

Mutation Nomenclature in Practice: Findings and Recommendations from the Cystic Fibrosis External Quality Assessment Scheme

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ABSTRACT: Currently, two nomenclature systems are in use to describe sequence variants for cystic fibrosis: the established traditional nomenclature system and the more recent Human Genome Variation Society (HGVS) nomenclature system. We have evaluated the use of both systems in the laboratory reports of 217 participants in the cystic fibrosis external quality assessment scheme of 2009. The mutation c.1521_1523delCTT (p.Phe508del, F508del) was described by traditional and HGVS nomenclature by 32 of 216 (15%) laboratories that correctly identified the mutation, whereas 171 (79%) laboratories used traditional nomenclature only and 13 (6%) laboratories used HGVS nomenclature only. Overall, 29 of 631 (5%) reports used nomenclature that was evaluated as being seriously incorrect and/or misleading and 136 (22%) reports contained attempts at HGVS coding, of which 104 (76%) contained no coding errors; just 33 (24%) mentioned the correct cDNA name and cited the nucleotide reference sequence. We recognized an urgent need for more consistent and correct usage of nomenclature. We recommended that cystic fibrosis transmembrane conductance regulator testing reports should include a description of the identified sequence variants in both HGVS and traditional nomenclature and provided basic recommendations and other guidance.

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KEY WORDS: cystic fibrosis; external quality assessment; HGVS nomenclature; mutation

Introduction

The purpose of a clinical laboratory report is to accurately and comprehensibly interpret and communicate the results of testing to the requesting physician and, in some cases, to other healthcare

workers. Otherwise, the report is at best not useful, and at worst could lead to inappropriate clinical management, and/or errors of carrier testing. In the field of medical genetic diagnostics, these exigencies are even stronger for three key reasons: (1) the results have an essentially unlimited lifespan, because the constitutional genetic status does not change and so the tests are typically performed only once per lifetime; (2) the results may be employed for the healthcare of relatives and future generations; (3) healthcare professionals do not all have the specialist knowledge required to fully interpret genetic results, meaning that the onus is on the laboratories to provide expert interpretation as well as the test results.

Being aware that correct description of sequence variants is of utmost importance to avoid misunderstanding among healthcare providers and to avoid incorrect testing or interpretation for family members, the Human Genome Variation Society (HGVS) published recommendations for the standardized description of genetic sequence variants [Antonarakis, 1998; den Dunnen and Antonarakis, 2000; den Dunnen and Antonarakis, 2001; Ogino et al., 2007; White et al., 1997]. This standard nomenclature system was developed to answer the need for an unambiguous and systematic description of changes at DNA and protein level and is gradually being adopted in clinical molecular genetics laboratories worldwide. The most recent Best Practice Guidelines for cystic fibrosis transmembrane conductance regulator (CFTR) testing, dating from 2009, recommended employing traditional nomenclature either alone or in conjunction with HGVS [Dequeker et al, 2009]; practice is now moving rapidly toward the ubiquitous use of HGVS, in conjunction with traditional nomenclature to maintain compatibility with the literature and laboratory reports.

There is, unfortunately, a gap between the existence of the HGVS recommendations and the complete and correct implementation within genetic testing services, among healthcare professionals, and in the scientific literature. Traditional, nonstandard nomenclature is still in widespread use for many reasons, including habit, its continued presence in the scientific literature, and the lack of awareness of HGVS nomenclature among nongenetics professionals. This situation has great potential to introduce errors and confusion.

The Cystic Fibrosis (CF) Network is one of the largest providers of external quality assessment (EQA) in molecular genetics, offering world-wide EQA schemes for CF since 1996 (<http://cf.eqascheme.org>). Because of the large number of laboratories testing CF and participating in CF Network schemes, we have access to a very wide range of genetic testing reports. In recent years, concomitant with

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Table 1. Variety of Nomenclature Observed in the 2009 Cystic Fibrosis (CF) External Quality Assessment (EQA) Scheme Reports

Mutations	Traditional nomenclature only		HGVS nomenclature only		Traditional and HGVS nomenclature		Total N
	N	%	N	%	N	%	
c.1521_1523delCTT (p.Phe508del, F508del)	171	79	13	6	32	15	216
c.1519_1521delATC (p.Ile507del, I507del)	163	79	13	6	33	16	209
c.489+1G>T (621+1G>T)	161	78	18	9	27	13	206
Total	495	78	44	7	92	15	631

N, number of CF EQA reports.

the steady adoption of HGVS nomenclature in clinical diagnostics, we have encountered a wide variation in nomenclature usage and accuracy in laboratory reports, leading potentially to misunderstanding or even errors in further testing in relatives. In an effort to encourage and facilitate the uptake of HGVS nomenclature in *CFTR* genetic testing, we have analyzed the use of nomenclature in over 600 reports from the 2009 CF EQA scheme. Although our study specifically addresses the context of *CFTR* testing, the findings are expected to be relevant to many other situations of clinical genetic testing.

The sample set for the 2009 CF EQA scheme included three mutations: c.1521_1523delCTT (p.Phe508del, F508del), c.1519_1521delATC (p.Ile507del, I507del), and c.489+1G>T (621+1G>T). Variability in nomenclature (traditional and HGVS) and mutation names (traditional, cDNA, and protein) for these three mutations were analyzed in the laboratory reports submitted. We elected to evaluate the nomenclature only when the EQA participant tested for the mutations, identified them correctly, and issued a formal laboratory report. We formulated basic recommendations and guidance for the correct and unambiguous application of nomenclature systems, specifically within the context of reporting *CFTR* test results. We employed the *CFTR* reference sequences NM_000492.3 and NG_016465.1, and the HGVS recommendations for the description of sequence variants V2.0 (<http://www.hgvs.org/mutnomen/>).

CF EQA Scheme Findings

Formal laboratory reports for the 2009 scheme were received from 217 laboratories in 33 countries, of which 215 offer CF testing as a diagnostic test. c.1521_1523delCTT (p.Phe508del, F508del), the most common cystic fibrosis mutation, was tested, correctly identified, and reported by 216 EQA participants, c.1519_1521delATC (p.Ile507del, I507del) by 209, and c.489+1G>T (621+1G>T) by 206.

Table 1 gives an overview of the usage of traditional and HGVS nomenclature in the CF EQA reports. In reporting c.1521_1523delCTT (p.Phe508del, F508del), 79% of laboratories used only traditional nomenclature, and 21% HGVS nomenclature, either solely or in parallel with traditional nomenclature. The laboratories that used both traditional and HGVS nomenclatures in their reports did this inconsistently: 32 laboratories reported c.1521_1523delCTT (p.Phe508del, F508del) in both nomenclatures, but only 25 of these 32 did so for c.489+1G>T (621+1G>T).

In addition to the inconsistency in nomenclature usage, we identified a considerable variability in the coding employed for the same mutation (Table 2). In the 216 reports for c.1521_1523delCTT (p.Phe508del, F508del), 18 different mutation names were observed; c.1519_1521delATC (p.Ile507del, I507del) was coded in 20 different ways. Some participants even used multiple names for the same mutation within the same report, which explains why the total number of mutation names in Table 2 is higher than the number of laboratories that participated in the EQA scheme.

Table 2. Variety of Mutation Names Observed in the 2009 CF EQA Scheme Reports

Traditional nomenclature	HGVS nomenclature				N
	N	cDNA name	N	Protein name	
Correct mutation names, complying with recommendations					
F508del	181	c.1521_1523delCTT	14	p.Phe508del	19
		c.1521_1523del	4		
I507del	172	c.1519_1521delATC	13	p.Ile507del	20
		c.1519_1521del	5		
621+1G>T	162	c.489+1G>T	28		
Mutation names not recommended or compliant, but unlikely to lead to error					
DeltaF508	13	c.1520_1522delTCT	1	p.F508del	15
ΔF508	7			pF508del	1
DF508	3				
DelF508	1				
Phe508del	1				
1653_1655del	2				
DeltaI507	13	c.1519_1521del3	1	p.I507del	17
ΔI507	7	c.del1519_1521ATC	1		
DI507	2	c.1516-1518delATC	1		
Dell507	2				
Ile507del	1				
1651_1653del	1				
621+1G->T	21				
621+1(G>T)	2				
621+1G-T	1				
621+1GtoT	1				
621+1g>t	1				
621+1(g>T)	1				
Incorrect mutation names, potentially leading to misidentification and error					
		c.1520_1523del3	1	p.PheF508del	1
		c.1653_1655del	1	p.508Phe del	1
		c.2421_2423delCTT	1		
		c.1651_1653del	1	p.Iso507del	1
		g.1651_1653del	1	p.507Ile del	1
		c.1516-1521del3	1		
		c.1519_1521delACT	1		
		c.621+1G>T	16		
		c.621+1G->T	1		
		p.621+1G->T	1		

N, number of CF EQA reports.

Although most EQA participants used nomenclature that was at least comprehensible, there were many errors in applying HGVS rules; in contrast, there were no such rules for using the traditional CF nomenclature that was instead developed by usage and convention. Twenty-nine of 631 reports (5%), from 20 of 217 laboratories (9%) from 10 different countries, used nomenclature

Table 3. Examples of Genotypes in Traditional and Human Genome Variation Society (HGVS) Nomenclature

<i>CFTR</i> testing result	Traditional nomenclature	HGVS nomenclature
No mutation detected	normal	c.[=]+[=]
Heterozygote	F508del/normal	c.[1521_1523delCTT]+[=]
One mutation found in a presumed compound heterozygote	F508del/unknown	c.[1521_1523delCTT]+[?]
Compound heterozygote	F508del/621+1G>T	c.[1521_1523delCTT]+[489+1G>T]
Two variants, phase unknown	F508del and L138P	c.[1521_1523delCTT(+)+413T>C] p.[F508del(+)+L138P]
Two heterozygote variants on one allele	R117H-T5/normal	c.[350G>A;1210-12T[5]]+[=]
Intron 8 polyT variants	T5/T7	c.1210-12T[5]+[7]

that was evaluated as being seriously incorrect and/or misleading with the potential to generate errors of interpretation or follow-up in a healthcare situation. The most common serious error was the use of traditional cDNA numbering (starting at the 5' nucleotide of the reference cDNA sequence) in place of HGVS numbering, notably "c.621+1G>T" instead of HGVS c.489+1G>T. A number of typing or syntax errors were encountered, for example, "c.1519_1521delACT" was used for c.1519_1521delATC (p.Ile507del, I507del). Variation in the numbering of deleted bases was observed: "c.1520_1522delTCT" was used for c.1521_1523delCTT (p.Phe508del, F508del).

Overall, 136 of 631 reports (22%) from 55 of 217 laboratories (25%) contained attempts at HGVS coding. Of these 136 reports, 104 contained no coding errors (76%); just 33 (24%) correctly coded the mutation name and complied with two fundamental HGVS recommendations, that is (1) coding the mutation at the nucleotide level, with nucleotide A of the ATG translation start codon numbered as nucleotide +1; and (2) citing a reference sequence.

When HGVS nomenclature was employed, mutations were described at cDNA level only, or at protein level only, or at both cDNA and protein level. In the case of c.1521_1523delCTT (p.Phe508del, F508del), 14 laboratories used both cDNA and protein descriptions, eight laboratories used only the cDNA mutation name, and 23 laboratories used only the protein description.

Finally, we analyzed the attempts to report genotypes (coding both alleles) in HGVS nomenclature. As with the coding of single alleles, a number of variations were present, of varying degrees of compliance to the guideline. Descriptions that were understandable, but not recommended or compliant with guidelines, included "[c.489+1G>T/p.F508del]" and "p.[Phe508del]+c.[489+1G>T]" instead of c.[1521_1523delCTT]+[489+1G>T] when referring to F508del/621+1G>T.

Recommendations

Based on the findings described above, and the fact that HGVS nomenclature is currently accepted as the de facto international standard, the CF Network makes the following basic recommendations for clinical molecular reporting for *CFTR* testing.

- (1) Reports should include a description of identified sequence variants in both HGVS and traditional nomenclature.
 - (a) The use of HGVS nomenclature ensures accuracy and future compatibility.
 - (b) The use of traditional nomenclature ensures legibility and compatibility with the existing literature and current practice, during a transitional period to facilitate accurate use and understanding of HGVS nomenclature by both laboratories and clinicians.
 - (c) Exception: for new sequence variants, only HGVS nomenclature should be used.
- (2) HGVS nomenclature should be used correctly. This implies the following in particular:
 - (a) Describing sequence variations at the nucleotide level. The use of DNA-based nomenclature is accurate and unambiguous, while the use of a protein-based nomenclature may be equivocal. Example: p.Phe508del (F508del) can be caused by several different changes at DNA level, including c.1521_1523delCTT and c.1522_1524delTTT.
 - (i) Both c.1521_1523delCTT and c.1521_1523del are HGVS compliant. Generally the shorter form is preferred for simplicity; in some cases, for example for deletion-insertions, clarity can be improved by specifying the nucleotides.
 - (ii) Note: Designation at the RNA level (r.) could theoretically be provided to illustrate the consequence of a change, but has been used neither in clinical practice nor in the literature.
 - (iii) Note: Description at the genomic DNA level (g.) would not be easily understandable by medical professionals and is not recommended for CF clinical reports.
 - (b) Specifying the reference sequences on the report, including the version number. Errors might occur in particular when designing an assay to amplify a gene fragment, based on a reference sequence that uses different nucleotide or exon numbering.
 - (i) For *CFTR*, the currently recommended reference sequences are NM_000492.3 for cDNA and NG_016465.1 for gDNA.
 - (ii) Citation of a *CFTR* locus reference genomic (LRG) sequence [Dagleish et al., 2010] is desirable as soon as it becomes publicly available.
 - (c) Using correct nucleotide numbering.
 - (i) cDNA position +1 is defined as the A of the ATG initiation codon. In contrast, in traditional notation, +1 is the first base of the mRNA that is considered as the major transcript; the A of the ATG was consequently nucleotide 133. Example: 621+1G>T is equivalent to c.489+1G>T and not "c.621+1G>T."
 - (ii) For deletions, insertions and duplications, the most 3' position possible is arbitrarily assigned. Example: c.1521_1523delCTT is preferred to c.1520_1522delTCT, although both accurately describe the deletion.
- (3) Traditional nomenclature, when used, should be used consistently throughout the report.
- (4) Compound genotypes, citing more than one variant or allele, should be written consistently. Some common situations are presented in Table 3. Mixed protein and cDNA level descriptions should not be used. Example: c.[1521_1523delCTT]+[489+1G>T] and not "p.[Phe508del]+c.[489+1G>T]".

Results:

Pathological result:

Two heterozygous CF-causing mutations identified:
c.3718-2477C>T (traditional name: 3849+10kbC>T)
c.3909C>G, p.Asn1303Lys (traditional name: N1303K)

Genotype: c.[3718-2477C>T(+)]3909C>G
(traditional: 3849+10kbC>T/N1303K)

Reference sequence: NM_000492.3, NG_016465.1

Mutations are written according to HGVS nomenclature (and to traditional nomenclature in parentheses).

Interpretation:

1. The patient is very probably a compound heterozygote for two CF-causing mutations. It is strongly recommended to confirm the phase of the mutations by testing both parents.
2. **A compound heterozygous genotype supports the diagnosis of cystic fibrosis.** This genotype is associated with disease of variable severity, typically with pancreatic sufficiency and a normal or borderline sweat test.
3. Genetic counselling should be provided to the patient and/or the parents.
4. Genetic counselling and carrier testing should be offered to relatives.

Figure 1. Example of a simple way of reporting cystic fibrosis transmembrane conductance regulator (CFTR) mutations. It is recommended that *CFTR* genotypes be given in both HGVS and traditional nomenclature. Human Genome Variation Society (HGVS) when used correctly guarantees a high degree of precision; the traditional mutation names provide easier understanding by clinicians and compatibility with the literature. As for all clinical molecular genetic testing reports, it is recommended that both a genotype and an interpretation in simple language are provided.

- (5) Effort should be made to make reports understandable for healthcare professionals, while maintaining accuracy. This implies the following:
 - (a) Using nomenclature consistently in all reports from the laboratory, for example with respect to the use of three-letter or one-letter codes for amino acids, and to the placement of HGVS and traditional coding within the text.
 - (b) Although both the three-letter and the one-letter amino acid codes are acceptable according to HGVS, the three-letter code is favored, to avoid potential confusion between amino acids and with nucleotide coding. Example: p.Gly551Asp is preferred to p.G551D.
 - (c) Describing sequence variations at protein level, where relevant and useful, always additionally to descriptions at cDNA level. "Relevant and useful" implies information that adds to the understanding of the clinician, without making the report excessively complex or confusing. Example: it is useful to indicate p.Phe508del in addition to c.1521_1523delCTT. In contrast, in clinical reports, there is little value in coding predicted protein changes for splice-site mutations.
- (6) Care should be taken with respect to the following specific difficulties:
 - (a) In transforming traditional into HGVS at cDNA level, it is not always appropriate merely to subtract 132 from the nucleotide count. Example: 1717-1G>A becomes c.1585-1G>A, but:
 - (i) 2183AA>G becomes c.2051_2052delAAinsG (not "c.2051AA>G").
 - (ii) 2711delT becomes c.2583delT (not "c.2579delT" because the most 3' T is considered deleted).
 - (iii) 3849+10kbC>T becomes c.3718-2477C>T, because the intronic mutation is closer to exon 20 than to exon 19; furthermore, the historical "+10 kb" is not accurate.
 - (b) Intron 8 polyT tract variations. c.1210-12T(5_9) describes the variable stretch of five to nine T residues in intron 8 of the *CFTR* gene, with allelic variants named as, for example, c.1210-12T[5] and c.1210-12T[9]. Likewise, variants at the intron 8 polyTG-polyT tract could be: c.1210-34TG[12]T[5] or c.1210-34TG[10]T[9].
 - (c) Exon numbering. The numbering of the *CFTR* exons has a historical basis, with the result that, for example, the 11th exon is called "exon 10" (www.genet.sickkids.on.ca). Because of the precision of HGVS nomenclature and because of the risk of confusion, referring to exon numbers in clinical reports is no longer useful or appropriate for a correct description of mutations. However, in case of negative results after partial *CFTR* gene analysis using scanning methods, reference to the exon numbering system used should be made.

Additional Guidance

An example of how *CFTR* mutations can be reported simply and clearly, with both nomenclatures during the transitional period, is presented in Figure 1. Table 4 provides a list of *CFTR* sequence variants in both HGVS and traditional nomenclatures.

Table 4. Traditional and HGVS Nomenclature, in Gene Order, for Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Sequence Variants Included in the Main Commercial Assays Used by the 2009 CF EQA Participants

Traditional nomenclature	HGVS nomenclature	
	cDNA name	Protein name
G85E ^a	c.254G>A	p.Gly85Glu
R117H ^a	c.350G>A	p.Arg117His
621+1G>T ^a	c.489+1G>T	
711+1G>T ^a	c.579+1G>T	
R334W ^a	c.1000C>T	p.Arg334Trp
R347P ^a	c.1040G>C	p.Arg347Pro
A455E ^a	c.1364C>A	p.Ala455Glu
I507del ^a	c.1519_1521del (c.1519_1521delATC)	p.Ile507del
F508del ^a	c.1521_1523del (c.1521_1523delCTT)	p.Phe508del
1717-1G>A ^a	c.1585-1G>A	
G542X ^a	c.1624G>T	p.Gly542X
G551D ^a	c.1652G>A	p.Gly551Asp
R553X ^a	c.1657C>T	p.Arg553X
R560T ^a	c.1679G>C	p.Arg560Thr
1898+1G>A ^a	c.1766+1G>A	
2184delA ^a	c.2052del (c.2052delA)	p.Lys684AsnfsX38
2789+5G>A ^a	c.2657+5G>A	
3120+1G>A ^a	c.2988+1G>A	
3659delC ^a	c.3528del (c.3528delC)	p.Lys1177SerfsX15
3849+10kbC>T ^a	c.3718-2477C>T	
N1303K ^a	c.3909C>G	p.Asn1303Lys
R1162X ^a	c.3484C>T	p.Arg1162X
W1282X ^a	c.3846G>A	p.Trp1282X
CFTRdel2,3	c.54-5940_273+10250del (c.54-5940_273+10250del21080)	p.?
E60X	c.178G>T	p.Glu60X
P67L	c.200C>T	p.Pro67Leu
R75X	c.223C>T	p.Arg75X
394delTT	c.262_263del (c.262_263delTT)	p.Leu88IlefsX22
405+3A>C	c.273+3A>C	
406-1G>A	c.274-1G>A	
444delA	c.313del (c.313delA)	p.Ile105SerfsX2
R117C	c.349C>T	p.Arg117Cys
Y122X	c.366T>A	p.Tyr122X
621+3A>G	c.489+3A>G	
G178R	c.532G>A	p.Gly178Arg
711+5G>A	c.579+5G>A	
L206W	c.617T>G	p.Leu206Trp
E217G	c.650A>G	p.Glu217Gly
852del22	c.720_741del (c.720_741delAGGGAGAAATGATGATGAAGTAC)	p.Gly241GlufsX13
935delA	c.803del (c.803delA)	p.Asn268IlefsX17
991del5	c.859_863del (c.859_863delAACTT)	p.Asn287LysfsX19
F311del	c.933_935del (c.933_935delCTT)	p.Phe312del
1078delT	c.948del (c.948delT)	p.Phe316LeufsX12
G330X	c.988G>T	p.Gly330X
R334Q	c.1001G>A	p.Arg334Gln
T338I	c.1013C>T	p.Thr338Ile
1154insTC	c.1021_1022dup (c.1021_1022dupTC)	p.Phe342HisfsX28
R347H	c.1040G>A	p.Arg347His
R352Q	c.1055G>A	p.Arg352Gln
S364P	c.1090T>C	p.Ser364Pro
1259insA	c.1130dup (c.1130dupA)	p.Gln378AlafsX4
T5	c.1210-12T[5]	
G480C	c.1438G>T	p.Gly480Cys
Q493X	c.1477C>T	p.Gln493X
I502T	c.1505T>C	p.Ile502Thr
1677delTA	c.1545_1546del (c.1545_1546delTA)	p.Tyr515X
V520F	c.1558G>T	p.Val520Phe
S549R(A>C)	c.1645A>C	p.Ser549Arg
S549N	c.1646G>A	p.Ser549Asn
S549R(T>G)	c.1647T>G	p.Ser549Arg
Q552X	c.1654C>T	p.Gln552X
A559T	c.1675G>A	p.Ala559Thr
1811+1.6kbA>G	c.1680-886A>G	
1812-1G>A	c.1680-1G>A	
D579G	c.1736A>G	p.Asp579Gly
1898+3A>G	c.1766+3A>G	
1898+5G>T	c.1766+5G>T	
G622D	c.1865G>A	p.Gly622Asp

(Continued)

Table 4. Continued

Traditional nomenclature	HGVS nomenclature	
	cDNA name	Protein name
2055del9>A	c.1923_1931delinsA (c.1923_1931delCTCAAAACTinsA)	p.Ser641ArgfsX5
2143delT	c.2012del (c.2012delT)	p.Leu671X
2141insA	c.2010dup (c.2010dupA)	p.Leu671IlefsX18
2183AA>G	c.2051_2052delinsG (c.2051_2052delAAinsG)	p.Lys684SerfsX38
K710X	c.2128A>T	p.Lys710X
2307insA	c.2175dup (2175dupA)	p.Glu726ArgfsX4
2347delG	c.2215del (c.2215delG)	p.Val739TyrfsX16
W846X	c.2538G>A	p.Trp846X
Q890X	c.2668C>T	p.Gln890X
2869insG	c.2737_2738insG	p.Tyr913X
3120G>A	c.2988G>A	
3199del6	c.3067_3072del (c.3067_3072delATAGTG)	p.Ile1023_Val1024del
3272-26A>G	c.3140-26A>G	
L1065P	c.3194T>C	p.Leu1065Pro
R1066C	c.3196C>T	p.Arg1066Cys
R1066H	c.3197G>A	p.Arg1066His
R1070Q	c.3209G>A	p.Arg1070Gln
W1089X	c.3266G>A	p.Trp1089X
Y1092X(C>A)	c.3276C>A	p.Tyr1092X
M1101K	c.3302T>A	p.Met1101Lys
D1152H	c.3454G>C	p.Asp1152His
R1158X	c.3472C>T	p.Arg1158X
S1196X	c.3587C>G	p.Ser1196X
3791delC	c.3659del (c.3659delC)	p.Thr1220LysfsX8
G1244E	c.3731G>A	p.Gly1244Glu
3876delA	c.3744del (c.3744delA)	p.Lys1250ArgfsX9
S1251N	c.3752G>A	p.Ser1251Asn
S1255X	c.3764C>A	p.Ser1255X
3905insT	c.3773dup (c.3773dupT)	p.Leu1258PhefsX7
4016insT	c.3889dup (c.3889dupT)	p.Ser1297PhefsX5
G1349D	c.4046G>A	p.Gly1349Asp
4382delA	c.4251del (c.4251delA)	p.Glu1418ArgfsX14
I148T ^b	c.443T>C	p.Ile148Thr
T7 ^b	c.1210-12T[7]	
T9 ^b	c.1210-12T[9]	
I506V ^b	c.1516A>G	p.Ile506Val
I507V ^b	c.1519A>G	p.Ile507Val
F508C ^b	c.1523T>G	p.Phe508Cys

^aACMG recommended testing panel.

^bConsidered as neutral variants.

The listed variants include those tested by the main commercial assays used by the 217 EQA participants in this study: INNO-LiPA CFTR17+Tn Update, INNO-LiPA CFTR19 and INNO-LiPA CFTR Italian Regional from Innogenetics; Cystic Fibrosis Genotyping Assay from Abbott Molecular; Elucigene CF29v2, CF30, CF4, CF-EU2 and CF poly-T from Gen-Probe Life Sciences; and xTAG® Cystic Fibrosis 39 kit v2 and xTAG® Cystic Fibrosis 72 kit v2 from Luminex Corporation.

Laboratories should be aware that HGVS recommendations are being regularly modified and expanded. Therefore, when using HGVS nomenclature, it is good practice always to consult the latest version on the HGVS website: www.hgvs.org/mutnomen. The website provides useful examples, in addition to the latest rules.

The Mutalyzer sequence variation nomenclature checker is an online tool that provides a convenient way to verify HGVS coding: www.mutalyzer.nl/2.0/check [Wildeman et al., 2008].

We recommend using the Cystic Fibrosis Mutation Database, maintained by the Cystic Fibrosis Centre at the Hospital for Sick Children in Toronto: www.genet.sickkids.on.ca. This well-established database contains more than 1,800 *CFTR* sequence variants and codes them according to both HGVS and traditional nomenclatures.

The UMD-CFTR mutation database includes more than 300 sequence variations in HGVS nomenclature, and provides tools to help assess the pathogenicity of mutations: www.umd.be/CFTR/W_CFTR [Bareil et al., 2010].

Discussion

Nomenclature and mutation names have been analyzed in laboratory reports of CF EQA participants. Our findings demonstrate a huge variety in mutation names in both HGVS and traditional nomenclatures. We showed that only 22% of reports and 25% of laboratories used HGVS nomenclature and that 5% of reports contained misleading errors. The incorrect use of mutation names in communication between healthcare providers has potentially severe implications for patients, as not only are clinical diagnostic decisions made based on laboratory reports, but also follow-up studies on family members, for further diagnosis or carrier testing. In addition, genetic testing reports can be kept for decades, to guide future family studies. The basic recommendations formulated here are an attempt to educate laboratories and to reduce the confusion in existing nomenclature systems. It is also our wish to ensure a smooth transition from traditional to HGVS nomenclature for the 75% of laboratories that have yet to adopt HGVS nomenclature.

It is crucial that laboratory personnel now educate themselves in the accurate use of HGVS nomenclature. Not only diagnostic laboratories, but also clinical geneticists, researchers submitting new sequence variants, manuscript reviewers, journal editors, database curators, manufacturers of diagnostic kits, developers of bioinformatics tools, and EQA providers have the responsibility to improve the consistent and unequivocal use of correct nomenclature. Organizations such as the Clinical Molecular Genetics Society (CMGS), European Molecular Genetics Quality Network (EMQN) and the College of American Pathologists (CAP), also recommend using traditional nomenclature referenced alongside the HGVS version [Gulley et al., 2007; Schwarz et al., 2008]. Correct and unambiguous nomenclature is of major importance and contributes to the overall improvement of quality within genetic testing services.

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