**Supplementary (originally in Excell)**

1. **Phenotype genotype summary**

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| **Phenotype** | **Zygosity** | **Allele 1** | **Allele 2** | **Reference** |
| ACG-1B | HMZ | p.[L483P] | p.[L483P] | Rossi et al., 1996a |
| ACG-1B | cHTZ | p.[R178\*] | p.[G678V] | Superti-Furga et al., 1996a |
| ACG-1B | cHTZ | p.[N425D] | p.[K575Sfs\*10] | Superti-Furga et al., 1996a |
| ACG-1B | cHTZ | p.[R178\*] | p.[S399Hfs\*61] | Superti-Furga et al., 1996a |
| ACG-1B | cHTZ | p.[R178\*] | p.[Y151Ifs\*21] | Superti-Furga et al.,1996a |
| ACG-1B | HMZ | p.[V340del] | p.[V340del] | Superti-Furga et al., 1996a; Cai et al., 1998 |
| ACG-1B | HMZ | p.[L132P] | p.[L132P] | Unger et al., 2001 |
| ACG-1B | HMZ | p.[G663R] | p.[G663R] | Sato et al., 2020 |
| ACG-1B | HTZ | p.[V340del] | unknown | **Present cohort (P1)** |
| ACG-1B | cHTZ | c.[−26+2T>C] | p.[G259V] | Unger et al., 2001 (described as severe AO-2/ACG-1B) |
| ACG-1B | cHTZ | c.[−26+2T>C] | p.[N425D] | Unger et al., 2001 (described as severe AO-2/ACG-1B) |
| AO-2 | cHTZ | p.[G255E] | p.[A715V] | Hästbacka et al., 1996 |
| AO-2 | cHTZ | p.[R279W] | p.[L131Cfs\*41] | Rossi et al., 1996b |
| AO-2 | HMZ | p.[L599F] | p.[L599F] | Miller et al., 2008; Vikraman et al., 2016 |
| AO-2 | cHTZ | c.[−26+2T>C] | p.[R49Dfs\*40] | Dwyer et al., 2010 |
| AO-2 | cHTZ | p.[R279W] | p.[T627Lfs\*23] | **Present cohort (P2)** |
| AO-2 | HMZ | p.[T512K] | p.[T512K] | Bonafé et al., 2008 |
| AO-2, DTD | cHTZ | p.[R279W] | p.[N425D] | Rossi et al., 1997; Barbosa et al., 2011 |
| AO-2, DTD | cHTZ | p.[R279W] | p.[K575Sfs\*10] | Hästbacka et al., 1996; **Present cohort (P5 and P6)** |
| AO-2, DTD | cHTZ | p.[R279W] | p.[R178\*] | Macías-Gómez et al.,2004 (described as excessively severe for DD and very mild for AO-2); Barbosa et al., 2011; Mattos et al., 2014 (described as AO-2 and severe DTD); Present cohort (P3 AO-2, P8 DD and P9 DD) |
| AO-2, DTD | HTZ | p.[R279W] | unknown | Rossi et al., 1996b (described as intermediate **AO-2** and DD) |
| DTD | HMZ | p.[Q454P] | p.[Q454P] | Mégarbane et al., 1999 (described as mild AO-2 and severe DD) |
| DTD | cHTZ | p.[R279W] | p.[G663R] | Maeda et al., 2006 (described as intermediate between AO-2 and DD) |
| DTD | HTZ | c.[727-1G>C] | unknown | Hästbacka et al., 1994 |
| DTD | HTZ | p.[A662Qfs\*6] | unknown | Hästbacka et al., 1994 |
| DTD | cHTZ | p.[R279W] | p.[V340del] | Hästbacka et al., 1999 |
| DTD | HTZ | c.[−26+2T>C] | unknown | Hästbacka et al., 1999; Remes et al., 2002 |
| DTD | HMZ | c.[−26+2T>C] | c.[−26+2T>C] | Hästbacka et al., 1999; Remes et al., 2002; Makitie et al., 2015 |
| DTD | cHTZ | p.[C653S] | p.[L707Pfs\*4] | Ramírez-Castro et al., 2005 |
| DTD | cHTZ | c.[−26+2T>C] | p.[T512K] | Bonafé et al., 2008 |
| DTD | cHTZ | p.[C653S] | p.[A715V] | Czarny-Ratajczak et al., 2010; Jackson et al., 2011 |
| DTD | cHTZ | p.[R279W] | c.[727-1G>C] | Barbosa et al., 2011 |
| DTD | cHTZ | p.[R279W] | p.[L707Pfs\*4] | Honório et al., 2013 |
| DTD | cHTZ | p.[R279W] | p.[S157T] | Pineda et al., 2013 |
| DTD | cHTZ | p.[R279W] | c.[727-1G>C] | **Present cohort (P4)** |
| DTD | cHTZ | p.[R279W] | p.[G115A] | **Present cohort (P7)** |
| DTD, AO-2 | HTZ | p.[K575Sfs\*10] | unknown | Hästbacka et al., 1994; Hästbacka et al., 1996 |
| DTD, rMED | cHTZ | p.[R279W] | c.[−26+2T>C] | Remes et al., 2002; Ballhausen et al., 2003; Dwyer et al., 2010; Zechi-Ceide et al., 2013; Makitie et al., 2015 |
| rMED | cHTZ | p.[R279W] | p.[G237V] | Ballhausen et al., 2003 |
| rMED | cHTZ | p.[R279W] | p.[N77H] | Ballhausen et al., 2003 |
| rMED | cHTZ | c.[−26+2T>C] | p.[C653S] | Ballhausen et al., 2003; Jackson et al., 2011; Kausar et al., 2018 |
| rMED | HMZ | p.[C653S] | p.[C653S] | Ballhausen et al., 2003; Matikie et al., 2003; Hinrichs et al., 2010 |
| rMED | cHTZ | p.[D385N] | p.[V162Gfs\*12] | Cho et al., 2010; Kim et al., 2011 |
| rMED | cHTZ | c.[−26+2T>C] | p.[F256S] | Jackson et al., 2011 |
| rMED | cHTZ | p.[R279W] | p.[T512K] | Syvänen et al., 2013; Mäkitie et al., 2015; Kausar et al., 2018 |
| rMED | cHTZ | p.[R279W] | p.[S522F] | Barreda-Bonis et al., 2017 |
| rMED | cHTZ | p.[L275P] | p.[L400F] | Zhou et al., 2018 |
| rMED | HMZ | p.[R279W] | p.[R279W] | Superti-Furga et al., 1999; Czarny-Ratajczak, et al., 2001; Huber et al., 2001; Ballhausen et al., 2003; Jakkula et al., 2005; Barbosa et al., 2011; Jackson et al., 2011; Martínez-Garcia et al., 2014; Barreda-Bonis et al., 2017; **Present cohort (P10 and P11)** |
| Intermediate phenotype |  |  |  |  |
| DTD/DBQD | cHTZ | p.[A133V] | p.[R178\*] | Panzer et al., 2008 |
| DTD/rMED/DBQD | cHTZ | p.[T266I] | p.[V340del] | Miyake et al., 2008 |
| rMED/DBQD | cHTZ | p.[R279W] | p.[A719Qfs\*16] | **Present cohort (P12)** |

1. **List of patients by references**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Origin** | **Family number** | **Patient** | **Consanguinity** | **Phenotype described** | **Zygosity** | **Allele 1** | **Allele 2** |
| Hästbacka et al., 1994 | United States of America | 1 | 1 | NS | DTD | HTZ | c.[727-1G>C] | unknown |
| Hästbacka et al., 1994 | Canada | 2 | 2 | NS | DTD | HTZ | p.[A662Qfs\*6] | unknown |
| Hästbacka et al., 1994 | France | 3 | 3 | N | DTD | HTZ | p.[K575Sfs\*10] | unknown |
| Hästbacka et al., 1994 | Germany | 4 | 4 | N | DTD | HTZ | p.[K575Sfs\*10] | unknown |
| Hästbacka et al., 1994 | Netherlands | 5 | 5 | N | DTD | HTZ | p.[K575Sfs\*10] | unknown |
| Superti-Furga et al., 1996a | NS | 13 | 13 | N | ACG-1B | cHTZ | p.[R178\*] | p.[G678V] |
| Superti-Furga et al., 1996a | NS | 14 | 14 | NS | ACG-1B | cHTZ | p.[R178\*] | p.[S399Hfs\*61] |
| Superti-Furga et al., 1996a | Netherlands | 15 | 15 | N | ACG-1B | cHTZ | p.[N425D] | p.[K575Sfs\*10] |
| Superti-Furga et al., 1996a | NS | 16 | 16 | N | ACG-1B | HMZ | p.[V340del] | p.[V340del] |
| Superti-Furga et al., 1996a | NS | 17 | 17 | NS | ACG-1B | cHTZ | p.[R178\*] | p.[Y151Ifs\*21] |
| Superti-Furga et al., 1996a | Turkey | 18 | 18 | **S** | ACG-1B | HMZ | p.[V340del] | p.[V340del] |
| Hästbacka et al., 1996 | NS | 6 | 6 | NS | AO-2 | cHTZ | p.[G255E] | p.[A715V] |
| Hästbacka et al., 1996 | NS | 7 | 7 | NS | AO-2 | HTZ | p.[K575Sfs\*10] | unknown |
| Hästbacka et al., 1996 | NS | 8 | 8 | NS | AO-2 | cHTZ | p.[R279W] | p.[K575Sfs\*10] |
| Rossi et al., 1996a | NS | 9 | 9 | **S** | ACG-1B | HMZ | p.[L483P] | p.[L483P] |
| Rossi et al., 1996b | Netherlands | 10 | 10 | NS | AO-2 | cHTZ | p.[R279W] | p.[L131Cfs\*41] |
| Rossi et al., 1996b | Netherlands | 11 | 11 | NS | AO-2 | HTZ | p.[R279W] | unknown |
| Rossi et al., 1996b | Netherlands | 12 | 12 | N | DTD | HTZ | p.[R279W] | unknown |
| Rossi et al., 1997 | NS | 19 | 19 | N | AO-2 | cHTZ | p.[R279W] | p.[N425D] |
| Cai et al., 1998 | Japan | 20 | 20 | N | ACG-1B | HMZ | p.[V340del] | p.[V340del] |
| Mégarbané et al., 1999 | Lebanon | 21 | 21 | **S** | DTD | HMZ | p.[Q454P] | p.[Q454P] |
| Superti-Furga et al., 1999 | German | 22 | 22 | N | rMED | HMZ | p.[R279W] | p.[R279W] |
| Czarny-Ratajczak, et al., 2001 | NS | 23 | 23 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Czarny-Ratajczak, et al., 2001 | NS | 24 | 24 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Huber et al., 2001 | France | 25 | 25 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Huber et al., 2001 | NS |  | 26 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Huber et al., 2001 | NS | 26 | 27 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Huber et al., 2001 | NS |  | 28 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Unger et al., 2001 | NS | 27 | 29 | NS | ACG-1B | cHTZ | c.[−26+2T>C] | p.[N425D] |
| Unger et al., 2001 | NS | 28 | 30 | NS | ACG-1B | cHTZ | c.[−26+2T>C] | p.[G259V] |
| Unger et al., 2001 | Somali | 29 | 31 | NS | ACG-1B | HMZ | p.[L132P] | p.[L132P] |
| Ballhausen et al., 2003 | NS | 30 | 32 | NS | rMED | cHTZ | c.[−26+2T>C] | p.[C653S] |
| Balhausen et al., 2003 | NS | 31 | 33 | NS | rMED | cHTZ | p.[R279W] | c.[−26+2T>C] |
| Balhausen et al., 2003 | NS | 32 | 34 | NS | rMED | HMZ | p.[C653S] | p.[C653S] |
| Balhausen et al., 2003 | NS | 33 | 35 | NS | rMED | HMZ | p.[C653S] | p.[C653S] |
| Balhausen et al., 2003 | NS | 34 | 36 | NS | rMED | HMZ | p.[C653S] | p.[C653S] |
| Balhausen et al., 2003 | NS | 35 | 37 | NS | rMED | cHTZ | p.[R279W] | p.[G237V] |
| Balhausen et al., 2003 | NS | 36 | 38 | NS | rMED | cHTZ | p.[R279W] | p.[N77H] |
| Balhausen et al., 2003 | NS | 48(12fam) | 39 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 40 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 41 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 42 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 43 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 44 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 45 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 46 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 47 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 48 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 49 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 50 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 51 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 52 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 53 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 54 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 55 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Balhausen et al., 2003 | NS |  | 56 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Matikie et al., 2003 | Hungary | 49 | 57 | N | rMED | HMZ | p.[C653S] | p.[C653S] |
| Matikie et al., 2003 | Hungary |  | 58 | N | rMED | HMZ | p.[C653S] | p.[C653S] |
| Matikie et al., 2003 | Russia | 50 | 59 | N | rMED | HMZ | p.[C653S] | p.[C653S] |
| Macías-Gómez et al., 2004 | Mexico | 51 | 60 | N | DTD | cHTZ | p.[R279W] | p.[R178\*] |
| Jakkula et al., 2005 | NS | 52 | 61 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Ramírez-Castro et al., 2005 | NS | 53 | 62 | N | DTD | cHTZ | p.[C653S] | p.[L707Pfs\*4] |
| Maeda et al., 2006 | Japan | 54 | 63 | N | DTD | cHTZ | p.[R279W] | p.[G663R] |
| Miller et al., 2008 | Bangladesh | 55 | 64 | S | AO-2 | HMZ | p.[L599F] | p.[L599F] |
| Miyake et al., 2008 | Japan | 56 | 65 | N | DTD/rMED/DBQD | cHTZ | p.[T266I] | p.[V340del] |
| Panzer et al., 2008 | NS | 57 | 66 | N | DTD/DBQD | cHTZ | p.[A133V] | p.[R178\*] |
| Bonafé et al., 2008 | Finland | 58 | 67 | S | AO-2 | HMZ | p.[T512K] | p.[T512K] |
| Bonafé et al., 2008 | Finland |  | 68 | S | AO-2 | HMZ | p.[T512K] | p.[T512K] |
| Cho et al., 2010 | Korea | 59 | 69 | N | rMED | cHTZ | p.[D385N] | p.[V162Gfs\*12] |
| Czarny-Ratajczak et al., 2010 | Poland | 60 | 70 | N | DTD | cHTZ | p.[C653S] | p.[A715V] |
| Czarny-Ratajczak et al., 2010 | Poland |  | 71 | N | DTD | cHTZ | p.[C653S] | p.[A715V] |
| Czarny-Ratajczak et al., 2010 | Poland |  | 72 | N | DTD | cHTZ | p.[C653S] | p.[A715V] |
| Dwyer et al., 2010 | NS | 61 | 73 | N | DTD | cHTZ | p.[R279W] | c.[−26+2T>C] |
| Dwyer et al., 2010 | NS |  | 74 | N | DTD | cHTZ | p.[R279W] | c.[−26+2T>C] |
| Dwyer et al., 2010 | NS |  | 75 | N | AO-2 | cHTZ | p.[R49Dfs\*40] | c.[−26+2T>C] |
| Hinrichs et al., 2010 | NS | 62 | 76 | NS | rMED | HMZ | p.[C653S] | p.[C653S] |
| Barbosa et al., 2011 | Portugal | 63 | 77 | N | DTD | cHTZ | p.[R279W] | p.[R178\*] |
| Barbosa et al., 2011 | Portugal | 64 | 78 | N | DTD | cHTZ | p.[R279W] | p.[R178\*] |
| Barbosa et al., 2011 | Portugal | 65 | 79 | N | DTD | cHTZ | p.[R279W] | p.[R178\*] |
| Barbosa et al., 2011 | Portugal | 66 | 80 | N | DTD | cHTZ | p.[R279W] | p.[R178\*] |
| Barbosa et al., 2011 | Portugal | 67 | 81 | N | DTD | cHTZ | p.[R279W] | p.[R178\*] |
| Barbosa et al., 2011 | Portugal |  | 82 | N | DTD | cHTZ | p.[R279W] | p.[R178\*] |
| Barbosa et al., 2011 | Portugal | 68 | 83 | N | DTD | cHTZ | p.[R279W] | p.[N425D] |
| Barbosa et al., 2011 | Portugal | 69 | 84 | N | DTD | cHTZ | p.[R279W] | p.[R178\*] |
| Barbosa et al., 2011 | Portugal | 70 | 85 | N | DTD | cHTZ | p.[R279W] | c.[727-1G>C] |
| Barbosa et al., 2011 | Portugal | 71 | 86 | N | DTD | cHTZ | p.[R279W] | c.[727-1G>C] |
| Barbosa et al., 2011 | Portugal | 72 | 87 | N | rMED | HMZ | p.[R279W] | p.[R279W] |
| Barbosa et al., 2011 | Portugal | 73 | 88 | N | rMED | HMZ | p.[R279W] | p.[R279W] |
| Barbosa et al., 2011 | Portugal | 74 | 89 | N | rMED | HMZ | p.[R279W] | p.[R279W] |
| Barbosa et al., 2011 | Portugal |  | 90 | N | rMED | HMZ | p.[R279W] | p.[R279W] |
| Jackson et al., 2011 | NS | 75 | 91 | NS | rMED | cHTZ | p.[F256S] | c.[−26+2T>C] |
| Jackson et al., 2011 | NS | 76 | 92 | NS | rMED | cHTZ | p.[C653S] | c.[−26+2T>C] |
| Jackson et al., 2011 | NS | 77 | 93 | NS | rMED | cHTZ | p.[R279W] | c.[−26+2T>C] |
| Jackson et al., 2011 | NS | 78 | 94 | NS | rMED | cHTZ | p.[C653S] | p.[A715V] |
| Jackson et al., 2011 | NS | 79 | 95 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Jackson et al., 2011 | NS | 80 | 96 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Jackson et al., 2011 | NS | 81 | 97 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Jackson et al., 2011 | NS | 82 | 98 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Jackson et al., 2011 | NS | 83 | 99 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Jackson et al., 2011 | NS | 84 | 100 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Jackson et al., 2011 | NS | 85 | 101 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Jackson et al., 2011 | NS | 86 | 102 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Jackson et al., 2011 | NS | 87 | 103 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Jackson et al., 2011 | NS | 88 | 104 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Jackson et al., 2011 | NS | 89 | 105 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Jackson et al., 2011 | NS | 90 | 106 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Kim et al., 2011 | Korea | 91 | 107 | NS | rMED | cHTZ | p.[V162Gfs\*12] | p.[D385N] |
| Honório et al., 2013 | Brazil | 92 | 108 | N | DTD | cHTZ | p.[R279W] | p.[L707Pfs\*4] |
| Pineda et al., 2013 | Colombia | 93 | 109 | N | DTD | cHTZ | p.[R279W] | p.[S157T] |
| Zechi-Ceide et al., 2013 | Brazil | 94 | 110 | N | DTD | cHTZ | p.[R279W] | c.[−26+2T>C] |
| Zechi-Ceide et al., 2013 | Brazil |  | 111 | N | DTD | cHTZ | p.[R279W] | c.[−26+2T>C] |
| Syvänen et al., 2013 | Finland | 95 | 112 | N | rMED | cHTZ | p.[R279W] | p.[T512K] |
| Martínez García et al., 2014 | NS | 96 | 113 | NS | rMED | HMZ | p.[R279W] | p.[R279W] |
| Mattos et al., 2014 | Brazil | 97 | 114 | N | AO-2 | cHTZ | p.[R279W] | p.[R178\*] |
| Makitie et al., 2015 | Sweden | 98 | 115 | NS | rMED | cHTZ | p.[R279W] | p.[T512K] |
| Makitie et al., 2015 | Finland/Sweden | 99 | 116 | NS | rMED | cHTZ | p.[R279W] | c.[−26+2T>C] |
| Makitie et al., 2015 | Finland/Sweden | 100 | 117 | NS | rMED | cHTZ | p.[R279W] | c.[−26+2T>C] |
| Makitie et al., 2015 | Finland | 101 | 118 | NS | rMED | cHTZ | p.[R279W] | c.[−26+2T>C] |
| Makitie et al., 2015 | Finland |  | 119 | NS | rMED | cHTZ | p.[R279W] | c.[−26+2T>C] |
| Vikraman et al., 2016 | India | 102 | 120 | **S** | AO-2 | HMZ | p.[L599F] | p.[L599F] |
| Barreda-Bonis et al., 2017 | NS | 103 | 121 | NS | rMED | cHTZ | p.[R279W] | p.[S522F] |
| Barreda-Bonis et al., 2017 | NS |  | 122 | N | rMED | HMZ | p.[R279W] | p.[R279W] |
| Kausar et al., 2018 | Finland | 104 | 123 | N | rMED | cHTZ | c.[−26+2T>C] | p.[C653S] |
| Kausar et al., 2018 | Finland | 105 | 124 | N | rMED | cHTZ | p.[R279W] | p.[T512K] |
| Zhou et al., 2018 | China | 106 | 125 | N | rMED | cHTZ | p.[L275P] | p.[L400F] |
| Zhou et al., 2018 | China |  | 126 | N | rMED | cHTZ | p.[L275P] | p.[L400F] |
| Sato et al., 2020 | Japan | 107 | 127 | N | ACG-1B | HMZ | p.[G663R] | p.[G663R] |
| Sato et al., 2020 | Japan |  | 128 | N | ACG-1B | HMZ | p.[G663R] | p.[G663R] |
| Sato et al., 2020 | Japan | 108 | 129 | N | ACG-1B | HMZ | p.[G663R] | p.[G663R] |
| Present cohort | Brazil | 109 | 130 | N | ACG-1B | HTZ | p.[V340del] | unknown |
| Present cohort | Brazil | 110 | 131 | N | AO-2 | cHTZ | p.[R279W] | p.[T627Lfs\*23] |
| Present cohort | Brazil | 111 | 132 | N | AO-2 | cHTZ | p.[R279W] | p.[R178\*] |
| Present cohort | Brazil | 112 | 133 | N | DTD | cHTZ | p.[R279W] | c.[727-1G>C] |
| Present cohort | Brazil | 113 | 134 | N | DTD | cHTZ | p.[R279W] | p.[K575Sfs\*10] |
| Present cohort | Brazil |  | 135 | N | DTD | cHTZ | p.[R279W] | p.[K575Sfs\*10] |
| Present cohort | Brazil | 114 | 136 | N | DTD | cHTZ | p.[R279W] | p.[G115A] |
| Present cohort | Argentina | 115 | 137 | N | DTD | cHTZ | p.[R279W] | p.[R178\*] |
| Present cohort | Brazil | 116 | 138 | N | DTD | cHTZ | p.[R279W] | p.[R178\*] |
| Present cohort | Brazil | 117 | 139 | N | rMED | HMZ | p.[R279W] | p.[R279W] |
| Present cohort | Brazil | 118 | 140 | N | rMED | HMZ | p.[R279W] | p.[R279W] |
| Present cohort | Brazil | 119 | 141 | N | rMED/DBQD | cHTZ | p.[R279W] | p.[A719Qfs\*16] |
| Total |  | 119 | 141 |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| Y: yes, N: No, NS: not specified | |  |  |  |  |  |  |  |
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1. **DTD Finnish**

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| --- | --- | --- | --- | --- | --- |
| **Reference** | **Family number** | **Patient** | **Zygosity** | **Allele 1** | **Allele 2** |
| Hästbacka et al., 1999 | 69fam | 122 (102 patients) | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Hästbacka et al., 1999 | 14fam |  | HTZ | c.[−26+2T>C] | unknown |
| Hästbacka et al., 1999 | 1fam |  | cHTZ | p.[R279W] | p.[V340del] |
| Remes et al., 2002 | 85 | 103 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 |  | 104 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 |  | 105 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 86 | 106 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 |  | 107 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 |  | 108 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 87 | 109 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 |  | 110 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 |  | 111 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 88 | 112 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 |  | 113 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 89 | 114 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 |  | 115 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 90 | 116 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 |  | 117 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 91 | 118 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 |  | 119 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 92 | 120 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 |  | 121 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 93 | 122 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 94 | 123 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 95 | 124 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 96 | 125 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 97 | 126 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 98 | 127 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 99 | 128 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 100 | 129 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 101 | 130 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 102 | 131 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 103 | 132 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 104 | 133 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 105 | 134 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 106 | 135 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 107 | 136 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 108 | 137 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 109 | 138 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 110 | 139 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 111 | 140 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 112 | 141 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 113 | 142 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 114 | 143 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 115 | 144 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 116 | 145 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 117 | 146 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 118 | 147 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 119 | 148 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 120 | 149 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 121 | 150 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 122 | 151 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 123 | 152 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 124 | 153 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 125 | 154 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 126 | 155 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 127 | 156 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 128 | 157 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 129 | 158 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Remes et al., 2002 | 130 | 159 | HTZ | c.[−26+2T>C] | unknown |
| Remes et al., 2002 |  | 160 | HTZ | c.[−26+2T>C] | unknown |
| Remes et al., 2002 | 131 | 161 | HTZ | c.[−26+2T>C] | unknown |
| Remes et al., 2002 | 132 | 162 | HTZ | c.[−26+2T>C] | unknown |
| Remes et al., 2002 | 133 | 163 | cHTZ | c.[−26+2T>C] | p.[R279W] |
| Remes et al., 2002 |  | 164 | cHTZ | c.[−26+2T>C] | p.[R279W] |
| Remes et al., 2002 | 134 | 165 | cHTZ | c.[−26+2T>C] | p.[R279W] |
| Remes et al., 2002 |  | 166 | cHTZ | c.[−26+2T>C] | p.[R279W] |
| Remes et al., 2002 | 135 | 167 | cHTZ | c.[−26+2T>C] | p.[R279W] |
| Remes et al., 2002 | 136 | 168 | cHTZ | c.[−26+2T>C] | p.[R279W] |
| Remes et al., 2002 | 137 | 169 | cHTZ | c.[−26+2T>C] | p.[R279W] |
| Remes et al., 2002 | 138 | 170 | cHTZ | c.[−26+2T>C] | p.[R279W] |
| Remes et al., 2002 | 139 | 171 | cHTZ | c.[−26+2T>C] | p.[R279W] |
| Bonafé et al., 2008 | 140 | 172 | cHTZ | c.[−26+2T>C] | p.[T512K] |
| Bonafé et al., 2008 | 141 | 173 | cHTZ | c.[−26+2T>C] | p.[T512K] |
| Bonafé et al., 2008 | 142 | 174 | cHTZ | c.[−26+2T>C] | p.[T512K] |
| Bonafé et al., 2008 | 143 | 175 | cHTZ | c.[−26+2T>C] | p.[T512K] |
| Bonafé et al., 2008 | 144 | 176 | cHTZ | c.[−26+2T>C] | p.[T512K] |
| Bonafé et al., 2008 | 145 | 177 | cHTZ | c.[−26+2T>C] | p.[T512K] |
| Bonafé et al., 2008 | 146 | 178 | cHTZ | c.[−26+2T>C] | p.[T512K] |
| Makitie et al., 2015 | 147 | 179 | HMZ | c.[−26+2T>C] | c.[−26+2T>C] |
| Total | 147 | 179 |  |  |  |

1. **Allelic Frequency Non-finnish DTD**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variant c.** | **Variant p.** | **NO of alleles** | **%** | **Protein domain** |
| c.862C>T | p.R279W | 137 | 50.2 | EC-loop |
| c.1984T>A | p.C653S | 22 | 8.1 | STAS |
| c.−26+2T>C | p? | 17 | 6.2 | - |
| c.559C>T | p.R178\* | 16 | 5.9 | EC-loop |
| c.1751del | p.K575Sfs\*10 | 8 | 2.9 | STAS |
| c.1045\_1047del | p.V340del | 8 | 2.9 | TD 7 |
| c.1987G>A | p.G663R | 7 | 2.6 | STAS |
| c.1535C>A | p.T512K | 7 | 2.6 | TD 13 |
| c.2171C>T | p.A715V | 5 | 1.8 | STAS |
| c.727-1G>C | p? | 4 | 1.5 | - |
| c.1824A>C | p.L599F | 4 | 1.5 | STAS |
| c.1300A>G | p.N425D | 4 | 1.5 | TD 9 |
| c.1153G>A | p.D385N | 2 | 0.7 | TD 8 |
| c.422T>C | p.L132P | 2 | 0.7 | TD 1 |
| c.851T>C | p.L275P | 2 | 0.7 | EC-loop |
| c.1225C>T | p.L400F | 2 | 0.7 | TD 8 |
| c.1475T>C | p.L483P | 2 | 0.7 | TD 12 |
| c.2147\_2148ins | p.L707Pfs\*4 | 2 | 0.7 | STAS |
| c.1388A>C | p.Q454P | 2 | 0.7 | TD 11 |
| c.485\_486del | p.V162Gfs\*12 | 2 | 0.7 | Cito-loop |
| c.425C>T | p.A133V | 1 | 0.4 | TD 1 |
| c.2010del | p.A662Qfs\*6 | 1 | 0.4 | STAS |
| c.2182del | p.A719Qfs\*16 | 1 | 0.4 | STAS |
| c.794T>C | p.F256S | 1 | 0.4 | TD 5 |
| c.371G>C | p.G115A | 1 | 0.4 | TD 1 |
| c.737G>T | p.G237V | 1 | 0.4 | Cito-loop |
| c.791G>A | p.G255E | 1 | 0.4 | TD 5 |
| c.803G>T | p.G259V | 1 | 0.4 | TD 5 |
| c.2060G>T | p.G678V | 1 | 0.4 | STAS |
| c.418del | p.L131Cfs\*41 | 1 | 0.4 | TD 1 |
| c.236A>C | p.N77H | 1 | 0.4 | N-terminal |
| c.172del | p.R49Dfs\*40 | 1 | 0.4 | N-terminal |
| c.496T>A | p.S157T | 1 | 0.4 | Cito-loop |
| c.1221del | p.S399Hfs\*61 | 1 | 0.4 | TD 8 |
| c.1565C>T | p.S522F | 1 | 0.4 | TD 13 |
| c.797C>T | p.T266I | 1 | 0.4 | TD 5 |
| c.1905del | p.T627Lfs\*23 | 1 | 0.4 | STAS |
| c.476del | p.Y151Ifs\*21 | 1 | 0.4 | TD 2 |
| unknown | unknown | 9 |  |  |
|  |  | 273 |  |  |
|  |  |  |  |  |
| TD: Transmembrane domains | |  |  |  |
| EC-loop:Extracellular loop | |  |  |  |
| Cito-loop:Citosolic loop | |  |  |  |
| EC-DB: Possible extracellular loop disulfide bridge | | |  |  |
| Sulfate Transporter and Anti-Sigma: STAS domain | | |  |  |
|  |  |  |  |  |

1. **Frequent genotypes**

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| --- | --- | --- | --- | --- |
| **Variant** | **Alleles** | **Number of patients** | **Genotypes** | **Number of patients with the genotype** |
| p.[R279W] | 137 | 91 | **p.[R279W];[R279W]** | **46/91 (46 rMED)** |
| p.[R279W];[R178\*] | 12/91 (10 DTD and 2 AO-2) |
| p.[R279W];c.[−26+2T>C] | 10/91 (6 rMED and 4 DTD) |
| p.[R279W];[T512K] | 3/91 (rMED) |
| p.[R279W];[K575Sfs\*10] | 3/91 (2 DTD and 1 AO-2) |
| p.[R279W];c.[727-1G>C] | 3/91 (DTD) |
| p.[R279W];[N425D] | 2/91 (1 AO-2 and 1 DTD) |
| p.[R279W];[N77H] | 1/91 (rMED) |
| p.[R279W];[G115A] | 1/91 (DTD) |
| p.[R279W];[L131Cfs\*41] | 1/91 ( AO-2) |
| p.[R279W];[S157T] | 1/91 (DTD) |
| p.[R279W];.[G237V] | 1/91 (rMED) |
| p.[R279W];[S522F] | 1/91 (rMED) |
| p.[R279W];[T627Lfs\*23] | 1/91 ( AO-2) |
| p.[R279W];[G663R] | 1/91 (DTD) |
| p.[R279W];[L707Pfs\*4] | 1/91 (DTD) |
| p.[R279W];[A719Qfs\*16] | 1/91 (rMED/DBQD) |
| p.[R279W];[wt] | 2/91 (1 DTD and 1 AO-2) |
| p.[C653S] | 22 | 15 | **p.[C653S];[C653S]** | **7/15 (rMED)** |
| p.[C653S];[A715V] | 4/15 (3 DTD and 1 rMED) |
| p.[C653S];c.[−26+2T>C] | 3/15 (rMED) |
| p.[C653S];[L707Pfs\*4] | 1/15 (DTD) |
| c.[−26+2T>C] | 17 | 17 | c.[−26+2T>C];p.[R279W] | 10/17 (6rMED and 4 DTD) |
| c.[−26+2T>C];p.[C653S] | 3/17 (rMED) |
| c.[−26+2T>C];p.[G259V] | 1/17 (ACG-1B) |
| c.[−26+2T>C];p.[N425D] | 1/17 (ACG-1B) |
| c.[−26+2T>C];p.[R49Dfs\*40] | 1/17 (AO-2) |
| c.[−26+2T>C];p.[F256S] | 1/17 (rMED) |
| p.[R178\*] | 16 | 16 | p.[R178\*];[R279W] | 12/16 (10 DTD and 2 AO-2) |
| p.[R178\*];[G678V] | 1/16 (ACG-1B) |
| p.[R178\*];[S399Hfs\*61] | 1/16 (ACG-1B) |
| p.[R178\*];[Y151Ifs\*21] | 1/16 (ACG-1B) |
| p.[R178\*];[A133V] | 1/16 (DTD/DBQD) |
| p.[K575Sfs\*10] | 8 | 8 | p.[K575Sfs\*10];[unknown] | 3/8 (DTD) |
| p.[K575Sfs\*10];[R279W] | 2/8 (DTD) |
| p.[K575Sfs\*10];[R279W] | 1/8 (AO-2) |
| p.[K575Sfs\*10];[N425D] | 1/8 (ACG-1B) |
| p.[K575Sfs\*10];[unknown] | 1/8 (AO-2) |
| p.[V340del] | 8 | 5 | **p.[V340del];[V340del]** | **3/5 (ACG-1B)** |
| p.[V340del];[unknown] | 1/5 (ACG-1B) |
| p.[T266I];[V340del] | 1/5 (DTD/rMED/DBQD) |
| p.[G663R] | 7 | 4 | **p.[G663R];[G663R]** | **3/4 (ACG-1B)** |
| p.[G663R];[R279W] | 1/4 (DTD) |
| p.[T512K] | 7 | 5 | p.[R279W];[T512K] | 3/5 (rMED) |
| **p.[T512K];[T512K]** | **2/5 (AO-2)** |
|  |  |  |  |  |

1. **Variants related known genotype**

|  |  |
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| **Variant** | **Phenotype** |
| p.[R49Dfs\*40] | AO-2 |
| p.[N77H] | rMED |
| p.[L131Cfs\*41] | AO-2 |
| p.[Y151Ifs\*21] | ACG-1B |
| p.[S399Hfs\*61] | ACG-1B |
| p.[V340del] | ACG-1B, DTD/rMED/DBQD |
| p.[G115A] | DTD |
| p.[S157T] | DD |
| p.[V162Gfs\*12] | rMED |
| p.[R178\*] | ACG-1B, AO-2, DTD, DTD/DBQD |
| p.[G237V] | rMED |
| p.[L132P] | ACG-1B |
| p.[A133V] | DTD/DBQD |
| p.[G255E] | AO-2 |
| p.[F256S] | rMED |
| p.[L275P] | rMED |
| p.[R279W] | AO-2, DTD, rMED, rMED/DBQD |
| p.[G259V] | ACG-1B |
| p.[T266I] | DTD/rMED/DBQD |
| p.[D385N] | rMED |
| p.[L400F] | rMED |
| p.[N425D] | ACG-1B, AO-2, DTD |
| p.[Q454P] | DTD |
| p.[L483P] | ACG-1B |
| p.[T512K] | AO-2, rMED |
| p.[S522F] | rMED |
| p.[K575Sfs\*10] | ACG-1B, AO-2, DTD |
| p.[T627Lfs\*23] | AO-2 |
| p.[A662Glnfs\*6] | DTD |
| p.[L707Pfs\*4] | DTD |
| p.[A719Qfs\*16] | rMED/DBQD |
| p.[L599F] | AO-2 |
| p.[C653S] | DTD, rMED |
| p.[G663R] | ACG-1B, DTD |
| p.[G678V] | ACG-1B |
| p.[A715V] | AO-2, DTD, rMED |
| c.[−26+2T>C] | AO-2, ACG-1B, DTD, rMED |
| c.[727-1G>C] | DTD |
|  |  |

1. **Functional Studies**

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| --- | --- | --- | --- |
| **Variant** | **Sulfate transport** | **Residual sultafe transport capacity** | **Reference** |
| p.[R178\*] | <10% | null variant | Karniski 2001; Karniski 2004 |
| p.[G255E] | <10% | null variant | Karniski 2001 |
| p.[R279W] | 32% (Xenopus laevis oocytes) and ~50% (HEK-293 cells) | intermediate/partial funcion variant | Karniski 2001; Karniski 2004 |
| p.[V340del] | 17% | null variant | Karniski 2001; Karniski 2004 |
| p.[N425D] | <10% | null variant | Karniski 2001; Karniski 2004 |
| p.[Q454P] | ~39% | partial funcion variant | Karniski 2001; Karniski 2004 |
| p.[L483P] | <10% | null variant | Karniski 2001; Karniski 2004 |
| p.[K575Sfs\*10] | <10% | null variant | Karniski 2001; Karniski 2004 |
| p.[G663R] | transporter trapped within the cytoplasm | null variant | Maeda et al.,2006 |
| p.[C653S] | 100% (Xenopus laevis oocytes); ~50% (HEK-293 cells) | near-normal activity/partial function variant | Karniski 2001; Karniski 2004 |
| p.[G678V] | >50% (Xenopus laevis oocytes) and ~20% (HEK-293 cells) | near-normal activity/null function variant | Karniski 2001; Karniski 2004 |
| p.[A715V] | ~60% | near-normal activity | Karniski 2001; Karniski 2004 |

1. **Other variants**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variant** | **AA** | **Variant Type** | **Reference** | **Observation** |
| p.S16\* | 16 | Nonsense | Rossi et al., 2001 |  |
| p.G19\* | 19 | Nonsense | Rossi et al., 2001 |  |
| p.N87Ifs\*2 | 87 | Frameshift | Rossi et al., 2001 |  |
| p.W98R | 98 | Missense | Yang et al., 2019 | only US image available |
| p.D111Y | 111 | Missense | Rossi et al., 2001 |  |
| p.Q135K | 135 | Missense | Rossi et al., 2001 |  |
| p.Val162Leu | 162 | Missense | Li et al., 2020 | Article in Chinese |
| p.G166R | 166 | Missense | Rossi et al., 2001 |  |
| p.M236Sfs\*16 | 236 | Frameshift | Rossi et al., 2001 |  |
| p.C303\* | 303 | Nonsense | Rossi et al., 2001 |  |
| p.A386V | 386 | Missense | Rossi et al., 2001 |  |
| p.N415Rfs\*44 | 415 | Frameshift | Rossi et al., 2001 |  |
| p.L465Cfs\*5 | 465 | Frameshift | Rossi et al., 2001 |  |
| p.Ser481Lysfs\*17 | 481 | Frameshift | Li et al., 2020 | Article in Chinese |
| p.G484D | 484 | Missense | Rossi et al., 2001 |  |
| p.S551Vfs\*34 | 551 | Frameshift | Rossi et al., 2001 |  |
| p.L659\* | 659 | Nonsense | Rossi et al., 2001 |  |
| p.H665P | 665 | Missense | Rossi et al., 2001 |  |
|  |  |  |  |  |
| p.R492W | 492 | Missense | Rossi et al., 2001 and Bonafe et al., 2008 | Polymorphism |
| p.T574I | 574 | Missense | Rossi et al., 2001 and others | Polymorphism |
| p.T689S | 689 | Missense | Cai et al., 1998 and others | Polymorphism |

1. **Genotypes\_Domain**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Phenotype** | **Zygosity** | **Allele 1** | **Variant Type** | **Protein Domain** | **Allele 2** | **Variant Type** | **Protein Domain** |
| ACG-1B | cHTZ | c.[−26+2T>C] | 5' splice donor of intron 1 | - | p.[G259V] | Missense | TD5 - midle |
| ACG-1B | cHTZ | c.[−26+2T>C] | 5' splice donor of intron 1 | - | p.[N425D] | Missense | TD9 - midle |
| DTD | HTZ | c.[727-1G>C] | Splice site | - | unknown | - | - |
| AO-2 | cHTZ | p.[R49Dfs\*40] | Frameshift | N-terminal | c.[−26+2T>C] | 5' splice donor of intron 1 | - |
| rMED | cHTZ | p.[V162Gfs\*12] | Frameshift | Cito-loop | p.[D385N] | Missense | TD8 - border |
| rMED | cHTZ | p.[C653S] | Missense | STAS | c.[−26+2T>C] | 5' splice donor of intron 1 | - |
| rMED, DTD | cHTZ | p.[C653S] | Missense | STAS | p.[A715V] | Missense | STAS |
| AO-2, DTD | HTZ | p.[K575Sfs\*10] | Frameshift | STAS | unknown | - | - |
| AO-2 | cHTZ | p.[R279W] | Missense | EC-loop | p.[L131Cfs\*41] | Frameshift | TD1 - border |
| AO-2 | cHTZ | p.[R279W] | Missense | EC-loop | p.[T627Lfs\*23] | Frameshift | STAS |
| DTD, rMED | cHTZ | p.[R279W] | Missense | EC-loop | c.[−26+2T>C] | 5' splice donor of intron 1 | - |
| DTD | cHTZ | p.[R279W] | Missense | EC-loop | c.[727-1G>C] | Splice site | - |
| rMED/DBQD | cHTZ | p.[R279W] | Missense | EC-loop | p.[A719Qfs\*16] | Frameshift | STAS |
| DTD | cHTZ | p.[R279W] | Missense | EC-loop | c.[727-1G>C] | Splice site | - |
| DTD | cHTZ | p.[R279W] | Missense | EC-loop | p.[G115A] | Missense | TD1 - midle |
| DTD | cHTZ | p.[R279W] | Missense | EC-loop | p.[G663R] | Missense | STAS |
| AO-2, DTD | cHTZ | p.[R279W] | Missense | EC-loop | p.[K575Sfs\*10] | Frameshift | STAS |
| DTD | cHTZ | p.[R279W] | Missense | EC-loop | p.[L707Pfs\*4] | Frameshift | STAS |
| rMED | cHTZ | p.[F256S] | Missense | TD5 - midle | c.[−26+2T>C] | 5' splice donor of intron 1 | - |
| rMED | HMZ | p.[R279W] | Missense | EC-loop | p.[R279W] | Missense | EC-loop |
| rMED | cHTZ | p.[L275P] | Missense | EC-loop | p.[L400F] | Missense | TD8 - border |
| rMED | cHTZ | p.[R279W] | Missense | EC-loop | p.[G237V] | Missense | Cito-loop |
| rMED | cHTZ | p.[R279W] | Missense | EC-loop | p.[N77H] | Missense | N-terminal |
| rMED | cHTZ | p.[R279W] | Missense | EC-loop | p.[S522F] | Missense | TD13 - border |
| rMED | cHTZ | p.[R279W] | Missense | EC-loop | p.[T512K] | Missense | TD13 - border |
| AO-2, DTD | cHTZ | p.[R279W] | Missense | EC-loop | p.[N425D] | Missense | TD9 - midle |
| DTD | cHTZ | p.[C653S] | Missense | STAS | p.[L707Pfs\*4] | Frameshift | STAS |
| rMED | HMZ | p.[C653S] | Missense | STAS | p.[C653S] | Missense | STAS |
| ACG-1B | HMZ | p.[G663R] | Missense | STAS | p.[G663R] | Missense | STAS |
| AO-2, DTD | cHTZ | p.[R279W] | Missense | EC-loop | p.[R178\*] | Nonsense | EC-loop |
| DTD | cHTZ | p.[R279W] | Missense | EC-loop | p.[S157T] | Missense | Cito-loop |
| AO-2, DTD | HTZ | p.[R279W] | Missense | EC-loop | unknown | - | - |
| DTD | HTZ | p.[A662Glnfs\*6] | Frameshift | STAS | unknown | - | - |
| AO-2 | cHTZ | p.[G255E] | Missense | TD 5 - border | p.[A715V] | Missense | STAS |
| DTD/DBQD | cHTZ | p.[A133V] | Missense | TD1 - border | p.[R178\*] | Nonsense | EC-loop |
| AO-2 | HMZ | p.[L599F] | Missense | STAS | p.[L599F] | Missense | STAS |
| DTD | HMZ | p.[Q454P] | Missense | TD 11 Core- N-terminal | p.[Q454P] | Missense | TD 11- N-terminal |
| DTD/rMED/DBQD | cHTZ | p.[T266I] | Missense | TD5 - midle | p.[V340del] | in frame del | TD7 - midle |
| ACG-1B | HMZ | p.[L132P] | Missense | TD1 Core - border | p.[L132P] | Missense | TD1 - border |
| ACG-1B | cHTZ | p.[N425D] | Missense | TD9 - midle | p.[K575Sfs\*10] | Frameshift | STAS |
| ACG-1B | HMZ | p.[L483P] | Missense | TD12 Gate - border | p.[L483P] | Missense | TD12 - border |
| AO-2 | HMZ | p.[T512K] | Missense | TD13 Gate - border | p.[T512K] | Missense | TD13 - border |
| ACG-1B | cHTZ | p.[R178\*] | Nonsense | EC-loop | p.[G678V] | Missense | STAS |
| ACG-1B | cHTZ | p.[R178\*] | Nonsense | EC-loop | p.[S399Hfs\*61] | Frameshift | TD8- midle |
| ACG-1B | HMZ | p.[V340del] | in frame del | TD7 Gate- midle | p.[V340del] | in frame del | TD7 - midle |
| ACG-1B | HTZ | p.[V340del] | in frame del | TD7 - midle | unknown | - | - |
| ACG-1B | cHTZ | p.[R178\*] | Nonsense | EC-loop | p.[Y151Ifs\*21] | Frameshift | TD2-border |
|  |  |  |  |  |  |  |  |

1. **Genotype\_Domains\_summary**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **VARIANT 2** | | | | | | | | | |
|  |  | **Missense** | | | **Nonsense** | **Frameshift** | | | **In frame del** | **Splice / 5' UTR** | **Unknown** |
| **VARIANT 1** | | **EC-loop/ Cito-loop/ N-terminal** | **STAS** | **TD** | **EC-loop/ Cito-loop** | **EC-loop/ Cito-loop** | **STAS** | **TD** | **TD** |  |
| **Missense** | **EC-loop/ Cito-loop / N-terminal** | DTD rMED | DTD | AO-2 DTD rMED | AO-2 DTD |  | AO-2 DTD rMED/DBQD | AO-2 |  | DTD rMED | AO-2 DTD |
| **STAS** |  | ACG-1B AO-2 DTD rMED |  |  |  | DTD |  |  | rMED |  |
| **TD** |  | AO-2 | ACG-1B AO-2 DTD | DTD/DBQD | rMED | ACG-1B |  | DTD/rMED/DBQD | ACG-1B rMED |  |
| **Nonsene** | **EC-loop/ Cito-loop** |  | ACG-1B |  |  |  |  | ACG-1B |  |  |  |
| **Frameshift** | **STAS** |  |  |  |  |  |  |  |  |  | AO-2 DTD |
| **N-terminal** |  |  |  |  |  |  |  |  | AO-2 |  |
| **In frame del** | **TD** |  |  |  |  |  |  |  | ACG-1B |  | ACG-1B |
| **Splice / 5'UTR** | |  | rMED |  |  |  |  |  |  |  | DTD |

1. **Protein Domains**

|  |  |
| --- | --- |
| **Domain** | **AA range** |
| Cito-loop | 154-166 |
| Cito-loop | 236-241 |
| Cito-loop | 247-250 |
| Cito-loop | 329-335 |
| Cito-loop | 407-414 |
| Cito-loop | 449-454 |
| Cito-loop | 492-494 |
| Cito-loop | 498-509 |
| Cito-loop | 546-550 |
| C-terminal | 721-739 |
| EC-loop | 133-137 |
| EC-loop | 176-221 |
| EC-loop | 272-302 |
| EC-loop | 350-380 |
| EC-loop | 431-440 |
| EC-loop | 477-480 |
| EC-loop | 524-527 |
| N-glycosylation cryptic site extracellular loop 4 | 357-357 |
| N-glycosylation site at extracellular loop | 199-199 |
| N-glycosylation site at extracellular loop | 205-205 |
| N-terminal | 1-105 |
| EC-DB | 212-216 |
| STAS | 551-720 |
| TD | 106-133 |
| TD | 137-154 |
| TD | 166-176 |
| TD | 221-236 |
| TD | 250-272 |
| TD | 302-329 |
| TD | 335-350 |
| TD | 380-407 |
| TD | 414-431 |
| TD | 440-449 |
| TD | 454-477 |
| TD | 480-492 |
| TD | 509-524 |
| TD | 527-546 |
|  |  |
|  |  |
| TD: Transmembrane domains |  |
| EC-loop:Extracellular loop |  |
| Cito-loop:Citosolic loop |  |
| EC-DB: Possible extracellular loop disulfide bridge |  |
| Sulfate Transporter and Anti-Sigma: STAS domain |  |

1. **Patients\_families summary**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Phenotype** | **Patients** | **Families** | **Family´s zygosity** | | |
| **HMZ** | **cHTZ** | **HTZ** |
| **DTD total** | 214 | 177 | 117 | 37 | 23 |
| DTD Finnish | 179 | 147 | 115 | 15 | 17 |
| DTD non-Finnish | 35 | 29 | 1 | 22 | 6 |
| **rMED** | 74 | 61 | 42 | 19 | 0 |
| **ACG-1B** | 15 | 14 | 7 | 6 | 1 |
| **AO-2** | 14 | 12 | 3 | 7 | 2 |
| **DTD/rMED/DBQD** | 1 | 1 | 0 | 1 | 0 |
| **DTD/DBQD** | 1 | 1 | 0 | 1 | 0 |
| **rMED/DBQD** | 1 | 1 | 0 | 1 | 0 |

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