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GDD1 Is Identical to TMEM16E, a Member of the TMEM16 Family

To the Editor:

In the June 2004 issue of *The American Journal of Human Genetics,* Tsutsumi et al. (2004) reported the identification and characterization of the *GDD1* gene, which is mutated in patients with gnathodiaphyseal dysplasia (MIM 166260). They claimed that human *GDD1* is a novel gene without any human homologs (Tsutsumi et al. 2004); however, we found that *GDD1* was identical to *TMEM16E* (MIM 608662), a member of the *TMEM16* gene family (Katoh and Katoh 2003, 2004*a*, 2004*b*).

In 2003, we identified and characterized the *TMEM16A* (*FLJ10261*) gene, which is located within the 11q13.3 amplicon (Katoh and Katoh 2003). The *CCND1-ORAOV1-FGF19-FGF4-FGF3-TMEM16A-FADD-PPFIA1-EMS1* amplicon at human chromosome 11q13.3 is one of the most frequently amplified regions in the human genome (Schwab 1998; Katoh and Katoh 2003). The *FLJ10261, C12orf3, C11orf25,* and *FLJ34272* genes, which encode mutually homologous eight-transmembrane proteins with N- and C-terminal tails facing the cytoplasm, were designated as "*TMEM16A,*" "*TMEM16B,*" "*TMEM16C,*" and "*TMEM16D,*" respectively, on the basis of our communication with the Human Gene Nomenclature Committee (see the HUGO Gene Nomenclature Committee Web site).

We then searched for novel members of the *TMEM16* gene family and identified the *TMEM16E, TMEM16F* (MIM 608663), and *TP53I5* genes (Katoh and Katoh 2004*a*, 2004*b*). TMEM16A, TMEM16B, TMEM16C, TMEM16D, TMEM16E, TMEM16F, and TP53I5 are eight-transmembrane proteins with TMEM16 homologous (TM16H1, TM16H2, and TM16H3) domains. Several Cys residues and Asn-linked glycosylation sites are included in the conserved residues (or the consensus sequence) of the TM16H1, TM16H2, and TM16H3 domains.

The *TMEM16E-NELL1* locus at human chromosome 11p15.1-p14.3 and the *TMEM16F-NELL2* locus at human chromosome 12q12 are paralogous regions (par-

alogons) within the human genome. Phylogenetic analysis revealed that TMEM16E and TMEM16F constitute a subfamily among TMEM16 family proteins. On the basis of these facts, we concluded that the *TMEM16E* and *TMEM16F* genes are paralogs within the human genome (Katoh and Katoh 2004*b*).

Tsutsumi et al. (2004) suggested that the human GDD1 protein showed no significant similarity to any other known proteins or protein classes except GDD1 orthologs in other species. They also reported that the human GDD1 protein showed 79%, 56%, 40%, and 41% identity with mouse, zebrafish, fruit fly, and mosquito orthologs (or homologs), respectively.

However, TMEM16E is identical to GDD1, as mentioned above, and BLAST programs reveal that TMEM16E (GDD1) is homologous to other members of the TMEM16 family, such as TMEM16F, TMEM16A, TMEM16B, TMEM16C, and TMEM16D. Human TMEM16E (GDD1) shows 50.3% total amino acid identity with human TMEM16F (Katoh and Katoh 2004*b*). Human TMEM16E (GDD1) is more homologous to human TMEM16F than to fruit fly or mosquito Tmem16e homologs.

Cys 356 of TMEM16E (GDD1) is substituted with Arg or Gly in patients with gnathodiaphyseal dysplasia (Tsutsumi et al. 2004). Because Cys 356 is conserved among members of the TMEM16 family (Katoh and Katoh 2004*b*), we can now predict that Cys residues might also be essential for the biological function of members of the TMEM16 family. In the postgenome era, comprehensive identification of related genes within the human genome is important for the progression of genome science and medical science.

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Electronic-Database Information

The URLs for data presented herein are as follows:

HUGO Gene Nomenclature Committee, http://www.gene.ucl.ac.uk/nomenclature/

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for gnathodiaphyseal dysplasia, *TMEM16E,* and *TMEM16F*)

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Response to Katoh and Katoh

To the Editor:

Gnathodiaphyseal dysplasia (GDD [MIM 166260]) is a syndrome characterized by bone fragility, sclerosis of tubular bone, and cemento-osseous lesions of the jawbone. We have mapped the GDD locus to an 8.7-cM interval on chromosome 11p14.3-15.1 by linkage analysis of a Japanese family with GDD (Tsutsumi et al. 2003). We studied a cDNA (GenBank accession number AL833271) in the candidate region, and, early in 2003, we detected a missense mutation (C356R [MIM 608662.0001]) in the affected members of the family. The gene was named "*GDD1*" (MIM 608662) and was submitted to the National Center for Biotechnology Information (NCBI) database on October 28, 2003 (GenBank accession number AB125267). The mouse homolog was also cloned and was submitted to the NCBI database on November 4, 2003 (GenBank accession number AB125740). We found cellular localization of the GDD1 protein to the endoplasmic reticulum, as well as another missense mutation (C356G [MIM 608662.0002]), in the affected members of an African American family with GDD. Overexpression of *GDD1* genes with both of the mutations found in the patients with GDD dramatically changed the cellular characteristics. Our study containing these results was electronically published in *The American Journal of Human Genetics* on April 29, 2004 (Tsutsumi et al. 2004).

On the other hand, Katoh and Katoh independently reported that they had found, through an *in silico* anal-