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The Human Mitochondrial Ribosomal Protein Genes: Mapping of 54 Genes to the Chromosomes and Implications for Human Disorders

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Mitochondria possess their own translational machinery, which is composed of components distinct from their cytoplasmic counterparts. To investigate the possible involvement of mitochondrial ribosomal defects in human disease, we mapped nuclear genes that encode mitochondrial ribosomal proteins (MRPs). We generated sequence-tagged sites (STSs) of individual MRP genes that were able to be detected by PCR. They were placed on an STS content map of the human genome by typing of radiation hybrid panels. We located 54 MRP genes on the STS-content map and assigned these genes to cytogenetic bands of the human chromosomes. Although mitochondria are thought to have originated from bacteria, in which the genes encoding ribosomal proteins are clustered into operons, the mapped MRP genes are widely dispersed throughout the genome, suggesting that transfer of each MRP gene to the nuclear genome occurred individually. We compared the assigned positions with candidate regions for mendelian disorders and found certain genes that might be involved in particular diseases. This map provides a basis for studying possible roles of MRP defects in mitochondrial disorders.

Key words: mitochondria, ribosomal protein, MRP gene, gene mapping, STS, human disease

INTRODUCTION

Mitochondria are thought to be descendants of ancient bacteria that became incorporated into the pre-eukaryotic cell by endosymbiosis during evolution [1,2]. They have their own translation system for production of 13 proteins essential for oxidative phosphorylation in mammals [3]. The mitochondrial ribosome, a central player in this translation system, is also distinct from its cytoplasmic counterpart, consisting of two RNA species (rRNAs) and over 70 different proteins (MRPs) [4,5]. Although the RNA molecules are transcribed from the mitochondrial DNA, the proteins involved in the mitochondrial translation system are encoded by the nuclear genome. They are synthesized in the cytoplasm and imported into the mitochondria where they are assembled into the ribosome. In the case of mammals, only limited information has been available regarding the identities of these proteins and their relationship to bacterial ribosomal proteins. Recently, however, we and other investigators have characterized 31 proteins of the large subunit and 24 proteins of the small subunit through peptide sequencing of purified proteins and extensive screening of the EST databases for corresponding cDNA sequences [6–12]. Interestingly, 38 of these proteins were found to have bacterial homologues and the other 17 proteins were found to fall into new classes of ribosomal proteins.

Mutations in mitochondrial DNA are known to be associated with a wide spectrum of human diseases with different clinical features, including neuromuscular disorders, diabetes, aplastic anemia, and deafness [reviewed in 13]. Because point mutations in mitochondrial tRNA and rRNA genes have been found in patients with neuromuscular disorders and deafness, respectively [14–17], we are intrigued by the possibility that mutations in MRP genes may result in mitochondrial dysfunction and thereby cause similar pathological conditions. *MRPS12*, the most extensively studied human MRP gene [18–20], has been proposed as a candidate gene for autosomal dominant sensorineural hearing loss, DFNA4 [21].

To systematically explore this possibility, we must first establish the chromosomal map position of each of the human MRP genes. Although a physical map of the human genome based on the genome sequence has been published [22,23], only six MRP genes appeared on the map. Here we localize 54 MRP genes within the human chromosomes using sequence-tagged sites (STSs) identified in individual MRP genes. The assigned positions were further compared with candidate regions for mendelian disorders to investigate the possible roles of MRPs in human disease.

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TABLE 1: Identification and localization of STSs for human mitochondrial ribosomal protein genes

Gene	Location	Forward primer	Reverse primer	Size (bp)	GeneBridge 4 Linked marker	GeneBridge 4 Dist. (cR)[a]	Stanford G3 Linked marker	Stanford G3 Dist. (cR)[a]	Accession n o.[b]
MRPL1	4q21.1	GTGGTACGTGCTTTCCTTCG	TTCTCCATTGCTTCTTAAACCA	161	WI-9200	5	SHGC-24579	14	AB049474
MRPL2	6p21.3	CGTTGATCATAACAAACGGG	ACAGGGATATCAGCTTTGGG	181	WI-4822	8	SHGC-30556	47	AB051617
MRPL3	3q21-q23	CCCAAGGCCCTGACTACAC	GACCAACTGCTTAATGAATGGG	209	WI-6248	13	SHGC-35112	0	AB051336
MRPL4	19p13.2	GCCTAAATGTGCACAGCATG	GAGGTGCTTCACATCAACAGTG	210	WI-7557	1	SHGC-12652	9	AB049635
MRPL7/L12	17q25	CGTGGACAAAGTGAAGCTGA	CTGAACACAAGTCCTCCGAG	291	no link		SHGC-31983	6	AB051337
MRPL9	1q21	GTCGTGAACTTTGAGAAGCC	CTTGCACATTTCTGCTCCAC	157	NIB288	2	SHGC-57939	33	AB049636
MRPL10	17q21.3	CCAGTACATCAGAGAGCAACG	TTGAGGAGAGCACAGCCAAT	148	D17S806	7	SHGC-68693	5	AB051618
MRPL11	11q13.3	TAAGATTGGACAGCCCACTG	GACAACAGACGACAGGGGTA	270	D11S913	10	SHGC-33767	7	AB051338
MRPL13	8q22.1-q22.3	CTCCACCTGAAGATTATCGGC	CAGGTGCTGAACTGTAGCAG	133	WI-5098	2	SHGC-69272	29	AB049640
MRPL14	6p21.3	GTCCTGACTTTCTGTTGCTGC	GGCCAGTAGTATCTGGTCGC	307	WI-5971	6	SHGC-32834	10	AB051339
MRPL15	8q11.2-q13	CTAGGAAGGATCCAAGGCAG	GATCCTTCAGCCCCTATTCC	176	AFMA084WH1	2	SHGC-5796	0	AB051619
MRPL16	11q12-q13.1	GAATAGCCACTGCCAACATG	AGGCTGAGGGGAATAGAAATG	175	D11S1965	5	SHGC-13951	0	AB049642
MRPL17	11p15.5-p15.4	ACTCCTAAACCAGCTGCTGC	GTAAAAGTGCTCCAAAGGCC	166	D11S922	14	SHGC-1124	5	AB051620
MRPL19	2p11.2-q11.2	GCTCAGAAGTGGAATCAGCC	GAGCCAATGTATCTTCTGCAA	154	CHLC.GATA85A06	48	SHGC-56989	18	AB051621
MRPL20	1p36.3-p36.2	CAGTAGGAGGCGACACGAAG	CCTCATGTCTGTTATTGGGTTG	188	NIB1364	-9	SHGC-57364	7	AB049644
MRPL22	5q33	GTGAAGTTGGTGGAAGGGC	ACACTGTGGAGTCTGAATCTCC	139	FB25D10	2	SHGC-13988	0	AB051622
MRPL23	11p15.5-p15.4	CTTACATTCCAGGCAGGGAC	AGCATGCTGTAGAGGTCGTC	261	D11S922	7	SHGC-57627	15	AB051340
MRPL24	1q21-q22	CTTAACAGATGGCCCCAAAG	GAAGTGCCTCAGCCTTCAAG	205	WI-8330	3	SHGC-34121	13	AB051341
MRPL27	17q21.3-q22	GCTGTGGATCTGATCACCAG	ACCCTTGACTTCTGGTATCACC	183	D17S797	5	SHGC-31935	15	AB049647
MRPL30	2q11.2	GCACATACCCCTCAAGTTCA	GCATTTTCCAATCGGAAGC	619	WI-4861	3	SHGC-15167	0	AB051342
MRPL32	7p14	CCTCATGTAGCCTGAACATCC	GCAGTAGGCACAAAGGACATG	182	D7S668	13	SHGC-6356	10	AB051343
MRPL33	2p21	CAAAGAGTCCTCTTCGTGGA	AGGAGGCAGTGATTCCATG	163	WI-4431	2	SHGC-33508	7	AB051623
MRPL34	19p13.1	CAGCCGAGCAACATCAAAC	CCAGCTCCCTGCAAAAATAG	205	WI-6344	12	SHGC-21082	7	AB049652
MRPL36	5p15.3	GGAAAATGGTGAACCCTCTG	CATTCTCCCAAGTGATGCG	348	WI-9907	8	SHGC-10589	15	AB049654
MRPL37	1p32.1	CAGGATCCTAATGAACCGTG	TTATTGTCAGCGAGAGCAGC	220	D1S417	2	SHGC-58180	5	AB051344
MRPL38	17q23-q25	GGTGAGGATGACCTGATGC	GTCATGGTGTCGTCTTCCAG	190	no link		SHGC-37061	5	AB051345
MRPL39	21q11.2-q21	ATAGAGCTCTGGCAAGCAGC	CGTCATAACAGAAGGCACCA	192	WI-7427	6	SHGC-6523	10	AB051346
MRPL40	22q11.2	CCTCCCAGTCCACGAATATC	CCTGTAATCCGAGCTACTCG	370	WI-326	4	SHGC-7831	56	AB051624
MRPL41	9q34.3	GCAGCTCTTCAGCGAAGC	GGAAGTTCCTGGGGTAGAGC	140	D9S158	5	SHGC-37250	6	AB051625
MRPL42	12q22	GGCCAGATCCTGTGCATAAT	CCGTCCATGAGGATACCAAC	155	D12S351	4	SHGC-31119	10	AB051626
MRPL43	10q24	CCCAGGCTTTGGACTGTTAC	GATGCCACTTGCATAAAAATG	195	AFM183XB12	3	SHGC-24148	7	AB049656
MRPS2	9q34	GCTTCCCAGCCCATAGTG	GTGGCTGTCTGTTCCAGGTC	199	WI-1405	4	SHGC-63472	38	AB051627
MRPS4	15q24	GGAGGACTTTGTCACTTGGG	GCACCCTCATAGAATCTCCAG	171	CHLC.GATA85D02	7	SHGC-13421	40	AB051628
MRPS5	2p11.2-q11.2	GGATCCAGAGCCAGAAGATG	GGCTGAGTCTCTCCTAGGTGC	174	CHLC.GATA85A06	73	SHGC-57042	24	AB049940
MRPS6	21q21.3-q22.1	GCCCTGATGGACAGAGGAG	GATCATAGTCCACGAAGGGC	296	WI-4888	10	SHGC-21163	31	AB051347
MRPS7	17q23-q25	GGTGAGGGAAGCTCGAAGA	CCGGCACTCAGTGATCATC	228	no link		SHGC-329	3	AB051348
MRPS11	15q25	GCAGAAAGTTGAACAGAACGC	CTCTGTACCACGGCTCATCTG	253	D15S151	3	SHGC-57656	14	AB051349

Table 1 continued on next page

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TABLE 1: continued

Gene	Location	Forward primer	Reverse primer	Size (bp)	GeneBridge 4 Linked marker	GeneBridge 4 Dist. (cR)[a]	Stanford G3 Linked marker	Stanford G3 Dist. (cR)[a]	Accession no.[b]
MRPS12	19q13.1-q13.2	CTGGGGTCCTCCAAATCTAC	CAAGTTAGGGACGTGTTGAGG	331	D19S425	8	SHGC-11892	11	AF058761
MRPS14	1q23-q25	GTAGACTGGAGAATGTGGCG	GCTGGCATAATGAAACAGTTG	333	WI-5780	3	SHGC-19939	5	AB051350
MRPS15	1p35-p34.1	GCTGAAGAAGCGAAGAAGAGC	GAACAGAATTTATTGGCTGTCT	127	WI-611	11	SHGC-57691	10	AB049946
MRPS16	10q22.1	GAGCCTAGTGAATGGCAAGC	CCACAATGCGGTAGAACG	322	WI-2997	7	SHGC-17474	14	AB051351
MRPS17	7p11-q11.21	CCTGGCTTGTTTTCCATACG	CCCAACTGTGCACTGCTG	158	WI-4253	5	SHGC-11581	7	AB051352
MRPS18A	6p21.3	GTCACCCCTTCTGAGGGAC	GGAGTATAGTTGTGGCCAAGG	148	WI-6092	3	SHGC-421	20	AB049952
MRPS21	1q21	GGACACCCAGTGCGAAAC	GTCCACTGCTGACTAATGGG	154	WI-497	7	SHGC-32206	16	AB051353
MRPS22	3q23	GCCTCCAGATTTCTCTCTAACC	GAATGGCGACTGAGTGCTTC	401	D3S1576	5	SHGC-12501	0	AB061314
MRPS23	17q22-q23	GTGTATGGGTCTGGTCAAAGAG	TTCCAAGCAGTCACATTTTAGG	189	WI-6277	4	SHGC-2434	25	AB061206
MRPS24	7p14	GAGAAGAGGCTGGGGGTG	GCGCTTTAAAACCAGCTGG	237	D7S668	12	SHGC-13468	0	AB061207
MRPS25	3p25	GCACCCTGCAATATCTGAGC	GTAAAATGGGGGTAACAGCG	246	WI-7376	0	SHGC-64041	7	AB061208
MRPS26	20p13	CTCAGTGGGGTGAGAGGC	GTGATGGCCCAGTTGTAGTTC	180	WI-3904	2	SHGC-14786	16	AB051354
MRPS28	8q21.1-q21.2	GTTCCAATGCCAAGGAGC	CGCAACTCCGGAAAACTG	229	CHLC.GATA85E10	10	SHGC-10609	38	AB061209
MRPS29	1q21-q22	AGCCTCCAACCTTTTCAAGG	GTTCCTCACCCGTGTTATGC	271	D1S305	3	SHGC-84872	20	AB061210
MRPS30	5p12-q11	TCAAACGGCAGTATGAAAACC	CATGCATGGCACAAATAGGA	392	no link		SHGC-56603	19	AB061211
MRP63	13p11.1-q11	AGTGGATCGGGAAGCACC	GTGACATTGAGATGGTCGAGC	247	WI-8572	-20	SHGC-6104	35	AB049957
MRP64	12p13.3-p13.1	CCAAAGTGGTTGATCGTTG	CACCAGCTAAGCTTTCAACC	412	CHLC.GATA7F09.414	5	SHGC-12737	16	AB051355

[a]Distance from the linked marker in centiRays, for example, *MRPL1* was placed at 5 cR from WI-9200 or at 14 cR from SHGC-24579.
[b]STS sequence or sequence from which the STS was generated.

RESULTS

Identification of STSs in Human MRP Genes

We have purified mitochondrial ribosomes from bovine liver and identified more than 70 bovine MRPs by two-dimensional gel electrophoresis [12]. The partial amino acid sequences of these proteins enabled us to obtain the cDNA sequences of the human MRP genes. We developed 54 STSs using these cDNA sequences (Table 1). Among them, 24 STSs contain only exon sequences, thus were chosen from a single exon of the gene, whereas the other 30 STSs contain a part of an intron sequence, as determined by resequencing of the draft sequence of the human genome. We confirmed the specificity of these STSs to the individual human MRP genes by PCR followed by sequencing of the products. The primer sequences along with the product size and the accession number for the cDNA sequence or the partial genomic sequence are listed in Table 1.

Mapping of 54 MRP Genes

The STSs were then subjected to typing on the basis of two different radiation hybrid mapping panels: GeneBridge 4 and Stanford G3 [24,25]. They were placed on the STS-content map of the human genome (Fig. 1). The results obtained from the two panels were in agreement, except in four cases (*MRPL7/12*, *MRPL38*, *MRPS7*, and *MRPS30*) in which the data vector obtained with the GeneBridge 4 panel indicated no linkage (Table 1). The 54 genes mapped are widely dispersed throughout the genome. Clustering of RP genes into operons, characteristic of bacteria [26], is not apparent in the case of the MRP genes, even though mitochondria are thought to have been generated originally by bacterial endosymbiosis.

Assignment to the Cytogenetic Map

To facilitate investigation of the possible involvement of MRP genes in human disease, it would be helpful to know the cytogenetic positions of these genes. We referred to a cytogenetic BAC-STS map of the human genome, constructed by FISH analysis of 957 human BACs(http://www.csmc.edu/genetics/korenberg/int-bac-sts.html) [27], and assigned the MRP genes to the cytogenetic bands of individual chromosomes (Fig. 1). Almost all of the genes were placed in a region corresponding to one or two cytogenetic bands. Furthermore, we compared the positions of these genes with candidate

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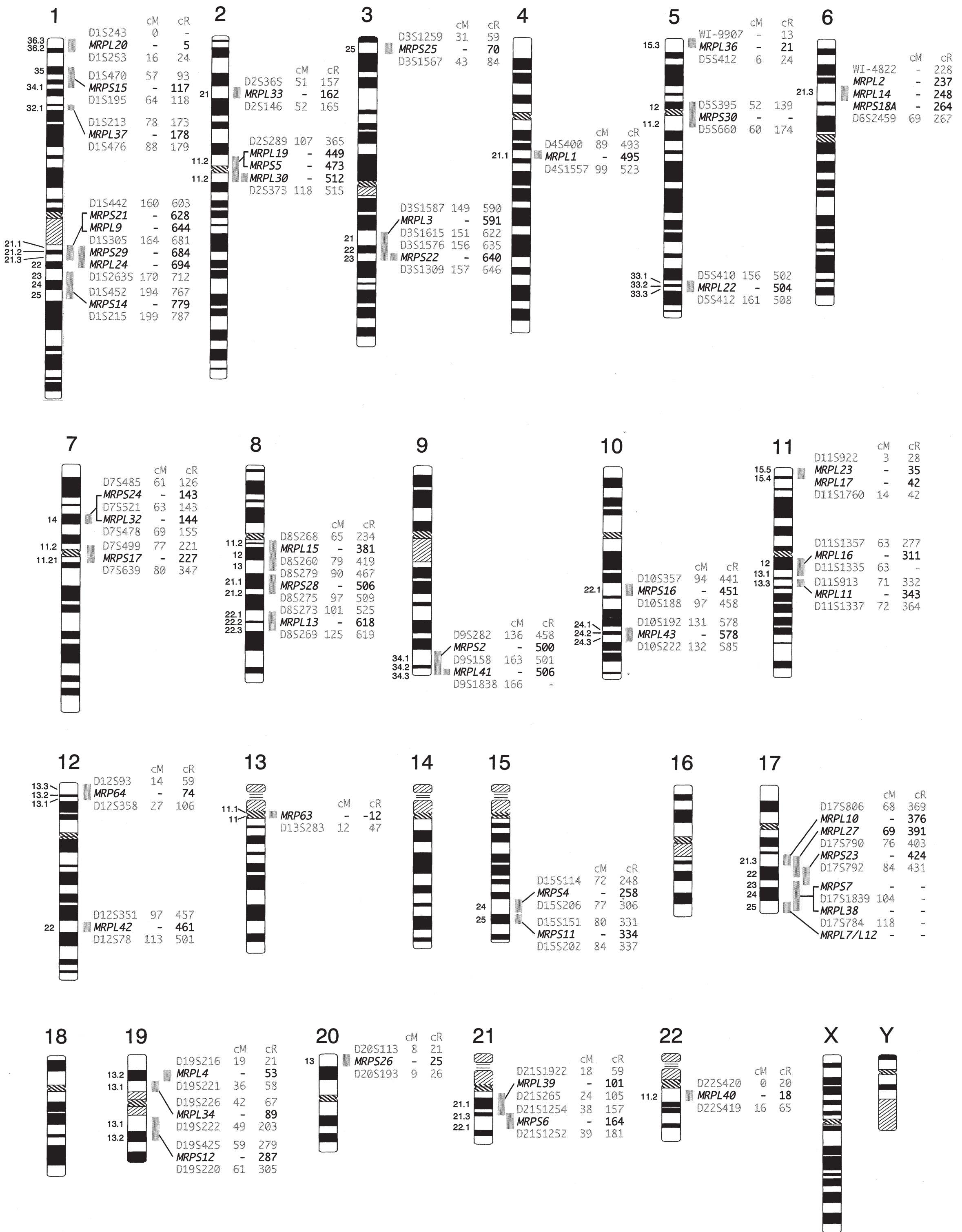

FIG. 1. A map of 54 human mitochondrial ribosomal protein (MRP) genes. To the right of each chromosome are shown the MRP genes, nearby markers, and the approximate distances (in cM and/or cR) from the most distal short-arm marker on the STS-content map constructed at the Whitehead Institute/MIT Center for Genome Research (http://www-genome.wi.mit.edu/cgi-bin/contig/phys-map) [24]. Bold vertical lines indicate the cytogenetic locations according to the cytogenetic BAC-STS map of the human genome (http://www.csmc.edu/genetics/korenberg/int-bac-sts.html) [27].

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TABLE 2: Intervals for human mitochondrial RP genes and linked disorders

Gene	Location	Region (cM)	Disorder	Region (cM)	MIM No.
MRPL3	3q21-q23	149–151	Moebius syndrome 2	144–156	601471
MRPL4	19p13.2	19–36	DFNB15[a]	11–36	601869
MRPL9	1q21	160–164	Retinitis pigmentosa 18	160–164	601414
MRPL39	21q11.2-q21	18–24	USH1E[b]	19–29	602097
MRPS12	19q13.1-q13.2	59–61	DFNA4[c]	59–70	600652
MRPS14	1q23-q25	194–199	DFNA7[d]	183–194	601412
MRPS23	17q22-q23	76–84	Retinitis pigmentosa 17	76–84	600852
MRPS26	20p13	8–9	Hallervorden-Spatz syndrome	8–11	234200

[a]Deafness, autosomal recessive 15.
[b]Usher syndrome, type 1E.
[c,d]Deafness, autosomal dominant nonsyndromic sensorineural 4 and 7, respectively.

regions for mendelian disorders and found certain MRP genes that reside within the small intervals for particular disorders (Table 2).

Discussion

Only six human MRP genes, *MRPS12*, *MRPL3*, *MRPL7/L12*, *MRPL19*, *MRPL23*, and *MRPL37*, have been mapped previously [21,23,28,29]. Here we have mapped an additional 48 genes to the chromosomes. Recent identification of mammalian MRPs [6–12] allowed us to accomplish this mapping. So far, 57 mammalian MRPs have been identified: 31 and 24 in the large and small subunits, respectively, and 2 proteins for which the subunit localization remains to be determined. To simplify the nomenclature, we have named the human MRPs after their bacterial homologues; that is, the MRP genes given the designations *MRPL1* to *MRPL36* correspond to the bacterial RPs L1 to L36, *MRPS1* to *MRPS21* correspond to the bacterial RPs S1 to S21, and those given other designations are specific to the human mitochondrion, for example, *MRPL37* and *MRPS22*. Although the exact number of MRPs is still unclear, we estimate that it is between 70 and 80 in total, based on the results of two-dimensional gel electrophoresis of these proteins (data not shown). Identification of the rest of the proteins and mapping of the genes are under way.

In contrast, localization of the cytoplasmic RP genes has been completed [30–32]. Though scattered about the genome like the MRP genes, each cytoplasmic RP gene has a large number of processed pseudogenes at sites dispersed throughout the genome. It is unlikely that the MRP genes also have such pseudogenes because no variation was detected in the sequences of the PCR products amplified using the genomic DNA as a template and all genes were mapped unambiguously even if the STS was chosen from a single exon sequence. If there were processed pseudogenes, such STSs would not have worked properly on the RH mapping panels because of possible cross-amplification of the pseudogene. The only exception is *MRPL10*. We found a possible pseudogene having a sequence slightly different from the original sequence. It was mapped to chromosome 5, whereas the original sequence was mapped to chromosome 17. To avoid cross-amplification of the pseudogene, we chose a primer from the intron sequence in many cases. We have compared the positions of 134 mitochondrial and cytoplasmic RP genes and have found no cross-linkage between any of these genes (data not shown). Clustering of RP genes into operons, characteristic of bacteria, is not evident in the case of the human mitochondrial or cytoplasmic RP genes, which are randomly scattered about the genome. Though encoded at dispersed genomic sites, these proteins are assembled into the ribosome with stoichiometric precision. It is of great interest to investigate the control mechanism for coordinate expression of these genes. Systematic analysis of the promoter regions is viewed as a key approach to understand such regulation at the transcriptional level.

We have compared the assigned positions of the MRP genes with candidate regions for human disorders. Because defects in the translation apparatus in mitochondria result in abnormal phenotypes such as MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), MERRF (myoclonus epilepsy associated with ragged-red fibers), and deafness [reviewed in 13], it is also possible that defects in MRPs result in mitochondrial dysfunction and associated pathological conditions. Particularly intriguing is the possible involvement of MRPs in deafness. In fact, we have placed several MRP genes in regions critical for hereditary hearing loss (Table 2). Among these genes, *MRPS12* has been extensively characterized as a candidate gene for autosomal dominant sensorineural hearing loss, DFNA4 [21]. In *Drosophila melanogaster*, the *MRPS12* gene was cloned on the basis of its ability to confer a phenotype known as technical knock-out, *tko* [33]. This allele was originally identified through the isolation of a viable mutant with a phenotype of temporary paralysis induced by mechanical vibration, caused by a mechanoreceptor cell defect, and thus it was considered to be a useful model of human deafness. Therefore, *MRPS12* and other MRP genes could be attractive candidates for genes involved in hereditary hearing loss. Our findings suggest that systematic screening to detect mutations in the MRP genes should be carried out. Besides deafness, we have found that certain MRP genes are present in candidate regions for retinitis pigmentosa and for disorders involving neural dysfunction such as Moebius syndrome and Hallervorden-Spatz syndrome (Table 2).

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Because patients with a mitochondrial disease frequently show features such as retinopathy, myopathy, and neuropathy, it is worthwhile pursuing the possibility that defects or mutations in the MRP genes may result in such pathological conditions.

Materials and Methods

Development of STSs. STSs were developed from either cDNA sequences or partial genomic sequences of the human MRP genes. The cDNA sequences were assembled *in silico* from retrieved human EST sequences by BLASTN search, using peptide sequences of bovine MRPs. The bovine MRPs were purified from liver [34,35], then separated by radical-free high-reducing (RFHR) two-dimensional PAGE [36,37]. The peptide sequences were determined by mass spectrometric analysis of the proteins using an LC/MS/MS spectrometry system [12]. The partial genomic sequences were retrieved from the public sequence database of the human genome by BLAST search using the assembled cDNA sequences as the query. Identified STSs were verified by PCR followed by sequencing of the products, using the human genomic DNA as template. The STS sequences and the sequences from which the STSs were generated will appear in the DDBJ/EMBL/GenBank DNA databases under the accession numbers listed in Table 1.

Radiation hybrid (RH) mapping. We used two different RH mapping panels, the GeneBridge 4 and G3 panels (Research Genetics, Huntsville, AL), for localizing MRP genes to the human chromosomes. We tested the panels by PCR using the above-mentioned STSs (Table 1). The data vectors were submitted to the RH servers at the Whitehead Institute/MIT Center for Genome Research (GeneBridge 4; http://www-genome.wi.mit.edu/cgi-bin/contig/rhmapper.pl) or the Stanford Human Genome Center (G3; http://shgc-www.stanford.edu).

Cytogenetic localization. A cytogenetic bacterial artificial chromosome (BAC)-STS map [27] was used for cytogenetic mapping of the MRP genes. The map was constructed by FISH analysis of 975 human BACs. BACs corresponding to the individual MRP genes were identified using the nearby markers obtained from RH mapping of the genes. Each MRP gene was assigned to a cytogenetic band according to the results of FISH analysis of these BACs. Detailed map information about these BACs is available (http://www.csmc.edu/genetics/korenberg/int-bac-sts.html).

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References

1. Yang, D., Oyaizu, Y., Oyaizu, H., Olsen, G. J., and Woese, C. R. (1985). Mitochondrial origins. *Proc. Natl. Acad. Sci. USA* **82:** 4443–4447.
2. Andersson, S. G. E., *et al.* (1998). The genome sequence of *Rickettsia prowazekii* and the origin of mitochondria. *Nature* **396:** 133–140.
3. Attardi, G., and Schatz, G. (1988). Biogenesis of mitochondria. *Annu. Rev. Cell Biol.* **4:** 289–333.
4. Matthews, D. E., Hessler, R. A., Denslow, N. D., Edwards, J. S., and O'Brien, T. W. (1982). Protein composition of the bovine mitochondrial ribosome. *J. Biol. Chem.* **257:** 8788–8794.
5. Graack, H. R., and Wittmann-Liebold, B. (1998). Mitochondrial ribosomal proteins (MRPs) of yeast. *Biochem. J.* **329:** 433–448.
6. Goldschmidt-Reisin, S., *et al.* (1998). Mammalian mitochondrial ribosomal proteins. N-terminal amino acid sequencing, characterization, and identification of corresponding gene sequences. *J. Biol. Chem.* **273:** 34828–34836.
7. Graack, H. R., Bryant, M. L., and O'Brien, T. W. (1999). Identification of mammalian mitochondrial ribosomal proteins (MRPs) by N-terminal sequencing of purified bovine MRPs and comparison to data bank sequences: the large subribosomal particle. *Biochemistry* **38:** 16569–16577.
8. O'Brien, T. W., *et al.* (1999). Mammalian mitochondrial ribosomal proteins (2). Amino acid sequencing, characterization, and identification of corresponding gene sequences. *J. Biol. Chem.* **274:** 36043–36051.
9. O'Brien, T. W., *et al.* (2000). Mammalian mitochondrial ribosomal proteins (4). Amino acid sequencing, characterization, and identification of corresponding gene sequences. *J. Biol. Chem.* **275:** 18153–18159.
10. Koc, E. C., *et al.* (2000). A proteomics approach to the identification of mammalian mitochondrial small subunit ribosomal proteins. *J. Biol. Chem.* **275:** 32585–32591.
11. Koc, E. C., *et al.* (2001). A new face on apoptosis: death-associated protein 3 and PDCD9 are mitochondrial ribosomal proteins. *FEBS Lett.* **492:** 166–170.
12. Suzuki, T., *et al.* (2001). Structural compensation for deficit of rRNA with proteins in mammalian mitochondrial ribosome; systematic analysis of protein components of the large ribosomal subunit from mammalian mitochondria. *J. Biol. Chem.* **276:** 21724–21736.
13. Wallace, D. C. (1999). Mitochondrial diseases in man and mouse. *Science* **283:** 1482–1488.
14. Shoffner, J. M., *et al.* (1990). Myoclonic epilepsy and ragged-red fiber disease (MERRF) is associated with a mitochondrial DNA tRNA(Lys) mutation. *Cell* **61:** 931–937.
15. Goto, Y., Nonaka, I., and Horai, S. (1990). A mutation in the tRNA(Leu)(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. *Nature* **348:** 651–653.
16. Prezant, T. R., *et al.* (1993). Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non-syndromic deafness. *Nat. Genet.* **4:** 289–294.
17. Schon, E. A., Bonilla, E., and DiMauro, S. (1997). Mitochondrial DNA mutations and pathogenesis. *J. Bioenerg. Biomembr.* **29:** 131–149.
18. Shah, Z. H., O'Dell, K. M., Miller, S. C., An, X., and Jacobs, H. T. (1997). Metazoan nuclear genes for mitoribosomal protein S12. *Gene* **204:** 55–62.
19. Johnson, D. F., Hamon, M., and Fischel-Ghodsian, N. (1998). Characterization of the human mitochondrial ribosomal S12 gene. *Genomics* **52:** 363–368, doi:10.1006/geno.1998.5448.
20. Mariottini, P., *et al.* (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:** 31853–31862.
21. Shah, Z. H., *et al.* (1998). Chromosomal locations of three human nuclear genes (RPSM12, TUFM, and AFG3L1) specifying putative components of the mitochondrial gene expression apparatus. *Genomics* **48:** 384–388, doi:10.1006/geno.1997.5166.
22. International Human Genome Sequencing Consortium (2001). Initial sequencing and analysis of the human genome. *Nature* **409:** 860–921.
23. The International Human Genome Mapping Consortium (2001). A physical map of the human genome. *Nature* **409:** 934–941.
24. Hudson, T. J., *et al.* (1995). An STS-based map of the human genome. *Science* **270:** 1945–1954.
25. Stewart, E. A., *et al.* (1997). An STS-based radiation hybrid map of the human genome. *Genome Res.* **7:** 422–433.
26. Nomura, M., Gourse, R., and Baughman, G. (1984). Regulation of the synthesis of ribosomes and ribosomal components. *Annu. Rev. Biochem.* **53:** 75–117.
27. Korenberg, J. R., *et al.* (1999). Human genome anatomy: BACs integrating the genetic and cytogenetic maps for bridging genome and biomedicine. *Genome Res.* **9:** 994–1001.
28. Tsang, P., *et al.* (1995). A novel L23-related gene 40 kb downstream of the imprinted H19 gene is biallelically expressed in mid-fetal and adult human tissues. *Hum. Mol. Genet.* **4:** 1499–1507.
29. Marty, L., Taviaux, S., and Fort, P. (1997). Expression and human chromosomal localization to 17q25 of the growth-regulated gene encoding the mitochondrial ribosomal protein MRPL12. *Genomics* **41:** 453–457, doi:10.1006/geno.1997.4691.
30. Kenmochi, N., Ashworth, L. K., Lennon, G., Higa, S., and Tanaka, T. (1998). High-resolution mapping of ribosomal protein genes to human chromosome 19. *DNA Res.* **5:** 229–233.
31. Kenmochi, N., *et al.* (1998). A map of 75 human ribosomal protein genes. *Genome Res.* **8:** 509–523.
32. Uechi, T., Tanaka, T., and Kenmochi, N. (2001). A complete map of the human ribosomal protein genes: assignment of 80 genes to the cytogenetic map and implications for human disorders. *Genomics* **72:** 223–230, doi:10.1006/geno.2000.6470.
33. Royden, C. S., Pirrotta, V., and Jan, L. Y. (1987). The *tko* locus, site of a behavioral mutation in *D. melanogaster*, codes for a protein homologous to prokaryotic ribosomal protein S12. *Cell* **51:** 165–173.
34. Schwartzbach, C. J., and Spremulli, L. L. (1989). Bovine mitochondrial protein synthesis elongation factors. Identification and initial characterization of an elongation factor Tu-elongation factor Ts complex. *J. Biol. Chem.* **264:** 19125–19131.
35. Liao, H. X., and Spremulli, L. L. (1991). Initiation of protein synthesis in animal mitochondria. Purification and characterization of translational initiation factor 2. *J. Biol. Chem.* **266:** 20714–20719.
36. Wada, A. (1986). Analysis of *Escherichia coli* ribosomal proteins by an improved two dimensional gel electrophoresis. I. Detection of four new proteins. *J. Biochem. (Tokyo)* **100:** 1583–1594.
37. Wada, A. (1986). Analysis of *Escherichia coli* ribosomal proteins by an improved two dimensional gel electrophoresis. II. Characterization of four new proteins. *J. Biochem. (Tokyo)* **100:** 1595–1605.

Sequence data from this article have been deposited with the DDBJ/EMBL/GenBank Data Libraries under accession numbers AB051336 to AB051355, AB051617 to AB051628, AB061206 to AB061211, and AB061314.

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