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Letter to the Editor

Revised Nomenclature for Mammalian Vacuolar-Type H^+-ATPase Subunit Genes

To date, the nomenclature of mammalian genes encoding the numerous subunits and their many isoforms that comprise the family of vacuolar H^+-ATPases has not been systematic, resulting in confusion both in the literature and among investigators. We present the official new system for these genes, approved by both Human and Mouse Gene Nomenclature Committees.

The multisubunit vacuolar-type proton pump (H^+- or V-ATPase) is essential for acidification of diverse intracellular compartments in eukaryotic cells. These include endosomes, lysosomes, clathrin-coated vesicles, secretory vesicles, chromaffin granules, and the central vacuoles of plants and fungi. H^+-ATPases are also found at high density in the plasma membrane of certain specialized cell types such as renal intercalated cells, neutrophils, osteoclasts, and some cells in the male genital tract, where they play important roles in urinary acidification, cytoplasmic pH homeostasis, bone resorption, and sperm maturation, respectively.

The general structure of H^+-ATPases comprises two functional sectors, V_1 and V_0. The peripheral V_1 domain binds and hydrolyzes ATP, providing the energy for H^+ translocation across the integral membrane V_0 domain. The complete identity of all the pump components has yet to be elucidated. The structural model put forward by Nishi and Forgac (2002), based mostly on topology studies of the yeast and bovine clathrin-coated vesicle H^+-ATPases, suggests that there are at least 13 different subunits (Table 1). In this model (Figure 1), the V_1 domain (640 kDa) comprises subunits A–H, in a proposed stoichiometry of $A_3B_3C_1D_1E_1F_1G_2H_1$, while V_0 (260 kDa) contains five subunits in a possible complex of $a_1d_1c''_1(c, c')_6$. Whether species other than yeast have an ortholog of the c′ subunit is currently unclear. The e subunit, another integral membrane protein also referred to as M9.7 or M9.2, has been identified as a subunit of the H^+-ATPase in *Manduca sexta*, *Arabidopsis thaliana*, and in bovine chromaffin granules (Ludwig et al., 1998; Sze et al., 2002; Wieczorek et al., 2000). These granules also contain M8-9, a further membrane sector-associated protein, (Ludwig et al., 1998). In addition, an accessory subunit named Ac45 or S1 has been proposed to associate with the H^+-ATPase in a subset of organelles (Supek et al., 1994).

The precise function(s) of many of the proton pump's subunits and the interactions between them remain undetermined. Moreover, in higher eukaryotes, several H^+-ATPase subunits have recently been shown to have multiple isoforms encoded by different genes and with differing tissue expression patterns. These include the B, C, E, G, a, d, and e subunits (Table 1) (Borthwick and Karet, 2002; Smith et al., 2002; Ueda et al., 2003). The two previously reported bovine H subunit isoforms are, in fact, splice variants of the same gene (Zhou et al., 1998). The existence of different subunit isoforms may play an important role in the localization and activity of proton pumps in specific cell types and subcellular compartments. In humans, for example, mutations in the genes encoding B1 and a4, isoforms of the B and a subunits that are predominantly expressed at the urinary surface of intercalated cells in the kidney, cause recessive distal renal tubular acidosis (Karet, 2002). In addition, osteopetrosis can be caused by mutations in a3, a different a subunit isoform chiefly expressed in osteoclasts (Frattini et al., 2000).

Unfortunately, the existence of so many different proton pump subunits and their respective isoforms has resulted in extremely varied and confusing nomenclature. Furthermore, although the sequence of human and many other eukaryotic genomes is almost complete, it is often difficult to identify and distinguish all the genes encoding H^+-ATPase subunits in existing databases because of inconsistencies in published nomenclature.

Previous Human H^+-ATPase Nomenclature

The HUGO Gene Nomenclature Committee (HGNC) approved the root symbol *ATP* to be used for a variety of ATP-associated genes, whereby the "ATPase, H^+ transporting, lysosomal (vacuolar proton pump)" genes have been assigned the root *ATP6*. A letter, generally indicating the subunit name, has then followed this root symbol. However, a number of subunits in the V_1 and V_0 domains are named with the same letter but in either upper- or lowercase, respectively. This has caused confusion, especially since names containing lowercase letters cannot be approved as symbols for human genes in accordance with the Guidelines for Human Gene Nomenclature (http://www.gene.ucl.ac.uk/nomenclature/guidelines.html). Therefore, some symbols reflected the subunit name, whereas others did not. For example, *ATP6D* encoded the d subunit in the V_0 domain, with V_1 D being encoded by *ATP6M*, and *ATP6A1* encoded the V_1 A subunit, whereas V_0 a1 was encoded by *ATP6N1A*. Further confusing examples included *ATP6F* encoding c″, whereas the F subunit gene was known as *ATP6S14*, while *ATP6H* symbolized the e/M9.2/M9.7 subunit gene, with that encoding V_1 H being referred to as *SFD*.

The New Nomenclature

Last year we instigated a review of the nomenclature of genes encoding human H^+-ATPase subunits. On the basis of our discussions, we suggested that the *ATP6* symbols be changed in order to reflect their subunit names more systematically. To facilitate this, and to avoid the issue of using lowercase letters, the *ATP6* root has now been lengthened to include either V1 or V0, thereby indicating the domain in which the subunit is found. This is now followed by the subunit letter code

Table 1. Revised Nomenclature of Human H^+-ATPase Subunit Genes

Subunit	Approx MW (kDa)	Revised Nomenclature	Previous Symbols	Aliases	Yeast Gene	Proposed Function/ Location
V_1 Peripheral Sector						
A	70	ATP6V1A[a]	VPP2, ATP6A1, ATP6V1A1	VA68	VMA1	Catalytic ATP binding
B1	56	ATP6V1B1	VPP3, ATP6B1	VATB, RTA1B	VMA2	Noncatalytic ATP binding
B2		ATP6V1B2	VPP3, ATP6B2	VATB, HO57		
C1	42	ATP6V1C1	ATP6D, ATP6C	VATC	VMA5	Peripheral stator
C2		ATP6V1C2		ATP6C2		
D	34	ATP6V1D	ATP6M	VATD	VMA8	Central rotor
E1	31	ATP6V1E1	ATP6E, ATP6V1E	P31, ATP6E2	VMA4	Peripheral stator
E2		ATP6V1E2	ATP6EL2, ATP6V1EL2	ATP6E1		
F	14	ATP6V1F		ATP6S14, VATF	VMA7	Central rotor
G1	13	ATP6V1G1	ATP6J, ATP6G1	ATP6GL	VMA10	Peripheral stator
G2		ATP6V1G2	ATP6G, ATP6G2	NG38		
G3		ATP6V1G3		ATP6G3		
H	50	ATP6V1H		SFD, SFD α, SFD β, CGI-11	VMA13	Peripheral stator
V_0 Membrane Sector						
a1	100	ATP6V0A1	VPP1, ATP6N1, ATP6N1A	a1	VPH1/STV1	Peripheral stator, H^+ translocation
a2		ATP6V0A2		a2, TJ6, TJ6s, TJ6M, ATP6a2, J6B7, ATP6N1D		
a3		TCIRG1[b]		a3, ATP6V0A3, TIRC7, OC116, ATP6N1C, ATP6i		
a4		ATP6V0A4	ATP6N1B, ATP6N2, RTA1C	a4, RDRTA2, VPP2, RTADR		
d1	38	ATP6V0D1	ATP6D	ATP6DV, VATX, VPATPD, P39	VMA6	Nonintegral membrane component
d2		ATP6V0D2		ATP6D2		
c	16	ATP6V0C	ATPL, ATP6C, ATP6L	VATL	VMA3	H^+ translocation
c″	21	ATP6V0B[c]	ATP6F	HATPL	VMA16	H^+ translocation
e	9	ATP6V0E	ATP6H	M9.2	VMA21	Membrane sector-associated
Accessory Subunits						
Ac45	45	ATP6AP1[d]	ATP6S1, ATP6IP1	ORF, XAP-3, VATPS1, 16A, Ac45, XAP3, CF2	–	Accessory subunit
M8-9	8-9	ATP6AP2[d]	ATP6IP2	M8-9, APT6M8-9, ATP6M8-9	–	Membrane sector-associated

[a] The *ATP6V1A1* and *ATP6V1A2* entries have been replaced by *ATP6V1A*, as there is probably only one A subunit isoform.
[b] For historical reasons *TCIRG1* remains the official symbol instead of *ATP6V0A3*.
[c] The nomenclature cannot reflect the subunit name, since ″ is not a recognized symbol.
[d] Described as accessory subunits as these are currently not regarded as being integral H^+-ATPase subunits.

in uppercase (even when the corresponding subunit is named in lowercase) and finally by the isoform number, if appropriate. Thus V_1 D is differentiated from V_0 d1 as follows: *ATP6V1D* (ATPase, H^+ transporting, lysosomal 34 kDa, V_1 subunit D) and *ATP6V0D1* (ATPase, H^+ transporting, lysosomal 38 kDa, V_0 subunit d isoform 1). For molecules previously described as "accessory subunits," the root symbol *ATP6AP* (ATPase, H^+ transporting, lysosomal accessory protein) has been introduced. A list of the proposed new nomenclature was sent to a number of researchers in the field for their comments and to ensure a consensus agreement. The changes were duly accepted, and the HGNC has released the new nomenclature (Table 1). The Mouse Genomic Nomenclature Committee has also adopted the new system within their convention of only the initial letter being uppercase. Thus *ATP6V1B1* and *Atp6v1b1* now encode human and mouse B1 subunits.

If members of the mammalian H^+-ATPase research community use the new nomenclature, it will allow more accurate information exchange regarding different subunits and their isoforms. This will further our understanding of the subunit differences that may play a key role in the structure, site, and function of H^+-ATPases within the cell. However, even though the new nomenclature has been in the public domain for some months, several recent publications still use the old system. We are hopeful that this brief review will draw attention to the existence of the revised mammalian nomenclature system and will improve scientific communication in this field.

More broadly across eukaryotes, there are several

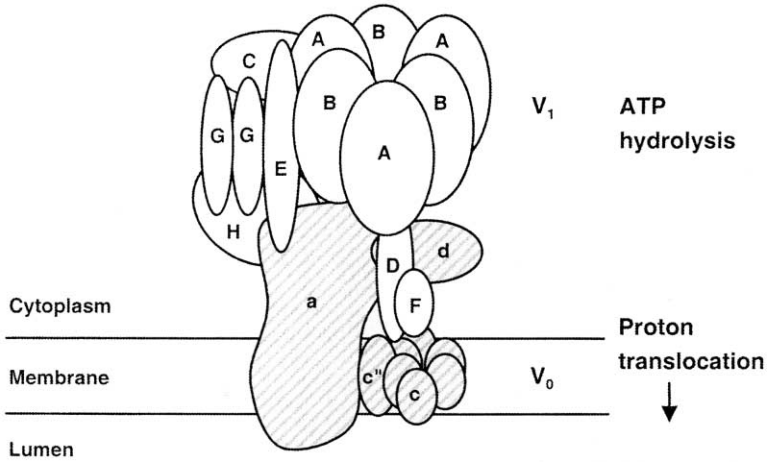

Figure 1. Schematic Model of the H^+-ATPase (Adapted from Nishi and Forgac, 2002)

The peripheral V_1 domain subunits A–H are indicated by open symbols, and the integral membrane V_0 domain subunits a, d, c, and c″ are shown as hatched symbols. The c′, e, Ac45, and M8-9 subunits are not shown since it is unclear whether they are present in all H^+-ATPases (see text).

different nomenclature systems for the H^+-ATPase genes. For example the yeast genes generally carry the root *VMA*, followed by a number for each subunit (Table 1). Interestingly, Sze et al. (2002) recently proposed that the genes encoding H^+-ATPase subunits in plants should be named *VHA-x*, where *x* represents the letter code for each subunit. They suggested that this system be applied to H^+-ATPase genes in animals, but unfortunately, as V_0 subunits would still require names with lowercase letters, this cannot be used for human gene symbols. We respectfully suggest that it would be useful if a similar unifying system to that developed for mammals, reflecting subunit names, could perhaps be adopted for other eukaryotic organisms.

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