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Do Human Chromosomal Bands 16p13 and 22q11-13 Share Ancestral Origins?

To the Editor:

Ancient duplications and rearrangements within a genome are believed to be important mechanisms of evolution. Although most duplications are of gene segments, single genes, or chromosomal segments, molecular evidence has been gathered suggesting that whole-genome duplication has facilitated evolution in yeast (Wolfe and Shields 1997). Identifying these duplicated genomic areas can be valuable not only for understanding the timing and nature of evolutionary events; additionally, this information can greatly facilitate the pinpointing of novel (disease-related) genes by positional cloning techniques.

While mapping and cloning the human gene encoding the CREB-binding protein (CBP, encoded by the *CREBBP* gene) on chromosome band 16p13.3 (Giles et al. 1997*b*), we noticed an emerging pattern concerning the genomic relationship between this chromosome band and a region of chromosome 22q. CBP exhibits extensive homology to the adenovirus E1A–associated protein p300, whose gene has been mapped to human chromosome band 22q13 (Eckner et al. 1994; Lundblad et al. 1995). At that time we noted with interest that the heme oxygenase-1 (*HMOX1*) gene, just centromeric of *CREBBP* on 16p13.3, has a paralogue mapping to chromosome band 22q12, heme oxygenase-2 (*HMOX2*; Kutty et al. 1993). Our interest was further piqued when the molecular defect in families with carbohydrate-deficient glycoprotein type I syndrome (CDG1) was determined to be caused by mutations in the phosphomannomutase 2 gene (*PMM2*) on 16p13 (Matthijs et al. 1997*a*); the same investigators had previously mapped the first phosphomannomutase gene (*PMM1*) to 22q13 (Matthijs et al. 1997*b*). Sequence comparison at the amino acid level revealed that homologies between these paralogous proteins are high: homology between CBP and p300 is 63% (Arany et al. 1995), that between PMM1 and PMM2 is 66% (Matthijs et al. 1997*a*), and that between HMOX1 and HMOX2 is 74% (authors' observation). Subsequent examination of genome databases (e.g., OMIM) resulted in six additional sets of paralogues mapping to chromosomes 16p13 and 22q11-13, although the extent of homology between these paralogue sets is not known (table 1). YAC contigs connecting outlying genes of each paralogous cluster, *CREBBP* to *MYH11* on chromosome 16 and the *CRYB* genes to *PMM1* on chromosome 22, suggest that the extent of the redundant area presented here is ~12–14 Mb. Furthermore, *CREBBP* and *MYH11* are also thought to be near the borders for the conserved synteny group in mouse chromosome 16 (Doggett et al. 1996).

We propose that the existence of these paralogous sets suggests that chromosome bands 16p13 and 22q11-13 share ancestral origins and that at some point a large-scale duplication gave rise to this second set of genes. It is well established that such duplicated regions exist (Lundin 1993; Holland et al. 1994), and a catalogue of putative paralogous regions can be found on-line (Database of Duplicated Human Chromosomal Regions). This database suggests two duplicated regions for areas of 16p: a well-documented gene cluster on chromosome band 16p11.1, which shares high homology with a locus on Xq28 (Eichler et al. 1996), and a region of 16p13, which resembles 19p13, although no specific genes are named.

A hypothesis set forth by Ohno (1993) suggests that at the stage of fish, the mammalian ancestral genome underwent tetraploid duplication. Although certain aspects of this hypothesis are not universally accepted, most scientists agree that the fourfold increase, in the number of genes, between invertebrates and vertebrates implies at least two rounds of genome duplication (Aparicio 1998). Paralogues such as the HOX-

Table 1

Paralogous Genes Mapped to Chromosome Bands 16p13 and 22q11-13

Paralogues		
Gene/Chromosome[a]	Gene /Chromosome	Description
SSTR5/16p13.3	SSTR3/22q13.1	Somatostatin receptors
CREBBP/16p13.3	p300/22q13	Transcriptional cofactors
CSNK2A1/16p13.3	CSNK1E/22q12-13	Casein kinase isoforms
UBE2I/16p13.3	UBE2L3/22q11.2-13.1	Ubiquitin-conjugating enzymes
PMM2/16p13.3	PMM1/22q13.1	Phosphomannomutase isoforms
HMOX2/16p13.3	HMOX1/22q12	Heme oxygenase isoforms
MYH11/16p13.13-13.12	MYH9/22q11.2	Myosin heavy-chain subunits
CRYM/16p13.11-12.3	CRYBB1/22q11.2-12.1	Crystallin isoforms
	CRYB2/22q11.2-12.2	
	CRYB3/22q11.2-12.2	
	CRYBA4/22q11.2-13.1	
IL4R/16p12	IL2RB/22q12	Interleukin receptors

[a] Listed from telomere to centromere

gene clusters, which are situated at four distinct chromosomal loci, bolster this hypothesis. If the gene redundancy observed on chromosomes 16 and 22 is a result of Ohno's proposed ancestral event, then one might expect that two additional loci exist in the human genome that shares at least partial homology. CBP and p300 do, in fact, count two additional protein family members, p270 (Dallas et al. 1997) and p400 (Barbeau et al. 1994), although the genes for these proteins have not yet been mapped. Candidate regions, however, can be inferred from the literature. For example, clues can be taken from the somatic translocation t(8;16)(p11;p13.3), associated with acute myeloid leukemia, which disrupts the *CREBBP* gene and fuses it to a gene on chromosome 8, called "*MOZ*" (Borrow et al. 1996; Giles et al. 1997*a*). Phenotype-identical variants of the t(8;16) have been described: the t(8;22)(p11;q13), postulated to fuse *p300* to *MOZ*, as well as t(6;8)(q27;p11) (Tanzer et al. 1988), t(8;19)(p11;q13.2) (Tanzer et al. 1988; Stark et al. 1995), t(8;14)(p11;q11.1) (Slovak et al. 1991), and t(3;8;17)(q27;p11;q12) (Bertheas et al. 1989). If it is assumed that these phenotypically similar leukemias all fuse *MOZ* to genes situated at the breakpoints on chromosome bands 3q27, 6q27, 14q11.1, 17q12, or 19q13.2, then these loci become good candidates for the *p270/p400* genes—and, thus, for additional redundant clusters. Interestingly, two of these loci do harbor additional gene-family members paralogous to those mapping to 16p13 and 22q11-q13 (table 1): the *SSTR1, UBE2L1, MYH6,* and *MYH7* genes map to chromosome bands 14q11-q13, whereas the *SSTR2, CSNK1D,* and *CRYBA1* genes map to chromosome 17q11-q25. The gene-mapping data coupled with the leukemia breakpoint locations strongly suggest that these gene families have arisen by tetrapoidization with members on chromosomes 14q, 16p, 17q, and 22q.

Genetic redundancy is potentially of great relevance to organismal evolution, since it may protect organisms from potentially harmful mutations and may provide a pool of diverse yet functionally similar proteins for further evolution. Transcription factors such as CBP and p300 are thought particularly to "profit" from redundancy, as demonstrated by recent knockout mouse studies, which show that the combined dose of CBP and p300 is essential for survival (reviewed by Giles 1998). The existence of these duplicated gene clusters is not just a matter of redundancy; in the cases of CBP/p300 and PMM1/PMM2, the proteins have been shown to be functionally divergent. Where in vitro experiments suggest almost complete functional redundancy, CBP and p300 are clearly not physiologically interchangeable (reviewed by Giles et al. 1998); inactivating germ-line mutations of one copy of the *CREBBP* gene cause the Rubinstein-Taybi syndrome (Petrij et al. 1995). Likewise, mutations in *PMM2,* but not those in *PMM1,* result in CDG1 (Matthijs et al. 1997*a;* Schollen et al. 1998).

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim

Database of Duplicated Human Chromosomal Regions, http://www.cib.nig.ac.jp/dda/timanish/dup.html

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How Sib Pairs Reveal Linkage

To the Editor:

The Haseman-Elston (1972) method, widely used for