	1.32	0.14	82.1	
Hs.181357	laminin receptor 1(67kD, RPSA)	194	109	156	14	80	66	2.03	3.60	2.35	1.70	2.65	3.13		
Hs.251247	RP, large P2	12	0	0	0	23	5	0.13	0.00	0.00	0.00	0.76	0.24	35.1	
Hs.73742	RP, large, P0	269	79	224	14	87	95	2.81	2.61	3.38	1.70	2.88	4.51		
Hs.274201	60S acidic RPPO	5	0	0	0	0	1	0.05	0.00	0.00	0.00	0.00	0.05		
Hs.177592	RP, large, P1	42	31	0	13	136	25	0.44	1.02	0.00	1.57	4.50	1.19	185.65	
Hs.4209	RP, mitochondrial, L2	12	5	20	3	4	4	0.13	0.17	0.30	0.36	0.13	0.00		
Hs.79086	RP, mitochondrial, L3	11	0	0	0	0	0	0.11	0.00	0.00	0.00	0.00	0.00		
Hs.109059	RP, mitochondrial, L12	7	0	0	0	0	0	0.07	0.00	0.00	0.00	0.00	0.00		
Hs.9964	RP, mitochondrial, S12	16	2	0	0	0	0	0.17	0.07	0.00	0.00	0.00	0.19		
Tissue totals		95 776	30 256	66 286	8257	30 231	21 054								

Although a differential translational and/or post-translational regulation may take place, thus re-equilibrating the molar ratio at the protein level (Pierandrei-Amaldi *et al.*, 1985; Bowman, 1987; Mariottini *et al.*, 1999), we may expect that large differences in concentration of mRNAs probably produce different concentrations of the corresponding proteins. Our approach is unable to detect differences in gene expression due to translational and post-translational regulation, but the same limitation is shared by all of the available techniques attempting to estimate individual gene expression on a large scale, including SAGE and cDNA arrays.

The overexpression of some RP genes could be typical of some specific conditions, including the differentiated state of some human tissues, probably related to the involvement of their products in extraribosomal functions. On the other hand, the possibility that massive transcription of individual ribosomal protein genes is due to fortuitous enhanced transcription of specific subsets of transcription factors cannot be completely ruled out.

In conclusion, according to our findings, regulation of the transcriptional activity of ribosomal protein genes in differentiated human tissues seems to be less concertedly regulated than previously supposed.

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REFERENCES

Audic,S. and Claverie,J.M. (1997) The significance of digital gene expression profiles. *Genome Res.*, **7**, 986–995.

Boguski,M.S. and Schuler,G.D. (1995) ESTablishing a human transcript map. *Nat. Genet.*, **10**, 369–371.

Bortoluzzi,S., Rampoldi,L., Simionati,B., Zimbello,R., Barbon,A., d'Alessi,F., Tiso,N., Pallavicini,A., Toppo,S., Cannata,N., Valle,G., Lanfranchi,G. and Danieli,G.A. (1998) A comprehensive, high-resolution genomic transcript map of human skeletal muscle. *Genome Res.*, **8**, 817–825.

Bortoluzzi,S., d'Alessi,F. and Danieli,G.A. (2000a) A computational reconstruction of the adult human heart transcriptional profile. *J. Mol. Cell. Cardiol.*, **32**, 1931–1938.

Bortoluzzi,S., d'Alessi,F. and Danieli,G.A. (2000b) A novel resource for the study of genes expressed in the adult human retina. *Invest. Ophthalmol. Vis. Sci.*, **41**, 3305–3308.

Bortoluzzi,S., d'Alessi,F., Romualdi,C. and Danieli,G.A. (2000c) The human adult skeletal muscle transcriptional profile reconstructed by a novel computational approach. *Genome Res.*, **10**, 344–349.

Bowman,L.H. (1987) The synthesis of ribosomal proteins S16 and L32 is not autogenously regulated during mouse myoblast differention. *Moll. Cell. Biol.*, **7**, 4464–4471.

Espinosa,L., Martin,M., Nicolas,A., Fabre,M. and Navarro,E. (1997) Primary sequence of the human, lysine-rich, ribosomal protein RPL38 and detection of an unusual RPL38 processed pseudogene in the promoter region of the type-1 angiotensin II receptor gene. *Biochem. Biophys. Acta*, **1354**, 58–64.

Go,H. and Taniguchi,S. (1998) Augmentation in the expression of a ribosomal protein associated with transformation. *Biochem. Mol. Biol. Int.*, **46**, 629–638.

Kondoh,N., Schweinfest,C.W., Henderson,K.W. and Papas,T.S. (1992) Differential expression of S19 ribosomal protein, laminin-binding protein, and human lymphocyte antigen class I messenger RNAs associated with colon carcinoma progression and differentiation. *Cancer Res.*, **52**, 791–796.

Mariottini,P., Shah,Z.H., Toivonen,J.M., Bagni,C., Spelbrink,J.N., Amaldi,F. and Jacobs,H.T. (1999) Expression of the gene for mitoribosomal protein S12 is controlled in human cells at the levels of transcription, RNA splicing, and translation. *J. Biol. Chem.*, **274**, 31 853–31 862.

Matsson,H., Klar,J., Draptchinskaia,N., Gustavsson,P., Carlsson,B., Bowers,D., de Bont,E. and Dahl,N. (1999) Truncating ribosomal protein S19mutations and variable clinical expression in Diamond–Blackfan anemia. *Hum. Genet.*, **105**, 496–500.

Naora,H. and Naora,H. (1999) Involvement of ribosomal proteins in regulating cell growth and apoptosis: translational modulation or recruitment for extraribosomal activity? *Immunol. Cell Biol.*, **77**, 197–205.

Okubo,K., Hori,N., Matoba,R., Niiyama,T., Fukushima,A., Kojima,Y. and Matsubara,K. (1992) Large scale cDNA sequencing for analysis of quantitative and qualitative aspects of gene expression. *Nature Genet.*, **2**, 173–179.

Pierandrei-Amaldi,P., Beccari,E., Bozzoni,I. and Amaldi,F. (1985) Ribosomal protein production in normal and anucleolate xenopus embryos: regulation at the posttranscriptional and translational levels. *Cell*, **42**, 317–323.

Preiherr,J., Hildebrandt,T., Klostermann,S., Eberhardt,S., Kaul,S. and Weidle,U.H. (2000) Transcriptional profiling of human mammary carcinoma cell lines reveals PKW, a new tumor-specific gene. *Anticancer Res.*, **20**, 2255–2264.

Shriver,S.P., Shriver,M.D., Tirpak,D.L., Bloch,L.M., Hunt,J.D., Ferrell,R.E. and Siegfried,J.M. (1998) Trinucleotide repeat length variation in the human ribosomal protein L14 gene (RPL14), localization to 3p21.3 and loss of heterozygosity in lung and oral cancers. *Mutat. Res.*, **406**, 9–23.

Shuda,M., Kondoh,N., Tanaka,k., Ryo,A., Wakatsuki,T., Hada,A., Goseki,N., Igari,T., Hatsuse,K., Aihara,T., Horiuchi,S., Shichita,M., Yamamoto,N. and Yamamoto,M. (2000) Enhanced expression of translation factor mRNAs in hepatocellular carcinoma. *Anticancer Res.*, **20**, 2489–2494.

Stekel,D.J., Git,Y. and Falciani,F. (2000) The comparison of gene expression from multiple cDNA libraries. *Genome Res.*, **10**, 2055–2061.

Tushinski,R.J. and Warner,J.R. (1982) Ribosomal proteins are synthesized preferentially in cells commencing growth. *J. Cell Physiol.*, **112**, 128–135.

Vaarala,M.H., Porvari,K.S., Kyllonen,A.P., Mustonen,M.V., Lukkarinen,O. and Vihko,P.T. (1998) Several genes encoding ribosomal proteins are over-expressed in prostate-cancer cell lines: confirmation of L7a and L37 over-expression in prostate-cancer tissue samples. *Int. J. Cancer*, **78**, 27–32.

Warner,J.R. and Nierras,C.R. (1998) Trapping human ribosomal protein genes. *Genome Res.*, **8**, 419–421.

Wimberly,B.T., Brodersen,D.E., Clemons,W.M., Morgan-Warren,R.J., Carter,A.P., Vonrhein,C. and Hartsch,T. (2000) Structure of the 30S ribosomal subunit. *Nature*, **407**, 327–339.