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# Large heterogeneity of mutations in the gene encoding the low-density lipoprotein receptor in subjects with familial hypercholesterolaemia

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**Abstract**

Molecular genetic testing for presymptomatic identification of subjects affected by familial hypercholesterolaemia (FH) is difficult due to the heterogeneity of the mutations in the gene encoding the low-density lipoprotein receptor (LDLR) in most populations. This investigation presents a detailed analysis of comparable, country-specific prevalence data of LDLR mutations in subjects with clinically defined FH and assesses the heterogeneous mutation diversity observed in most geographic regions.


*Keywords:* Low-density lipoprotein receptor; Familial hypercholesterolemia; Mutation; Prevalence

## 1. Introduction

Molecular genetic testing for presymptomatic identification of subjects affected by familial hypercholesterolaemia (FH) is difficult due to the heterogeneity of the mutations in the gene encoding the low-density lipoprotein receptor (LDLR) in most populations. Hence, the knowledge of the predominant mutations in certain geographical regions may simplify the molecular genetic confirmation of FH. We, therefore, surveyed country-specific prevalence data of functional LDLR mutations according to standardized criteria in samples of subjects with clinically diagnosed FH to provide a scientific basis for further screening strategies.

## 2. Methods

The term 'mutation prevalence' was defined as the ratio of subjects having a particular LDLR mutation confirmed by molecular genetic methods (FH molecularly confirmed, FHM) to subjects having the FH phenotype (clinically defined by hypercholesterolaemia and/or tendon xanthomas, coronary heart disease (CHD) in the index patient and a family history of hypercholesterolaemia and/or CHD in further relatives; FH clinically diagnosed, FHC), thus FHM/FHC ratio. Inclusion of datasets was based on the following criteria. (i) Number of unrelated subjects with FHC in a sample screened for LDLR gene mutations: $N \geq 10$. (ii) Number of unrelated subjects having the same mutation in such a sample: $N \geq 2$, but at least 1%. (iii) If $\geq 2$ publications describe the same mutation in the same country, the publication with the largest number of unrelated subjects with diagnosed FHC was considered. Nucleotide positions were numbered from the `a` of the `atg` translation initiation codon as +1. Amino acid (AA) positions were numbered from the first AA of the mature peptide as +1, according to Hobbs et al. [1] and mutations were designated according to Dunnan and Antonarakis [2].

## 3. Results

More than 400 original investigations published between 1986 and 2002 were analyzed. Forty-five investigations comprising 143 datasets from 25 countries fulfilled the above criteria. These 143 datasets described 101 different mutations including 70 missense (49.0%), 26 nonsense (18.2%), and 17

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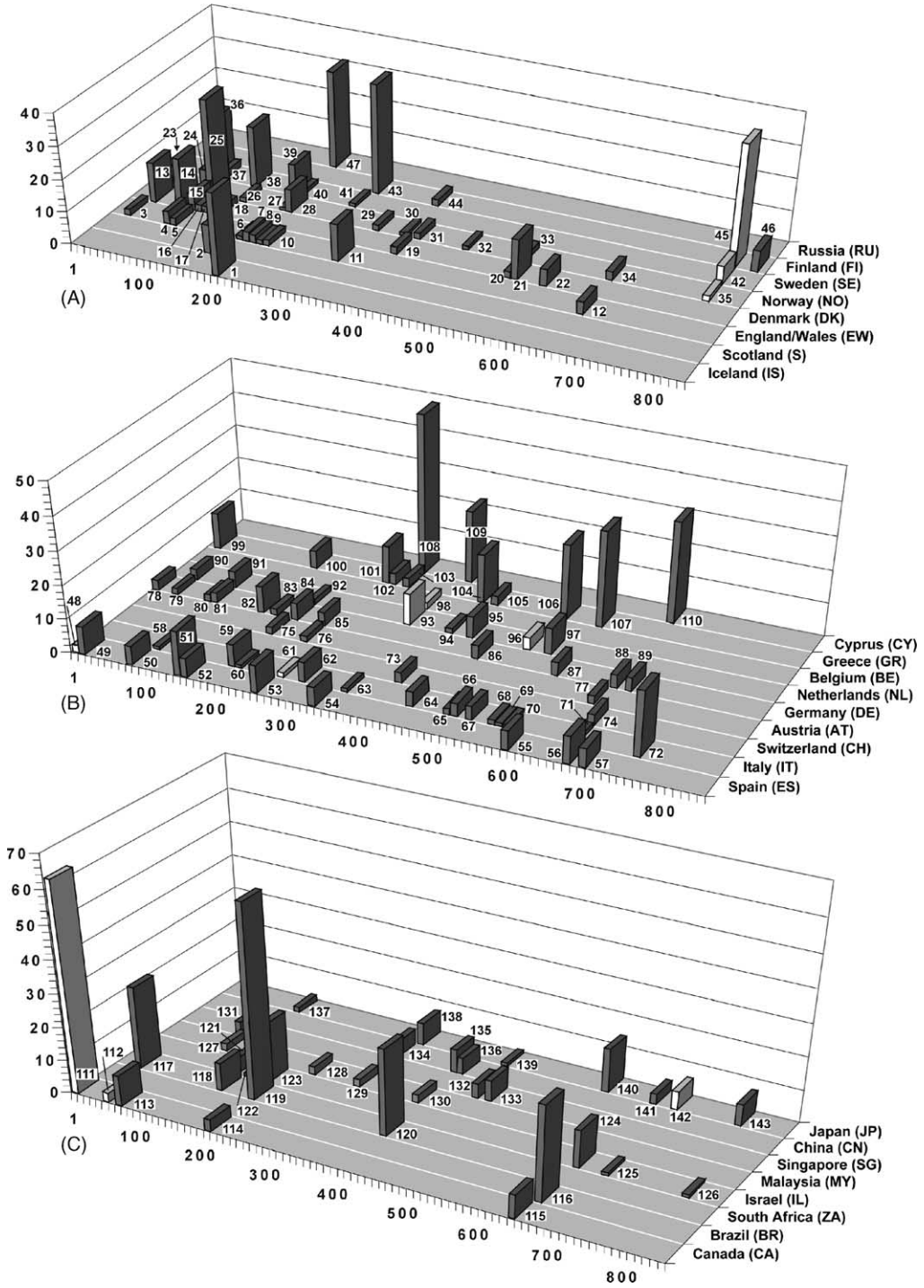


Fig. 1. Country-specific prevalence of LDL receptor mutations in a true-scale map relative to the amino acid positions of the LDL receptor. (A) Northern Europe; (B) Central and Southern Europe; (C) America, Africa, Asia. Amino acid positions of the LDL receptor (*x*-axis); prevalence data in percent (*y*-axis); countries (*z*-axis). Large insertions and deletions (>25 bp) are in light grey and the corresponding bars are, for clearness reasons, positioned in the middle of the respective insertion/deletion.

splice-site mutations (11.9%) as well as 11 micro-deletions (7.7%), 2 micro-insertions (1.4%), 11 large deletions (7.7%), 1 large insertion (0.7%), and 5 combined mutations (3.5%) (Table 1). Fig. 1A–C summarize the country-specific LDLR mutation prevalence distributions relative to the AA positions.

## 4. Discussion

Strong founder effects have been reported in population groups descended from European settlers, such as the Afrikaner population in South Africa [3] and the French-speaking population in the Quebec region in Canada [4].

Table 1
Country-specific LDL receptor mutation prevalence data

| # | C | Mut | Ex | SI | MC | % | Ref | # | C | Mut | Ex | SI | MC | % | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | IS | 694 + 2T > C | Int 4 | 47 | 12 | 25.5 | Hum Mutat 1997;10:36–44 | 72 | IT | 2312-3C > A | Int 15 | 51 | 10 | 19.6 | Hum Mutat 2001;17:433 |
| 2 | S | C163Y | 4 | 80 | 7 | 8.8 | J Med Genet 1998;35:573–8 | 73 | CH | V408M | 9 | 64 | 2 | 3.1 | ATVB 1995;15:1719–29 |
| 3 | EW | 118 del | 2 | 99 | 2 | 2.0 | Atherosclerosis 1999;143:41–54 | 74 | CH | P664L | 14 | 64 | 2 | 3.1 | ATVB 1995;15:1719–29 |
| 4 | EW | E80K | 3 | 99 | 4 | 4.0 | Atherosclerosis 1999;143:41–54 | 75 | AT | D200G | 4 | 950 | 20 | 2.1 | Atherosclerosis 2000;148:431–2 |
| 5 | EW | 313 + 1G > A | Int 3 | 277 | 6 | 2.2 | ATVB 1995;15:219–27 | 76 | AT | D245E | 5 | 950 | 16 | 1.7 | Atherosclerosis 2000;148:431–2 |
| 6 | EW | G197 del | 4 | 227 | 3 | 1.3 | Eur J Hum Genet 2001;9:244–52 | 77 | AT | W645L | 14 | 950 | 23 | 2.4 | Atherosclerosis 2000;148:431–2 |
| 7 | EW | D200G | 4 | 99 | 3 | 3.0 | Atherosclerosis 1999;143:41–54 | 78 | DE | M-21V | 1 | 100 | 3 | 3.0 | Hum Mutat 2001;18:165–6 |
| 8 | EW | 680–681 del | 4 | 200 | 5 | 2.5 | Arterioscler Thromb 1993;13:56–63 | 79 | DE | 195–196insAT | 3 | 218 | 4 | 1.8 | Clin Chem Lab Med 1998;36:279–82 |
| 9 | EW | D206E | 4 | 227 | 3 | 1.3 | Eur J Hum Genet 2001;9:244–52 | 80 | DE | 313 + 1G > A | Int 3 | 100 | 2 | 2.0 | Hum Mutat 2001;18:165–6 |
| 10 | EW | E207X | 4 | 227 | 4 | 1.8 | Eur J Hum Genet 2001;9:244–52 | 81 | DE | 313 + 2T > C | Int 3 | 100 | 3 | 3.0 | Hum Mutat 2001;18:165–6 |
| 11 | EW | R329X | 7 | 78 | 9 | 11.5 | J Med Genet 1997;34:111–6 | 82 | DE | C152G | 4 | 50 | 4 | 8.0 | ATVB 1995;15:2176–80 |
| 12 | EW | P664L | 14 | 227 | 7 | 3.1 | Eur J Hum Genet 2001;9:244–52 | 83 | DE | F179L | 4 | 100 | 2 | 2.0 | Hum Mutat 2001;18:165–6 |
| 13 | DK | W23X | 2 | 97 | 12 | 12.4 | Atherosclerosis 1999;146:337–44 | 84 | DE | E207X | 4 | 100 | 5 | 5.0 | Hum Mutat 2001;18:165–6 |
| 14 | DK | W66G | 3 | 97 | 15 | 15.5 | Atherosclerosis 1999;146:337–44 | 85 | DE | D245E | 5 | 100 | 4 | 4.0 | Hum Mutat 2001;18:165–6 |
| 15 | DK | 313 + 1G > A | Int 3 | 97 | 5 | 5.2 | Atherosclerosis 1999;146:337–44 | 86 | DE | W469X | 10 | 50 | 2 | 4.0 | ATVB 1995;15:2176–80 |
| 16 | DK | E92X | 4 | 97 | 2 | 2.1 | Atherosclerosis 1999;146:337–44 | 87 | DE | 1783–1789 del | 12 | 50 | 2 | 4.0 | ATVB 1995;15:2176–80 |
| 17 | DK | C112X | 4 | 97 | 2 | 2.1 | Atherosclerosis 1999;146:337–44 | 88 | DE | C660Y | 14 | 50 | 2 | 4.0 | ATVB 1995;15:2176–80 |
| 18 | DK | E119K | 4 | 97 | 2 | 2.1 | Atherosclerosis 1999;146:337–44 | 89 | DE | P678L | 14 | 50 | 2 | 4.0 | ATVB 1995;15:2176–80 |
| 19 | DK | T383P | 9 | 97 | 2 | 2.1 | Atherosclerosis 1999;146:337–44 | 90 | NL | W23X | 2 | 1223 | 38 | 3.1 | Clin Genet 2000;57:116–24 |
| 20 | DK | [N543H; 2393–2401 del] | 11/17 | 97 | 2 | 2.1 | Atherosclerosis 1999;146:337–44 | 91 | NL | 313 + 1G > A | Int 3 | 1223 | 61 | 5.0 | Clin Genet 2000;57:116–24 |
| 21 | DK | W556S | 12 | 97 | 12 | 12.4 | Atherosclerosis 1999;146:337–44 | 92 | NL | E207X | 4 | 1223 | 21 | 1.7 | Clin Genet 2000;57:116–24 |
| 22 | DK | 1846-1G > A | Int 12 | 97 | 5 | 5.2 | Atherosclerosis 1999;146:337–44 | 93 | NL | 4 kb del | 7–8 | 53 | 5 | 9.4 | Atherosclerosis 1990;83:127–36 |
| 23 | NO | W23X | 2 | 476 | 11 | 2.3 | J Int Med 1997;241:185–94 | 94 | NL | V408M | 9 | 1228 | 19 | 1.5 | Hum Genet 1993;92:567–70 |
| 24 | NO | S78X | 3 | 476 | 37 | 7.8 | J Int Med 1997;241:185–94 | 95 | NL | 1359-1G > A | Int 9 | 1223 | 78 | 6.4 | Clin Genet 2000;57:116–24 |
| 25 | NO | 313 + 1G > A | Int 3 | 476 | 144 | 30.3 | J Int Med 1997;241:185–94 | 96 | NL | 4.4 kb ins | 9–12 | 53 | 2 | 3.8 | Atherosclerosis 1990;83:127–36 |
| 26 | NO | C134X | 4 | 476 | 7 | 1.5 | J Int Med 1997;241:185–94 | 97 | NL | [N543H; 2393–2401 del] | 11/17 | 1223 | 98 | 8.0 | Clin Genet 2000;57:116–24 |
| 27 | NO | E207X | 4 | 476 | 5 | 1.1 | J Int Med 1997;241:185–94 | 98 | BE | 3 kb del | 7–8 | 100 | 2 | 2.0 | Hum Genet 1997;100:266–70 |
| 28 | NO | C210G | 4 | 476 | 34 | 7.1 | J Int Med 1997;241:185–94 | 99 | GR | C6W | 2 | 73 | 8 | 11.0 | Hum Mutat 2001;17:432–3 |
| 29 | NO | D335Y | 8 | 476 | 8 | 1.7 | J Int Med 1997;241:185–94 | 100 | GR | C152R | 4 | 150 | 8 | 5.3 | Hum Genet 1998;102:343–7 |
| 30 | NO | L380V | 9 | 476 | 5 | 1.1 | J Int Med 1997;241:185–94 | 101 | GR | S265R | 6 | 150 | 17 | 11.3 | Hum Genet 1998;102:343–7 |
| 31 | NO | R395W | 9 | 476 | 9 | 1.9 | J Int Med 1997;241:185–94 | 102 | GR | D280G | 6 | 150 | 5 | 3.3 | Hum Genet 1998;102:343–7 |
| 32 | NO | W469X | 10 | 476 | 5 | 1.1 | J Int Med 1997;241:185–94 | 103 | GR | C292X | 6 | 150 | 4 | 2.7 | Hum Genet 1998;102:343–7 |
| 33 | NO | W541X | 11 | 476 | 8 | 1.7 | J Int Med 1997;241:185–94 | 104 | GR | V408M | 9 | 150 | 22 | 14.7 | Hum Genet 1998;102:343–7 |
| 34 | NO | P664L | 14 | 476 | 13 | 2.7 | J Int Med 1997;241:185–94 | 105 | GR | I430T | 9 | 73 | 2 | 2.7 | Hum Mutat 2001;17:432–3 |
| 35 | NO | 9.6 kb del | 16–17 | 181 | 3 | 1.7 | Clin Genet 1992;42:288–95 | 106 | GR | D528G | 11 | 150 | 34 | 22.7 | Hum Genet 1998;102:343–7 |
| 36 | SE | W66G | 3 | 21 | 4 | 19.0 | Eur J Clin Invest 1998;28:740–7 | 107 | GR | G571E | 12 | 73 | 21 | 28.8 | Hum Mutat 2001;17:432–3 |
| 37 | SE | S78X | 3 | 182 | 4 | 2.2 | J Int Med 1998;244:19–25 | 108 | CY | C292X | 6 | 23 | 11 | 47.8 | Hum Mutat 2000;15:380 |
| 38 | SE | C122X | 4 | 21 | 4 | 19.0 | Eur J Clin Invest 1998;28:740–7 | 109 | CY | [Q363X; D365E] | 8/8 | 23 | 5 | 21.7 | Hum Mutat 2000;15:380 |
| 39 | SE | E187K | 4 | 21 | 2 | 9.5 | Eur J Clin Invest 1998;28:740–7 | 110 | CY | C660X | 14 | 23 | 7 | 30.4 | Hum Mutat 2000;15:380 |
| 40 | SE | D200G | 4 | 182 | 2 | 1.1 | J Int Med 1998;244:19–25 | 111 | CA | 10 kb del | P | 249 | 157 | 63.1 | Hum Genet 1992;88:529–36 |
| 41 | SE | C275X | 6 | 182 | 2 | 1.1 | J Int Med 1998;244:19–25 | 112 | CA | 5 kb del | 2–3 | 141 | 4 | 2.8 | J Clin Invest 1990;85:1014–23 |
| 42 | SE | 9.5 kb del | 16–18 | 182 | 10 | 5.5 | J Int Med 1998;244:19–25 | 113 | CA | W66G | 3 | 141 | 13 | 9.2 | J Clin Invest 1990;85:1014–23 |

Table 1 (*Continued*).

| # | C | Mut | Ex | SI | MC | % | Ref | # | C | Mut | Ex | SI | MC | % | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 43 | Fl | 925–931 del | 6 | 201 | 69 | 34.3 | J Clin Invest 1992;90:219–28 | 114 | CA | E207K | 4 | 141 | 5 | 3.5 | J Clin Invest 1990;85:1014–23 |
| 44 | Fl | L380H | 9 | 213 | 4 | 1.9 | Am J Hum Genet 1995;57:789–97 | 115 | CA | C646Y | 14 | 141 | 10 | 7.1 | J Clin Invest 1990;85:1014–23 |
| 45 | Fl | 9.5 kb del | 16–18 | 199 | 75 | 37.7 | J Int Med 1992;231:227–34 | 116 | BR | C660X | 14 | 31 | 9 | 29.0 | Braz J Med Biol Res 1999;32:739–45 |
| 46 | Fl | G823D | 17 | 213 | 14 | 6.6 | Am J Hum Genet 1995;57:789–97 | 117 | ZA | 137–142 del | 2 | 16 | 4 | 25.0 | J Med Genet 2000;37:514–9 |
| 47 | RU | G197 del | 4 | 23 | 7 | 30.4 | Hum Mutat 1998;12:255–8 | 118 | ZA | D154N | 4 | 106 | 9 | 8.5 | Hum Genet 1991;88:204–8 |
| 48 | ES | 6.8 kb del | P-1 | 89 | 2 | 2.2 | Eur J Clin Invest 2001;31:309–17 | 119 | ZA | D206E | 4 | 106 | 62 | 58.5 | Hum Genet 1991;88:204–8 |
| 49 | ES | E10X | 2 | 36 | 3 | 8.3 | Hum Mutat 2000;15:483–4 | 120 | ZA | V408M | 9 | 106 | 28 | 26.4 | Hum Genet 1991;88:204–8 |
| 50 | ES | [Q71E; 313 + 1G > C] | 3/Int 3 | 36 | 2 | 5.6 | Hum Mutat 2000;15:483–4 | 121 | IL | D147H | 4 | 193 | 9 | 4.7 | Hum Genet 1996;98:581–6 |
| 51 | ES | 518 del | 4 | 30 | 4 | 13.3 | Clin Genet 1996;49:180–5 | 122 | IL | Y167X | 4 | 193 | 2 | 1.0 | Hum Genet 1996;98:581–6 |
| 52 | ES | S156L | 4 | 36 | 2 | 5.6 | Hum Mutat 2000;15:483–4 | 123 | IL | G197 del | 4 | 193 | 35 | 18.1 | Hum Genet 1996;98:581–6 |
| 53 | ES | E256K | 6 | 36 | 3 | 8.3 | Hum Mutat 2000;15:483–4 | 124 | IL | C660X | 14 | 193 | 22 | 11.4 | Hum Genet 1996;98:581–6 |
| 54 | ES | [1061-8T > C; T705I] | Int 7/15 | 36 | 2 | 5.6 | Hum Mutat 2000;15:483–4 | 125 | IL | 2140 + 2T > A | 14 | 193 | 2 | 1.0 | Hum Genet 1996;98:581–6 |
| 55 | ES | 1845 + 1G > C | Int 12 | 36 | 2 | 5.6 | Hum Mutat 2000;15:483–4 | 126 | IL | Y807C | 17 | 193 | 2 | 1.0 | Hum Genet 1996;98:581–6 |
| 56 | ES | 2085–2103 del | 14 | 36 | 3 | 8.3 | Hum Mutat 2000;15:483–4 | 127 | MY | R94H | 4 | 86 | 2 | 2.3 | Clin Genet 2000;58:98–105 |
| 57 | ES | 2140 + 5G > A | Int 14 | 36 | 2 | 5.6 | Hum Mutat 2000;15:483–4 | 128 | MY | R232W | 5 | 86 | 2 | 2.3 | Clin Genet 2000;58:98–105 |
| 58 | IT | 313 + 1G > A | Int 3 | 725 | 7 | 1.0 | ATVB 2000;20:E41–52 | 129 | MY | C308Y | 7 | 86 | 2 | 2.3 | Clin Genet 2000;58:98–105 |
| 59 | IT | D200G | 4 | 725 | 48 | 6.6 | ATVB 2000;20:E41–52 | 130 | MY | L393R | 9 | 86 | 2 | 2.3 | Clin Genet 2000;58:98–105 |
| 60 | IT | E207K | 4 | 725 | 7 | 1.0 | ATVB2000;20:E41–52 | 131 | SG | 313 + 1G > A | Int 3 | 47 | 2 | 4.3 | Atherosclerosis 2001;Suppl. 2:66–7 |
| 61 | IT | 24 kb del | 2–12 | 725 | 10 | 1.4 | ATVB2000;20:E41–52 | 132 | SG | G457R | 10 | 47 | 2 | 4.3 | Atherosclerosis 2001;Suppl. 2:66–7 |
| 62 | IT | C297F | 7 | 51 | 3 | 5.9 | Hum Mutat 2001;17:433 | 133 | SG | D471N | 10 | 47 | 3 | 6.4 | Atherosclerosis 2001;Suppl. 2:66–7 |
| 63 | IT | C358R | 8 | 725 | 7 | 1.0 | ATVB2000;20:E41–52 | 134 | CN | C308Y | 7 | 42 | 2 | 4.8 | Hum Mutat 1998;Suppl.:S310–3 |
| 64 | IT | 1418–1419 insACAT | 10 | 725 | 31 | 4.3 | ATVB2000;20:E41–52 | 135 | CN | L393R | 9 | 42 | 3 | 7.1 | Hum Mutat 1998;Suppl.:S310–3 |
| 65 | IT | V502M | 10 | 725 | 13 | 1.8 | ATVB 2000;20:E41–52 | 136 | CN | V408M | 9 | 42 | 2 | 4.8 | Hum Mutat 1998;Suppl.:S310–3 |
| 66 | IT | 1586 + 1G > A | Int 10 | 51 | 2 | 3.9 | Hum Mutat 2001;17:433 | 137 | JP | E119K | 4 | 120 | 2 | 1.7 | ATVB 1995;15:1713–8 |
| 67 | IT | G528D | 11 | 725 | 29 | 4.0 | ATVB2000;20:E41–52 | 138 | JP | C317S | 7 | 120 | 8 | 6.7 | ATVB 1995;15:1713–8 |
| 68 | IT | D558Y | 12 | 725 | 10 | 1.4 | ATVB2000;20:E41–52 | 139 | JP | 13 kb del | 7–14 | 210 | 2 | 1.0 | J Int Med 1990;227:247–51 |
| 69 | IT | 1778 del | 12 | 725 | 8 | 1.1 | ATVB2000;20:E41–52 | 140 | JP | 1845 + 2T > C | Int 12 | 120 | 16 | 13.3 | ATVB 1995;15:1713–8 |
| 70 | IT | G571E | 12 | 725 | 7 | 1.0 | ATVB2000;20:E41–52 | 141 | JP | P664L | 14 | 120 | 4 | 3.3 | ATVB 1995;15:1713–8 |
| 71 | IT | P664L | 14 | 725 | 10 | 1.4 | ATVB2000;20:E41–52 | 142 | JP | 6 kb del | 15 | 35 | 2 | 5.7 | Arteriosclerosis 1988;8:187–92 |
| | | | | | | | | 143 | JP | K790X | 17 | 120 | 8 | 6.7 | ATVB 1995;15:1713–8 |

#: Number in Fig. 1; C: Country; Mut: LDL receptor mutation(s); Ex: Exon(s); SI: Subjects investigated; MC: Mutation carriers; %: Percentage (FHM/FHC); Ref: Reference. The overall sum of prevalences may exceed 100% in certain countries due to differences in the selection criteria in the different original investigations combined to characterize a country. Such slight differences in the inclusion criteria of the FHC patients in the studies considered in the present survey may not always allow direct comparison of the country-specific mutation prevalence data.

Less pronounced founder effects have also been discovered in Scandinavia [7–9], in particular in Finland [10], as well as in Israel [11]. Similarly, a reduced admixture in geographically isolated populations explains the more homogeneous mutation spectra in the populations of the islands of Iceland [5] and Cyprus [6].

In genetically more heterogeneous populations (missing founder effects, weaker geographic boundaries), a large spectrum of mutations is observed and thus, a screening approach must usually consider the entire LDLR gene. In particular in Central and Southern Europe, the mutation diversity is extremely heterogeneous (Fig. 1B). With few exceptions [12,13], no single mutation at the LDLR locus accounts for more than 10% of the subjects diagnosed as having FHC. In Asia, the mutation spectrum is also heterogeneous (Fig. 1C): 17 out of 23 mutations (73.9%) are not prevalent enough to fulfil the inclusion criteria in other geographical regions. Similarly, no missense mutations in the region encoding AA 680–800 of the LDLR could be included according to our criteria. The region of AA 680–800 (exons 14–17) contains the *O*-glycosylation and the transmembrane domains. In the *O*-glycosylation domain (AA 693–750), only few missense mutations have been described so far [14]. This finding suggests that the domain is less susceptible to missense mutations causing clinically manifest hypercholesterolaemia and/or that missense mutations in the *O*-glycosylation domain may cause less severe forms of FH and, therefore, the probability that individuals with these mutations are molecularly investigated is lower (selection bias). The extremely high overall, but – as shown above – non-uniform, mutation rate of functional point mutations is most likely due the absence of a strong selection pressure: complications of FH, such as severe CHD, affect individuals typically not before 40 years of age, i.e. after the usual age of reproduction. Similarly, the LDLR locus is characterized by an extremely high overall recombination rate causing a large number of insertions and deletions [15]. Recombination rates have previously been demonstrated to be non-uniform [15]. Again, the region between exons 14–17 is extraordinary because the recombination rates are particularly high in this region in most populations investigated [15].

In summary, we present a detailed overview on comparable, country-specific prevalence data of LDLR mutations in subjects with clinically defined FH. This data reflects the heterogeneous mutation diversity in most countries participating in the Make Early Diagnosis–Prevent Early Death (MED–PED) programme and, thus, may have an impact on future diagnostic strategies.

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