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Localization of the Human *UbB* Polyubiquitin Gene to Chromosome Band 17p11.1-17p12

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Summary

The chromosomal location of the human ubiquitin genes has been evaluated by in situ hybridization. Because of the conservation of the ubiquitin sequence, coding-region probes cannot distinguish between specific ubiquitin genes and reveal ubiquitin sequences in a number of different chromosomal regions. The major sites of hybridization with a coding-region probe include 17p11.1-p12, 12p24.2-q24.32, and 2q21-q24, with weaker hybridization over 1p3, 1q4, 2q3, and 13q. Hybridization with a probe isolated from the *UbB* gene intron indicated that this gene is located within the region 17p11.1-17p12. This region showed the strongest hybridization with the coding-region probe and is presumably also the location of the duplicated UbB pseudogene.

Introduction

Molecular studies on the eukaryotic protein ubiquitin have revealed two major features: (1) it is perhaps evolution's most conserved protein, and (2) the genes encoding it exhibit a completely novel structure. The former feature (reviewed by Sharp and Li 1987*b*) is presumably dictated by its role in several important cellular processes, including the cytoplasmic ATP-dependent proteolytic system (reviewed by Hershko and Ciechanover 1986), the stress response (Bond and Schlesinger 1985; Finley et al. 1987), and the formation of metabolically stable conjugates with other proteins, including histones (reviewed by Finley and Varshavsky 1985), cell-surface receptors (Siegelman et al. 1986; Yarden et al. 1986), and several pathological fibers (Mori et al. 1987; Lowe et al. 1988).

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The uniquely structured ubiquitin genes exist as two types of natural gene fusions, either of ubiquitin to itself in a tandem repeat array to produce the polyubiquitin gene or to an unrelated "tail" protein, known as the ubiquitin fusion gene (reviewed by Schlesinger and Bond 1987). Both structural arrangements have been strongly conserved during evolution. The ubiquitin-free tail proteins have recently been identified as ribosomal proteins (Finley et al. 1989; Redman and Rechsteiner 1989).

The human ubiquitin gene family consists of two ubiquitin fusion gene subfamilies, UbA_{52} and UbA_{80}, which encode a single ubiquitin protein fused to a 52- or 80-amino-acid tail, respectively (Lund et al. 1985; Salvesen et al. 1987; Baker 1988), and two polyubiquitin subfamilies UbB and UbC. The *UbB* gene contains three coding units, whereas *UbC* alleles contain predominantly nine but occasionally eight or seven coding units (Wiborg et al. 1985; Baker and Board 1987*a*, 1989). In addition, processed and/or nonprocessed pseudogenes have been observed in each subfamily except UbC (Wiborg et al. 1985; Baker and Board 1987*a*, 1987*b*; Baker 1988; Cowland et al. 1988).

As a continuation of our studies on the human ubiquitin gene family, we have begun to map the chromosomal location of these genes by in situ hybridization. Here we describe the main sites of localization of a ubiquitin-coding-unit cDNA—to the short arm of

chromosome 17, to the tip of the long arm of 12, and to an interstitial site on the long arm of chromosome 2—plus the assignment of the three-coding-unit polyubiquitin gene *UbB* and its nonprocessed pseudogene to chromosome bands 17p11.1-17p12.

Material and Methods

Hybridization Probes

Probes derived from *UbB* included the ubiquitin-coding-region and 3′ noncoding-region probes and the partial *UbB* cDNA clone pRBL26, which contains 2.2 ubiquitin-coding units plus the 3′ noncoding region and has been described elsewhere (Baker and Board 1987*a*). A UbB intron-specific probe (pINT) was constructed from *UbB* by subcloning a 752-bp *Bam*HI/*Bgl*II fragment containing the entire 715-bp intron, 28 bp of 5′ noncoding region, and the first 9 bp of ubiquitin-coding sequence (see fig. 1).

Southern Blot Analysis

Human genomic DNA was prepared from peripheral blood, digested with restriction enzymes, electrophoresed, transferred to nylon membranes (GeneScreen Plus™; Du Pont), and hybridized according to a method described elsewhere (Baker and Board 1987*a*).

In Situ Hybridization

Chromosome preparation and in situ hybridization were performed essentially as described most recently by Board et al. (1989), with some exceptions. The two hybridization probes used, pINT and pRBL26, were utilized as intact plasmids. The probes were tritium labeled by nick-translation to specific activities of 1.2×10^8 CPM/μg for pINT and 2.9×10^8 CPM/μm for pRBL26. The pINT probe was applied to slides under standard conditions, at a concentration of 200 ng/ml, with salmon-sperm carrier DNA at 1,000 times this concentration. Acetylation (Pardue 1985) was not used with pINT but would probably have been beneficial in reducing background. The pRBL26 probe usually gave high background under standard conditions of in situ hybridization; the slides which were eventually analyzed were hybridized at a probe concentration of 100 ng/ml, with 4,000 times this concentration of carrier DNA, and they were acetylated. In each case hybridized chromosome preparations were exposed to Ilford L4 emulsion for 6 d.

After the slides were stained to produce GBG-banding (G-banding by incorporation of 5-bromodeoxyuridine and Giemsa staining), grains on the chromosomes or within a one-half-chromatid width (fig. 2) were scored either onto 450-band standard idiograms for scoring all chromosomes or onto 550-band idiograms for detailed scoring.

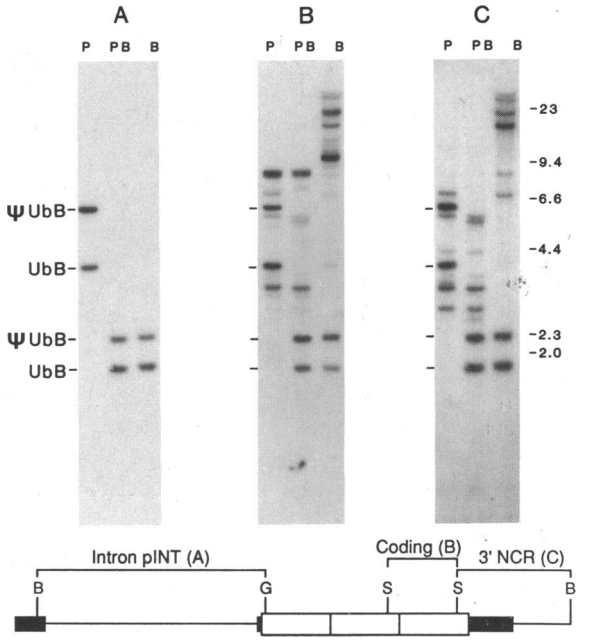

Figure 1 Hybridization analysis of total human genomic DNA. The DNA was digested with *Pst*I (lanes P), *Pst* I/*Bam*HI (lanes PB), or *Bam*HI (lanes B). Panels *A*–*C* represent hybridization from different regions of the *UbB* gene shown schematically below the figure. Panel *A* was probed with pINT, a subclone spanning the entire intron. Panel *B* was hybridized with a coding-region probe, and panel *C* was probed with a 3′ noncoding-region subclone. The size standards on the right are from a *Hin*dIII digest of λ DNA and are given in kilobases. In the schematic showing the position of the region-specific probes, restriction-enzyme sites are shown as *Bam*HI (B), *Bgl*II (G) and (*Sal*I) S. The open boxes represent ubiquitin-coding-region repeats, and the heavily black area represents noncoding regions.

Results

Southern Blot Analysis

We have previously reported Southern blot analysis employing probes derived from the 5′ noncoding and coding and from the 3′ noncoding regions of the *UbB* polyubiquitin gene (Baker and Board 1987*a*). This analysis indicated that the UbB subfamily contains several members and suggested the presence of a duplicated *UbB* gene. Extension of this analysis, employing as a probe the single *UbB* intron (located within the 5′ noncoding region), provided stronger evidence for such a duplicated gene: the *UbB* intron is a two-copy sequence

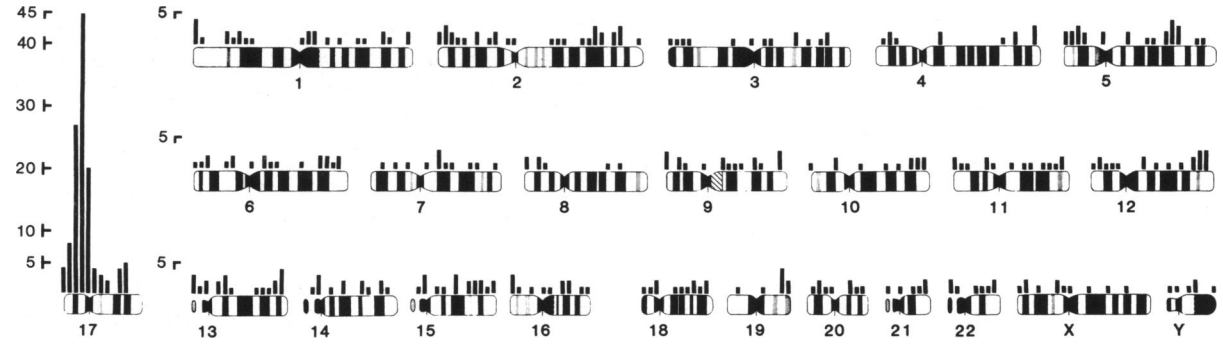

Figure 2 Score of grains over all chromosomes from a normal male that were probed with pINT. The tallest peak of grains is over the faint subband 17p11.2, and the tallest background peak, over the long arm of chromosome 17, is due to a consistent technical artifact. Background is less than five grains over the other chromosomes.

in the human genome, hybridizing to restriction fragments corresponding to *UbB* and the apparently duplicated gene (fig. 1*A*). Recent results of Cowland et al. (1988) confirm the prediction of a duplicated *UbB* gene and reveal that it is in fact a four-coding-unit nonprocessed UbB pseudogene (ψUbB). These authors report that 85 bp from the 3′ end of the pseudogene intron exhibits 89.4% sequence similarity to the corresponding region of *UbB*. Presumably a similar level of similarity exists over the entire intron, explaining the approximately equal intensity with which the intron probe hybridizes to both loci at the moderate stringency employed in figure 1. Conversely, none of the other *UbB* subfamily members identified by the *UbB* 3′ noncoding-region probe (fig. 1*C*) hybridize to pINT, suggesting that all remaining *UbB* subfamily members represent processed (i.e., intronless) pseudogenes. Three of these loci have been cloned and sequenced to reveal processed pseudogenes, in support of this conclusion (Baker and Board 1987*a*, 1987*b*). The *UbB* intron thus provides an ideal probe for in situ hybridization, allowing us to distinguish the *UbB* and ψ*UbB* genes from all other potentially cross-hybridizing ubiquitin sequences.

pRBL26 can potentially hybridize to all ubiquitin genes, whereas pINT specifically hybridizes to the *UbB* gene and to its nonprocessed pseudogene.

Chromosomal Localization of the UbB Gene

The results of in situ hybridization of the *UbB* intron probe pINT to chromosome spreads prepared from a normal male are presented in figure 2, as total grain counts over all metaphase chromosomes observed in approximately 140 cells. The main peak of grains, over the short arm and centromere of chromosome 17, contains 113 grains, of which 39.8% are in the tallest peak over subband 17p11.2; the next tallest peak is over the grey band 17p12; 63.7% of the grains are in these two tallest peaks. The third tallest peak is over subband 17p11.1, next to the centromere; 81.4% of the grains in the target region are in the three tallest peaks, over a region from the centromere to band p12. Background is relatively high compared with results of some of our other experiments (Webb et al. 1989). The background is highest on the two dark bands on the long arm of chromosome 17 (fig. 2), but this peak appears in all of our current hybridizations with various probes and presumably is a technical aberration.

Hybridization was further quantitated by a detailed scoring of grains over prophasic chromosomes 17 from 145 cells from the same male as used for figure 2 (fig. 3). This analysis revealed that this tallest peak was over the distal half of band 17p11.2 and that the next tallest peak was over band 17p12, with the third tallest being over the proximal half of 17p11.2. The two tallest peaks contained 48.9% of the 135 grains over the short arm and centromere region of chromosome 17, and the three tallest peaks contained 61.5% of these grains. Subband p11.1 and the centromere continue to be labeled above background. It is clear that pINT is identifying the region 17p11.1-p12 as the probable location of the *UbB* gene, with 17p11.2 as a likely single subband location and with the distal half of 17p11.2 as the possible point location of this gene complex. Furthermore, as no other significant accumulation of grains was observed at any other chromosomal location (fig. 2), the duplicated ψ*UbB* gene (the four-coding-unit nonprocessed UbB pseudogene described by Cowland et al. [1988]) must also map to the same location.

The result obtained with pINT was repeated with scoring of the grains over the chromosomes of a normal female (data not shown). Qualitatively similar

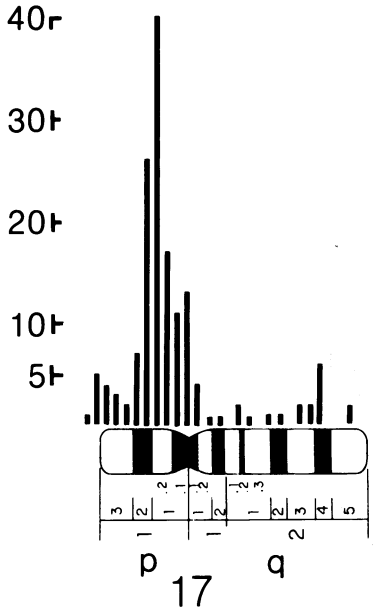

Figure 3 Scores of grains over prophasic chromosomes 17 when pINT is used as a probe. The tallest peak of grains is over the distal half of the subband 17p11.2, and the next tallest peak is over the proximal half of band 17p12. The genes of the *UbB* complex are probably in bands 17p11.1-p12, with a possible point location in 17p11.2, near the interface of this subband with 17p12.

results were also observed in three further normal individuals, without scoring. As an additional check on the localization of pINT, it was used to probe the chromosomes of a female patient with deletion of part of subband 17p11.2. The patient showed most of the features of the consistent clinical phenotype now associated with deletion of 17p11.2 (Lockwood et al. 1988). Of 64 chromosome spreads with label on chromosome 17, 11 had both chromosomes 17 labeled over the short arm or centromere, 22 showed labeling of the deleted 17, and 31 showed labeling of the intact 17. The excess of labeled normal chromosomes (42) over deleted (33) is not significant, indicating that the deletion in the patient is not removing all of the *UbB* genes from chromosome 17; however, it remains possible that some of the genes have been removed.

Chromosomal Localization of Ub Sequences

In situ hybridization was also performed with the *UbB* cDNA clone pRBL26 described previously. The scoring of grains resulting from this hybridization produced peaks over several chromosomes. In order to resolve the consistency of these peaks, four normal individuals were investigated in detail and one other was investigated qualitatively; all five gave essentially similar results, so only one representation plot is shown (fig. 4). Two of the individuals studied with *UbB* cDNA were also the subjects of detailed investigation with the pINT probe.

The most obvious concentration of grains occurs over the short arm of chromosome 17 and is centered over band 17p11.2, which supports the assignment of the *UbB* genes to this region. Detailed scoring was carried out on the prophasic chromosomes of the individual in figure 4 (fig. 5). In the detailed scoring, the tallest peak of grains is over band 17p11.2, with the next tallest peak being over 17p11.1 and the third tallest peak being over the interface of 17p11.2 and 17p12 (fig. 5); these three peaks contain 53.2% of the 109 grains over the short arm of 17 and the long arm to band 17q21.2. This detailed scoring is supported by the results from overall scoring (fig. 4) and leads to the conclusion that there is a concentration of ubiquitin sequences on chromosome 17p11.1-17p12, with a possibility of precise localization to the distal region of band 17p11.2 quite close to its interface with band 17p12. This is precisely the location found for the *UbB* complex.

A strong secondary peak on the distal tip of the long arm of chromosome 12 was identified by the *UbB* cDNA probe (fig. 4). Detailed scoring (fig. 5) shows the tallest peak of grains to be over band 12q24.31 and the next tallest to be over band 12q24.32; 51.3% of the 78 grains over the distal half of arm 12q are in these two tallest peaks. The third peak is over band 12q24.2, and 71.8% of grains are in the three tallest peaks. Therefore, there are probably ubiquitin sequences in the region 12q24.2-q24.32, with a possible precise localization to band q24.31.

There is one more consistent peak identified by the Ub cDNA probe, on the long arm of chromosome 2 (fig. 4). Detailed scoring shows this peak to be in the vicinity of band 2q22, and 54.8% of the 26 grains scored over the proximal half of arm 2q (fig. 5) are in the two columns over this band. However, the overall scoring (fig. 4) shows some differences, with the peak of grains being over 2q23 in two individuals, one of whom is the same individual who was used for detailed scoring. The bands in the 2q region in question are very difficult to recognize, so although there was agreement with a second cytogeneticist for some of the scoring, it seems advisable to quote the interval 2q21-q24 as the probable location of this site of hybridization.

Weak peaks of hybridization are identified by the ubiquitin cDNA probe in the regions 1p3, 1q4, 2q3, and 13q (fig. 4). In the absence of further study, it re-

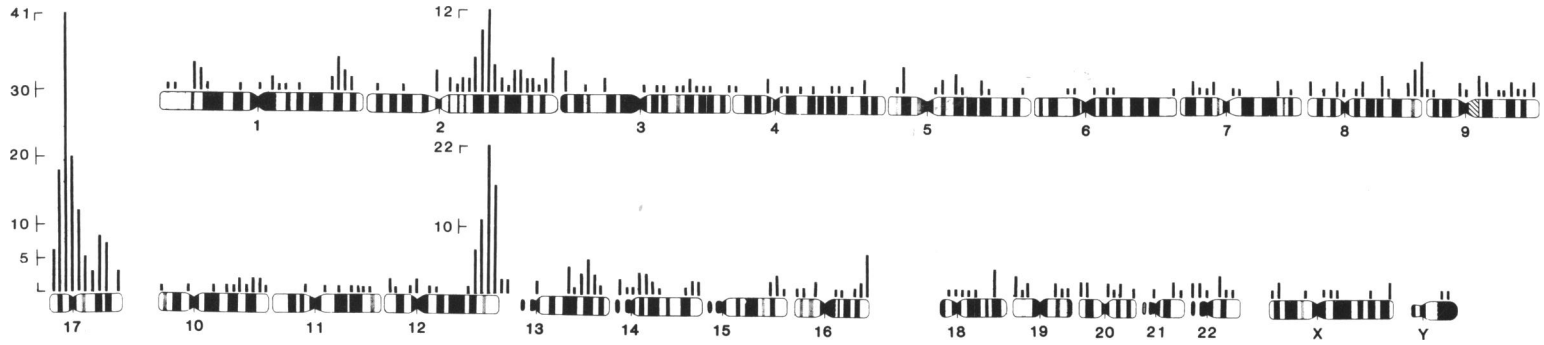

Figure 4 Scores of grains over all chromosomes probed with ubiquitin cDNA (pRBL26). The tallest peaks are over subband 17p11.2, the next tallest are over subband 12p24.3, and the third tallest are over band 2q22. The peak on the long arm of chromosome 17, due to technical artifact, is noticeable, and there are minor peaks at 1p3, 1q4, 2q3, and 13q. This male individual was also used for fig. 5.

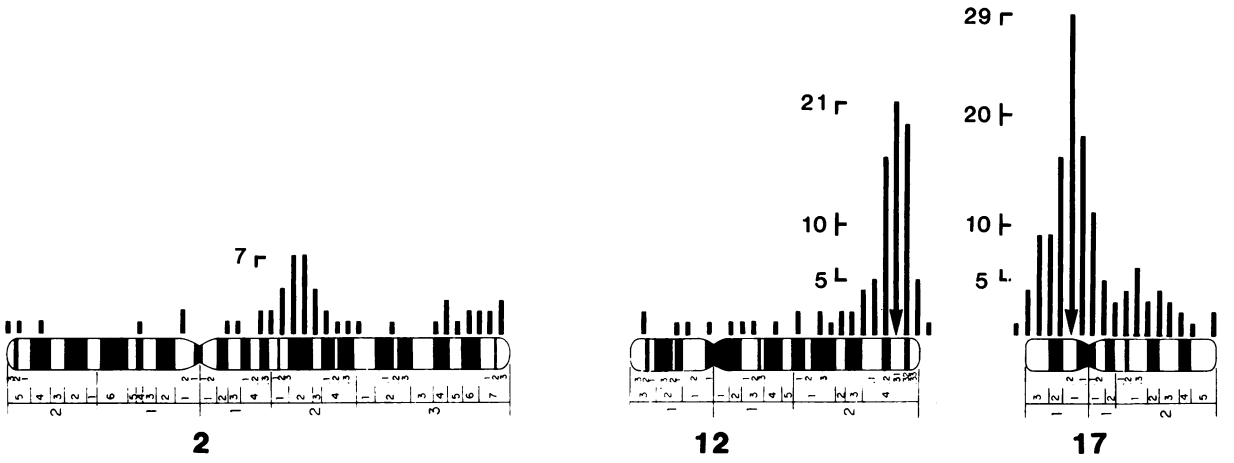

Figure 5 Scores of grains over prophasic chromosomes 2, 12, and 17 of the male used for fig. 4. The two equally tallest columns of grains on chromosome 2 are over band 2q22, and there is a minor peak over 2q34-q37. The positions of the peaks of grains on chromosomes 12 and 17 are shown with arrows, at 12q24.31 and 17p11.2, respectively.

mains uncertain whether these minor peaks are the sites of ubiquitin genes or of pseudogenes.

The large number of peaks observed is not inconsistent with the large number of restriction fragments that hybridize to a ubiquitin-coding-region probe on a Southern blot (fig. 1*B*) and also indicates that all ubiquitin sequences are not clustered at one chromosomal location. In fact, the processed UbB pseudogenes (of which three have been cloned and sequenced [Baker and Board 1987*a*, 1987*b*]) would be expected to occur at different genomic loci to that of their parent *UbB* gene, as processed pseudogenes integrate at random into the genome (Sharp 1983).

Discussion

The in situ hybridization employing the *UbB* intron described above clearly localizes the *UbB* three-coding-unit polyubiquitin gene to chromosome bands 17p11.2-17p12. Furthermore, it is equally apparent that the four-coding-unit nonprocessed (i.e., intron-containing) UbB pseudogene described by Cowland et al. [1988] also maps to the same region. Whereas Southern hybridization analysis with the *UbB* intron probe resolves the gene and nonprocessed pseudogene to separate *Bam*HI or *Pst*I restriction fragments, in situ hybridization with the same probe produces only one peak, placing both genes within the same general chromosomal location. This observation is in agreement with theories on the origin of nonprocessed pseudogenes, which result from DNA duplication events to produce a gene pair, which is followed by mutational inactivation of one of the pair (Sharp 1983). A classic example of this phenomenon is the α-globin gene cluster, which contains three active genes and four nonprocessed pseudogenes (Karlsson and Nienhuis 1985; Proudfoot 1986), all which have apparently arisen from duplication of a single ancestral gene. In the α-globin gene cluster, adjacent genes are spaced by approximately 1–4 kb. If the duplicated *UbB* genes were similarly spaced, they would be nonresolvable by in situ hybridization, as we have observed above. The exact spacing of *UbB* and its nonprocessed pseudogene has not been determined. However, the regions 12.5 kb upstream and 1.2 kb downstream of *UbB* are devoid of ubiquitin-homologous sequences (as determined by Southern hybridization analysis of the genomic clone from which *UbB* was isolated [Baker and Board 1987*a*]), and thus the pseudogene is placed outside these limits.

Cowland et al. (1988) have speculated that the nonprocessed pseudogene resulted from an ancestral unequal crossover at the *UbB* locus. We have previously described unequal crossovers at the *UbC* locus (Baker and Board 1989), but we have not observed any RFLP indicative of unequal crossovers at the *UbB* locus in a study of 39 unrelated individuals (R. T. Baker and P. G. Board, unpublished data). We have, however, determined additional nucleotide sequences upstream and downstream of *UbB* (Baker 1988), to reveal that it is flanked by *Alu* repeats. While purely speculative, it is possible that the nonprocessed pseudogene arose via *Alu*-mediated gene duplication, by a mechanism similar to the *Alu*-mediated duplication of seven exons of the low-density-lipoprotein-receptor gene described by Lehrman et al. (1987). Identification of a role for the *Alu* sequences flanking *UbB* in its duplication must

await both the determination of nucleotide sequence data on the flanking regions of the UbB processed pseudogene and comparison with the corresponding regions of *UbB* to determine the endpoints of the duplication event.

The observed hybridization of the UbB cDNA to several human chromosomes indicates that all of the ubiquitin-homologous loci observed on a Southern blot are not clustered at the one chromosomal locus. However, the nonspecific nature of this probe precludes peak assignment for several reasons. First, the UbB cDNA contains 2.2 ubiquitin-coding units, which would cross-hybridize, to varying extents, with all ubiquitin loci. Second, Southern blots (e.g., see fig. 1) indicate that hybridization signal is proportional to the number of coding units per locus, which ranges from one to nine. Third, the cDNA contains the intact UbB 3′ noncoding regions and would thus have higher affinity for UbB loci. Finally, Baker and Board (1987*a*, 1987*b*) have isolated at least three UbB processed pseudogenes which will presumably occur at chromosomal locations different to that of their parent gene. With these considerations in mind, tentative analysis can be made. The nine-coding-unit *UbC* gene would be expected to produce a major peak, whereas the strongest peak observed is over bands 17p11.2-17p12, the location of the duplicated *UbB* genes. The second most intense peak, over 12q24.3, is considerably smaller, prompting speculation that the *UbC* gene is also located on the short arm of chromosome 17 and contributes to the peak height observed there. Such a location would be in agreement with the possibility that the *UbB* and *UbC* genes arose from an early unequal crossover event of a single polyubiquitin precursor gene, as Sharp and Li (1987*a*, 1987*b*). However, the same authors suggest, that the human ubiquitin loci may have different chromosomal locations, based on the basis of an apparent lack of interlocus gene conversion. In this respect, it must be noted that the peaks observed by in situ hybridization cover at least tens of thousands of kilobases, and thus the *UbB* and *UbC* loci may still be sufficiently isolated to reduce the frequency of gene conversion events.

The UbB processed pseudogenes are expected to be dispersed throughout the genome and may correspond to some of the peaks observed with the UbB cDNA probe on chromosomes other than 17. The second largest peak (over subband 12q24.3) may represent the two-coding-unit UbB processed pseudogene, while smaller peaks may represent the one-coding-unit UbB processed pseudogenes (Baker and Board 1987*a*, 1987*b*) and other, as yet uncharacterized, UbB, UbA_{80}, and UbA_{52} genomic loci. Assignment of these loci must await the development of gene-specific probes, as was required for the localization of the duplicated *UbB* gene described above.

The assignment of the *UbB* intron probe to chromosome bands 17p11.2-17p12 may provide a useful marker for linkage studies in a chromosomal region where few markers have yet been localized and where deletions have been associated both with colorectal cancers (Baker et al. 1989) and with a syndrome characterized by mental retardation and multiple congenital malformations (Lockwood et al. 1988).

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