

**Table S2. Study characteristics articles included in meta-analysis**

| Study                     | Nationality | Population | Study design | Detection method | Exons screened | Mutation rate |           | Control | Diagnostic category | FALS     | Note |
|---------------------------|-------------|------------|--------------|------------------|----------------|---------------|-----------|---------|---------------------|----------|------|
|                           |             |            |              |                  |                | FALS(n/N)     | SALS(n/N) |         |                     |          |      |
| <b>SOD1</b>               |             |            |              |                  |                |               |           |         |                     |          |      |
| Jones CT, 1995[1]         | Scottish    | European   | HB           | SSCP             | All            | 5/10          | 4/57      | -       | Clinical criteria   | No       |      |
| Deng HX, 1995[2]          | USA         | European   | HB           | SSCP             | All            | 37/222        | -         | -       | Clinical criteria   | Possible |      |
| Pramatarova A, 1995[3]    | European    | European   | HB           | SSCP             | All            | 15/114        | -         | 67      | Clinical criteria   | No       |      |
| Andersen PM, 1997[4]      | European    | European   | HB           | SSCP             | All            | 27/72         | 14/355    | -       | Clinical criteria   | No       |      |
| Cudkowicz ME, 1997[5]     | USA         | European   | HB           | SSCP             | All            | 68/290        | -         | 313     | Clinical criteria   | Possible |      |
| Jackson M,1997[6]         | British     | European   | HB           | SSCP             | All            | -             | 4/155     |         | EEC def/pro/pos/sus | -        |      |
| Aoki M, 1998[7]           | Japanese    | Asian      | HB           | SSCP             | All            | 6/12          | -         | -       | Clinical creteria   | Probable |      |
| Boukaftane Y,1998[8]      | Canadian    | European   | HB           | SSCP             | All            | 10/70         | -         | 300     | EEC                 | No       |      |
| Shaw CE,1998[9]           | British     | European   | HB           | SSCP             | All            | 8/38          | 5/175     | -       | EEC def/pro         | No       |      |
| Aguirre T,1999[10]        | Belgium     | European   | HB           | SSCP             | All            | 7/11          | 1/69      | 75      | EEC                 | No       |      |
| Orell RW, 1999[11]        | British     | European   | HB           | SSCP             | All            | 17/85         | -         | -       | EEC                 | Possible |      |
| Gellera C,2001[12]        | Italian     | European   | HB           | SSCP             | All            | 7/36          | 3/48      | -       | EEC def/pro         | No       |      |
| Skvortsova VI,2001[13]    | Russian     | European   | HB           | SSCP sequencing  | All            | -             | 2/20      | -       | EEC                 | -        |      |
| Garcia-Redondo A,2002[14] | Spanish     | European   | HB           | SSCP             | All            | 2/11          | 1/87      | 100     | EEC                 | Possible |      |
| Niemann S,2004[15]        | German      | European   | HB           | Sequencing       | All            | 9/75          | -         | 90      | EEC def/pro         | Probable |      |
| Sato T,2004[16]           | Japanese    | Asian      | HB           | Sequencing       | All            | 10/33         | -         | -       | EEC                 | No       |      |
| Battistini S,2005[17]     | Italian     | European   | HB           | SSCP sequencing  | All            | 7/39          | 0/225     | -       | rEEC def/pro        | Possible |      |
| Corrado L,2006[18]        | Italian     | European   | HB           | DHPLC sequencing | All            | 0/4           | 3/66      | 181     | rEEC                | Possible |      |
| Gamez J,2006[19]          | Spanish     | European   | HB           | Sequencing       | All            | 5/30          | 2/94      | -       | rEEC                | Possible |      |
| Chio A,2008[20]           | Italian     | European   | PB           | DHPLC sequencing | All            | 2/21          | 2/303     | 186     | rEEC def/pro        | Possible |      |
| Eisen A,2008[21]          | Canadian    | European   | HB           | SSCP             | All            | 10/47         | 3/159     | -       | rEEC def/pro        | No       |      |

|                              |             |          |    | sequencing     |     |        |        |      |                      |          |  |  |
|------------------------------|-------------|----------|----|----------------|-----|--------|--------|------|----------------------|----------|--|--|
| Luquin N,2008[22]            | Australian  | European | HB | Sequencing     | All | -      | 0/23   | 115  | rEEC def/pro         | -        |  |  |
| Takahashi Y,2008[23]         | Japanese    | Asian    | HB | NGS            | All | 2/7    | 1/35   | 238  | rEEC                 | No       |  |  |
| DeJesus-Hernandez M,2010[24] | USA         | European | HB | Sequencing     | All | 3/17   | 0/99   | -    | rEEC                 | Possible | TARDBP, FUS mutations screened                 |  |
| Rabe M,2010[25]              | German      | European | HB | Sequencing     | All | 28/217 | -      | -    | rEEC def             | Probable |  |  |
| Akimoto C,2011[26]           | Japanese    | Asian    | HB | HRM sequencing | All | 4/10   | 7/439  | -    | rEEC def/pro/pos/sus | No       |  |  |
| Niu YF,2011[27]              | Chinese     | Asian    | HB | Sequencing     | All | 3/8    | -      | -    | rEEC                 | No       |  |  |
| Chiò A,2012[28]              | Italian     | European | PB | Sequencing     | All | 4/44   | 6/429  | 196  | rEEC def/pro         | Possible |  |  |
| Conte A,2012[29]             | Italian     | European | HB | Sequencing     | All | 7/53   | -      | -    | rEEC                 | Possible | Other definition of FALS available             |  |
| Kwon MJ,2012[30]             | Korean      | Asian    | HB | Sequencing     | All | 7/9    | 3/249  | 100  | rEEC def/pro         | Possible | Mutation in FUS, OPTN, TARDBP also screened    |  |
| Lattante S,2012[31]          | Italian     | European | HB | Sequencing     | All | 7/48   | 10/480 | -    | rEEC def/pro         | Possible | Mutation in C9orf72, FUS, TARDBP also screened |  |
| Li XG,2012[32]               | Chinese     | Asian    | HB | Sequencing     | All | 3/7    | 3/142  | -    | rEEC def/pro         | No       |  |  |
| Millecamps S,2012[33]        | French      | European | HB | Sequencing     | All | 26/225 | -      | 500  | rEEC def/pro         | Possible | SALS was deleted due to no results available   |  |
| van Blitterswijk M,2012[34]  | Netherlands | European | PB | Sequencing     | All | 1/97   | 2/451  | 1894 | rEEC                 | No       |  |  |
| Zhang HG,2012[35]            | Chinese     | Asian    | HB | Sequencing     | All | 10/43  | -      | -    | rEEC                 | No       |  |  |
| Debray S,2013[36]            | Belgium     | European | HB | Sequencing     | All | 14/62  | -      | 384  | rEEC/AC def/pro      | Probable | C9orf72 mutation screened                      |  |
| Harms MB,2013[37]            | USA         | European | HB | Sequencing     | All | 8/51   | -      | 526  | rEEC def/pro         | Probable | Mutation in C9orf72, FUS, TARDBP also screened |  |
| Kenna KP,2013[38]            | Irish       | European | PB | NGS            | All | 0/50   | 0/394  | 311  | rEEC def/pro/pos     | Possible | Mutation in C9orf72, FUS, TARDBP also screened |  |
| Liu R,2013[39]               | Chinese     | Asian    | HB | Sequencing     | All | 14/61  | -      | 100  | rEEC                 | No       | Mutation in C9orf72, FUS, TARDBP also screened |  |
| Alavi A,2014[40]             | Iranian     | Asian    | HB | Sequencing     | All | 6/17   | 2/61   | 400  | rEEC def             | Possible | C9orf72 mutation screened                      |  |
| Bertolin C,2014[41]          | Italian     | European | HB | Sequencing     | All | 3/46   | 2/307  | -    | rEEC                 | Probable | Mutation in FUS, TARDBP also screened          |  |
| Borghero G,2014[42]          | Sardinian   | European | HB | Sequencing     | All | 4/100  | 0/275  | 262  | rEEC def/pro/pos     | Possible | Mutation in C9orf72, FUS, TARDBP also screened |  |
| Liu ZJ,2014[43]              | Chinese     | Asian    | HB | NGS            | All | 3/8    | -      | 200  | rEEC                 | No       | Mutation in C9orf72, FUS, TARDBP also screened |  |

|                          |           |          |    |            |     |       |        |     |                   |          |   |
|--------------------------|-----------|----------|----|------------|-----|-------|--------|-----|-------------------|----------|---|
| Soong BW,2014[44]        | Chinese   | Asian    | HB | Sequencing | All | 8/30  | 4/131  | -   | rEEC def/pro      | Possible | Mutation in C9orf72, FUS, TARDBP also screened  |
| Cady J,2015[45]          | USA       | European | HB | NGS        | All |       | 4/349  | -   | rEEC def/pro      | No       | Mutation in C9orf72, FUS, TARDBP also screened; FALS deleted due to duplicated with Harms MB,2013 |
| Lysogorskaia EV,2015[46] | Russian   | European | HB | Sequencing | All | 4/8   | 6/199  | 149 | rEEC def/pro      | Possible | Mutation in TARDBP, C9orf72 screened  |
| Özoğuz A,2015[47]        | Turkey    | European | HB | Sequencing | All | 10/82 | 0/361  | 200 | rEEC              | No       | Mutation in C9orf72, FUS, TARDBP also screened  |
| Tarlarini C,2015[48]     | Italian   | European | HB | Sequencing | All | 5/40  | 6/500  | 150 | rEEC/AC           | No       | Mutations in FUS, TARDBP screened   |
| Vats A,2015[49]          | Indian    | Asian    | HB | Sequencing | All | 1/11  | 0/48   | 35  | rEEC              | No       | TARDBP mutations screened   |
| Vrabec K, 2015[50]       | Slovenian | European | HB | Sequencing | All | -     | 2/85   | -   | Clinical criteria | -        | Mutation in C9orf72, FUS, TARDBP also screened  |
| Kim HJ,2016[51]          | Korean    | Asian    | HB | NGS        | All | 1/4   | 0/148  | 622 | rEEC def/pro      | Possible | Mutation in FUS, TARDBP also screened   |
| Nakamura R,2016[52]      | Japanese  | Asian    | HB | NGS        | All | 14/39 | 11/469 | 190 | rEEC def/pro/pos  | Possible | Mutation in C9orf72, FUS, TARDBP also screened  |
| Zou ZY, 2016[53]         | Chinese   | Asian    | HB | Sequencing | All | 5/20  | 3/324  | 355 | rEEC def/pro      | Possible | Mutation in C9orf72, FUS, TARDBP also screened  |

#### TARDBP

|                        |                    |          |    |            |     |      |       |        |              |          |                                     |
|------------------------|--------------------|----------|----|------------|-----|------|-------|--------|--------------|----------|-------------------------------------|
| Daoud H,2008[54]       | French             | European | HB | Sequencing | All | -    | 6/285 | Ref 56 | rEEC def/pro | -        |                                     |
| Guerreiro RJ,2008[55]  | USA                | European | HB | Sequencing | All | -    | 0/279 | 979    | rEEC def/pro | -        |                                     |
| Kabashi E,2008[56]     | Canadian French    | European | HB | Sequencing | All | -    | 6/120 | 360    | rEEC def/pro | -        | FALS deleted due to enrollment bias |
| Kühnlein P,2008[57]    | German             | European | HB | Sequencing | All | -    | 0/134 | 400    | rEEC def/pro | -        | FALS deleted due to enrollment bias |
| Rutherford NJ,2008[58] | USA                | European | HB | Sequencing | All | 3/92 | 0/24  | 825    | rEEC def/pro | Possible |                                     |
| Sreedharan J,2008[59]  | Australian British | European | HB | Sequencing | All | -    | 2/372 | 1262   | rEEC def/pro | -        | FALS deleted due to enrollment bias |
| Bäumer D,2009[60]      | British            | European | HB | Sequencing | All | -    | 1/113 | -      | rEEC         | -        | FALS deleted due to enrollment bias |
| Del Bo R,2009[61]      | Italian            | European | HB | Sequencing | All | -    | 3/298 | 181    | rEEC def/pro | -        | FALS deleted due to enrollment bias |
| Gijselinc I,2009[62]   | Belgian            | European | HB | Sequencing | All | -    | 0/237 |        | rEEC def/pro | -        |                                     |
| Kamada M,2009[63]      | Japanese           | Asian    | HB | Sequencing | 6   | -    | 0/220 | 105    | rEEC def/pro | -        | FALS deleted due to enrollment bias |
| Yokoseki A,2008[64]    | Japanese           | Asian    | HB | Sequencing | All | -    | 0/112 | -      | rEEC def/pro | -        | FALS deleted due to enrollment bias |

|                              |             |          |    |            |     |       |        |        |                  |          |  |
|------------------------------|-------------|----------|----|------------|-----|-------|--------|--------|------------------|----------|--|
| Williams KL,2009[65]         | Australian  | European | HB | Sequencing | All | -     | 0/74   | Ref 55 | rEEC def/pro     | -        | FALS deleted due to enrollment bias          |
| DeJesus-Hernandez M,2010[24] | USA         | European | HB | Sequencing | 6   | 0/17  | 0/99   | 700    | rEEC             | Possible | SOD1,FUS mutations screened                  |
| Kirby J,2010[66]             | British     | European | HB | Sequencing | All | -     | 2/474  | 499    | rEEC def/pro     | -        | FALS deleted due to enrollment bias          |
| Xiong HL,2010[67]            | Chinese     | Asian    | HB | Sequencing | All | -     | 0/71   | 200    | rEEC def         | -        | FALS deleted due to enrollment bias          |
| Conforti FL,2011[68]         | Italian     | European | HB | Sequencing | 4,6 | -     | 3/298  | 150    | rEEC             | -        | FALS deleted due to enrollment bias          |
| Piaceri I,2011[69]           | Italian     | European | HB | Sequencing | All | 0/6   | 4/55   | -      | rEEC def/pro     | Possible |  |
| Ticozzi N,2011[70]           | USA         | European | HB | Sequencing | 6   | -     | 1/188  | -      | rEEC             | -        | FALS deleted due to enrollment bias          |
| Huang R,2012[71]             | Chinese     | Asian    | HB | Sequencing | All | -     | 1/165  | 400    | rEEC             | -        |  |
| Iida A,2012[72]              | Japanese    | Asian    | HB | Sequencing | All | 0/21  | 3/700  | 732    | rEEC def/pro     | No       |  |
| Mentula HK,2012[73]          | Finnish     | European | HB | Sequencing | All | -     | 0/44   | 101    | rEEC             | -        | FALS deleted due to enrollment bias          |
| Chiò A,2012[28]              | Italian     | European | PB | Sequencing | All | 2/44  | 5/429  | 196    | rEEC def/pro     | Possible |  |
| Conte A,2012[29]             | Italian     | European | HB | Sequencing | All | 1/53  | -      | -      | rEEC             | Possible | Other definition of FALS available           |
| Kwon MJ,2012[30]             | Korean      | Asian    | HB | Sequencing | All | 0/9   | 0/249  | 100    | rEEC def/pro     | Possible | Mutation in SOD1, FUS also screened          |
| Lattante S,2012[31]          | Italian     | European | HB | Sequencing | All | 1/48  | 13/480 | -      | rEEC def/pro     | Possible | Mutation in SOD1, FUS, C9orf72 also screened |
| Millegamps S,2012[33]        | French      | European | HB | Sequencing | All | 8/225 | -      | 500    | rEEC def/pro     | Possible | SALS was deleted due to no results available |
| van Blitterswijk M,2012[34]  | Netherlands | European | PB | Sequencing | All | 7/97  | 4/1192 | 1415   | rEEC             | No       |  |
| Debray S,2013[36]            | Belgium     | European | HB | Sequencing | All | 1/62  | -      | 384    | rEEC/AC def/pro  | Probable | Mutation in SOD1, FUS, C9orf72 also screened |
| Harms MB,2013[37]            | USA         | European | HB | Sequencing | All | 2/51  | -      | -      | rEEC def/pro     | Probable | Mutation in SOD1, FUS, C9orf72 also screened |
| Kenna KP,2013[38]            | Irish       | European | PB | NGS        | All | 0/50  | 2/394  | 311    | rEEC def/pro/pos | Possible | Mutation in SOD1, C9orf72, FUS also screened |
| Liu R,2013[39]               | Chinese     | Asian    | HB | Sequencing | All | 2/61  | -      | 100    | rEEC             | No       | Mutation in SOD1, FUS, C9orf72 also screened |
| Czell D,2013[74]             | Switzerland | European | HB | Sequencing | All | 4/43  | 0/182  | 225    | rEEC             | Possible |  |
| Ye CH,2013[75]               | Chinese     | Asian    | HB | Sequencing | 6   | -     | 0/207  | 230    | rEEC             | -        |  |
| Bertolin C,2014[41]          | Italian     | European | HB | Sequencing | 4,6 | 2/46  | 3/307  | -      | rEEC             | Probable | Mutation in SOD1, FUS also                   |

|                              |                  |          |    |            |           |        |        |      |                  |          |   |
|------------------------------|------------------|----------|----|------------|-----------|--------|--------|------|------------------|----------|---|
| Borghero G,2014[42]          | Sardinian        | European | HB | Sequencing | 6         | 35/100 | 63/275 | 262  | rEEC def/pro/pos | Possible | screened<br>Mutation in SOD1, FUS, C9orf72 also screened                                      |
| Liu ZJ,2014[43]              | Chinese          | Asian    | HB | NGS        | All       | 0/8    | -      | 200  | rEEC             | No       | Mutation in SOD1, C9orf72, FUS also screened  |
| Soong BW,2014[44]            | Chinese          | Asian    | HB | Sequencing | All       | 7/30   | 0/131  | -    | rEEC def/pro     | Possible | Mutation in SOD1, C9orf72, FUS also screened  |
| Cady J,2015[45]              | USA              | European | HB | NGS        | All       | -      | 2/349  | -    | rEEC def/pro     | No       | Mutation in SOD1,C9orf72,FUS also screened; FALS deleted due to duplicated with Harms MB,2013 |
| Lysogorskaia EV,2015[46]     | Russian          | European | HB | Sequencing | All       | 0/8    | 0/199  | 149  | rEEC def/pro     | Possible | Mutation in SOD1, C9orf72 screened  |
| Özoğuz A,2015[47]            | Turkey           | European | HB | Sequencing | All       | 3/82   | 0/361  | 200  | rEEC             | No       | Mutation in SOD1, C9orf72, FUS also screened  |
| Tarlarini C,2015[48]         | Italian          | European | HB | Sequencing | All       | 5/40   | 8/500  | 150  | rEEC/AC          | No       | Mutations in SOD1,FUS screened  |
| Vats A,2015[49]              | Indian           | Asian    | HB | Sequencing | All       | 0/11   | 0/38   | 35   | rEEC             | No       | SOD1 mutations screened   |
| Vrabec K, 2015[50]           | Slovenian        | European | HB | Sequencing | 6         | -      | 0/85   | -    | rEEC             | -        | Mutation in SOD1, C9orf72, FUS also screened  |
| Kim HJ,2016[51]              | Korean           | Asian    | HB | NGS        | All       | 0//4   | 0/148  | 622  | rEEC def/pro     | Possible | Mutation in SOD1, FUS also screened   |
| Nakamura R,2016[52]          | Japanese         | Asian    | HB | NGS        | All       | 1/39   | 1/469  | 190  | rEEC def/pro/pos | Possible | Mutation in SOD1, C9orf72, FUS also screened  |
| Zou ZY, 2016[53]             | Chinese          | Asian    | HB | Sequencing | All       | 0/20   | 3/324  | 355  | rEEC def/pro     | Possible | Mutation in SOD1, C9orf72, FUS also screened  |
| <b>FUS</b>                   |                  |          |    |            |           |        |        |      |                  |          |   |
| Belzil VV,2009[76]           | Canada<br>France | European | HB | Sequencing | All       | 1/80   | 3/405  | 475  | rEEC def/pro     | No       |   |
| Kwiatkowski TJ Jr,2009[77]   | USA              | European | HB | Sequencing | All       | 12/290 | 0/293  | 1446 | rEEC def/pro/pos | No       |   |
| Baumer D,2010[78]            | British          | European | HB | Sequencing | 14,15     | -      | 0/113  | -    | rEEC             | No       | FALS deleted due to enrollment bias   |
| Corrado L,2010[79]           | Italian          | European | HB | Sequencing | 5,6,14,15 | 2/52   | 6/978  | 793  | rEEC             | Possible |   |
| DeJesus-Hernandez M,2010[24] | USA              | European | HB | Sequencing | All       | 0/17   | 2/99   | 700  | rEEC             | Possible | SOD1,TARDBP mutations screened  |
| Yan J,2010[80]               | USA              | European | HB | Sequencing | All       | -      | 0/41   | 726  | rEEC             | -        | FALS deleted due to enrollment bias   |
| Belzil VV,2011[81]           | Canadian         | European | HB | Sequencing | All       | 1/154  | -      | 475  | rEEC def/pro     | No       |   |
| Belzil VV,2011[82]           | Canada<br>France | European | HB | Sequencing | All       | -      | 5/454  | 475  | rEEC def/pro     | -        |   |

|                             |             |          |    |            |           |        |        |       |                  |          |  |
|-----------------------------|-------------|----------|----|------------|-----------|--------|--------|-------|------------------|----------|--|
| Drepper C,2011[83]          | German      | European | HB | Sequencing | 14,15     | 1/41   | 1/596  | 361   | rEEC def/pro     | No       |  |
| Lai SL,2011[84]             | Italian,USA | European | HB | Sequencing | All       | -      | 4/1523 | 979   | rEEC def/pro     | -        |  |
| Syriani E[85]               | Spanish     | European | HB | Sequencing | All       | 2/30   | -      | -     | rEEC def/pro     |          |  |
| Chiò A,2012[28]             | Italian     | European | PB | Sequencing | 14,15     | 1/44   | 0/429  | 280   | rEEC def/pro     | Possible |  |
| Conte A,2012[29]            | Italian     | European | HB | Sequencing | All       | 1/53   | -      | -     | rEEC             | Possible | Other definition of FALS available   |
| Kwon MJ,2012[30]            | Korean      | Asian    | HB | Sequencing | All       | 1/9    | 4/249  | 100   | rEEC def/pro     | Possible | Mutation in SOD1, TARDBP also screened   |
| Lattante S,2012[31]         | Italian     | European | HB | Sequencing | All       | 1/48   | 3/480  | -     | rEEC def/pro     | Possible | Mutation in SOD1, TARDBP, C9orf72 also screened  |
| Millecamps S,2012[33]       | French      | European | HB | Sequencing | All       | 13/225 | -      | -     | rEEC def/pro     | Possible | SALS was deleted due to no results available   |
| van Blitterswijk M,2012[34] | Netherlands | European | PB | Sequencing | 5,6,14,15 | 5/97   | 3/1192 | 970   | rEEC             | No       |  |
| Rutherford NJ,2012[86]      | USA         | European | HB | Sequencing | 15        | 2/148  | 0/482  | 1063  | rEEC def/pro     | Possible |  |
| Debray S,2013[36]           | Belgium     | European | HB | Sequencing | All       | 2/62   | -      | 384   | rEEC/AC def/pro  | Probable | Mutation in SOD1, TARDBP, C9orf72 also screened  |
| Harms MB,2013[37]           | USA         | European | HB | Sequencing | All       | 2/51   | -      | -     | rEEC def/pro     | Probable | Mutation in SOD1, TARDBP, C9orf72 also screened  |
| Kenna KP,2013[38]           | Irish       | European | PB | NGS        | All       | 0/50   | 2/394  | 311   | rEEC def/pro/pos | Possible | Mutation in SOD1, C9orf72, TARDBP also screened  |
| Liu R,2013[39]              | Chinese     | Asian    | HB | Sequencing | All       | 3/61   | -      | 0/100 | rEEC             | No       | Mutation in SOD1, TARDBP, C9orf72 also screened  |
| Waibel S,2013[87]           | German      | European | HB | Sequencing | 5,6,13-15 | 8/184  | 0/200  | 50    | AC               | No       |  |
| Bertolin C,2014[41]         | Italian     | European | HB | Sequencing | 4-6,13-15 | 1/46   | 2/307  | -     | rEEC             | Probable | Mutation in SOD1, TARDBP also screened   |
| Borghero G,2014[42]         | Sardinian   | European | HB | Sequencing | 14,15     | 0/100  | 0/275  | 262   | rEEC def/pro/pos | Possible | Mutation in SOD1, TARDBP, C9orf72 also screened  |
| Liu ZJ,2014[43]             | Chinese     | Asian    | HB | NGS        | All       | 0/8    | -      | 200   | rEEC             | No       | Mutation in SOD1, C9orf72, TARDBP also screened  |
| Soong BW,2014[44]           | Chinese     | Asian    | HB | Sequencing | All       | 2/30   | 2/131  | -     | rEEC def/pro     | Possible | Mutation in SOD1, C9orf72, TARDBP also screened  |
| Cady J,2015[45]             | USA         | European | HB | NGS        | All       | 2/42   | 3/349  | -     | rEEC def/pro     | No       | Mutation in SOD1, C9orf72, TARDBP also screened; FALS deleted due to duplicated with Harms MB,2013 |
| Özoğuz A,2015[47]           | Turkey      | European | HB | Sequencing | 14,15     | 3/82   | 1/361  | 200   | rEEC             | No       | Mutation in SOD1, C9orf72, TARDBP also screened  |
| Tarlarini C,2015[48]        | Italian     | European | HB | Sequencing | 5,6,13-15 | 3/40   | 5/500  | 150   | rEEC/AC          | No       | Mutations in SOD1, TARDBP  |

|                              |                |                |    |            |           |         |          |        |                      |          |  |
|------------------------------|----------------|----------------|----|------------|-----------|---------|----------|--------|----------------------|----------|--|
| Vrabec K, 2015[50]           | Slovenian      | European       | HB | Sequencing | 6,14,15   | -       | 0/85     | -      | rEEC                 | -        | screened<br>Mutation in SOD1, C9orf72, TARDBP also screened            |
| Kim HJ,2016[51]              | Korean         | Asian          | HB | NGS        | All       | 0/4     | 0/148    | 622    | rEEC def/pro         | Possible | Mutation in SOD1, TARDBP also screened                                 |
| Nakamura R,2016[52]          | Japanese       | Asian          | HB | NGS        | All       | 4/39    | 2/469    | 190    | rEEC def/pro/pos     | Possible | Mutation in SOD1, C9orf72, TARDBP also screened                        |
| Zou ZY, 2016[53]             | Chinese        | Asian          | HB | Sequencing | 3-6,12-15 | 2/20    | 6/324    | 355    | rEEC def/pro         | Possible | Mutation in C9orf72, TARDBP also screened                              |
| <b>C9orf72</b>               |                |                |    |            |           |         |          |        |                      |          |  |
| Dejesus-Hernandez M,2011[88] | USA            | European       | HB | RP-PCR1    | 30        | 8/34    | 8/195    | 0/909  | rEEC def/pro/pos/sus | Possible |  |
| Byrne S,2012[89]             | Irish          | European       | PB | RP-PCR1    | 30        | 20/49   | 19/386   | 0/188  | rEEC def/pro/pos     | No       |  |
| Chiò A,2012[28]              | Italian        | European       | PB | RP-PCR2    | 30        | 24/44   | 8/429    | 0/245  | rEEC def/pro         | Possible |  |
| Conte A,2012[29]             | Italian        | European       | HB | RP-PCR2    | 30        | 10/53   | -        | -      | rEEC                 | Possible | Other definition of FALS available                                     |
| Cooper-Knock J,2012[90]      | British        | European       | HB | RP-PCR2    | 30        | 27/63   | 35/500   | 2/361  | rEEC def/pro         | Probable |  |
| Gijssels I,2012[91]          | Belgium        | European       | HB | RP-PCR     | 30        | 7/16    | 6/125    | 0/859  | rEEC def/pro         | Possible |  |
| Ishiura H,2012[92]           | Japanese       | Asian          | HB | RP-PCR1    | 30        | 2/41    | 2/237    | -      | rEEC                 | No       |  |
| Konno T,2012[93]             | Japanese       | Asian          | HB | RP-PCR     | 30        | 2/58    | 0/110    | 0/180  | rEEC def/pro         | Probable |  |
| Lattante S,2012[31]          | Italian        | European       | HB | RP-PCR2    | 30        | 9/48    | 12/480   | -      | rEEC def/pro         | Possible | Mutation in SOD1, TARDBP, FUS also screened                            |
| Majounie E,2012[94]          | European Asian | European Asian | HB | RP-PCR2    | 30        | 220/568 | 244/3622 | 1/2285 | rEEC                 | Possible | Japanese population were deleted due to duplicated with Ishiura H,2012 |
| Mok KY,2012[95]              | Greek          | European       | HB | RP-PCR2    | 30        | 5/10    | 11/136   | 0/228  | rEEC                 | No       |  |
| Ogaki K,2012[96]             | Japanese       | Asian          | HB | RP-PCR1    | 30        | 0/11    | 2/552    | 0/197  | rEEC def/pro/pos/sus | Possible |  |
| Pamphlett R,2012[97]         | Australian     | European       | HB | RP-PCR2    | 30        | -       | 2/43     | -      | rEEC                 | -        |  |
| Ratti A,2012[98]             | Italian        | European       | HB | RP-PCR1    | 30        | 62/259  | 66/1275  | 2/862  | rEEC                 | Possible |  |
| Rutherford NJ,2012[99]       | USA            | European       | HB | RP-PCR1    | 30        | 49/132  | -        | -      | rEEC def/pro         | Possible | SALS deleted due to duplicated with Harms MB,2013                      |
| Stewart H,2012[100]          | Canadian       | European       | HB | RP-PCR1    | 30        | 17/62   | 6/169    | -      | rEEC def/pro         | Probable |  |
| Millecamps S,2012[33]        | French         | European       | HB | RP-PCR1    | 50        | 104/225 | 57/725   | 0/500  | rEEC def/pro         | Possible | SALS was deleted due to no results available                           |

|                             |             |          |    |         |    |        |         |        |                     |          |   |
|-----------------------------|-------------|----------|----|---------|----|--------|---------|--------|---------------------|----------|---|
| van Blitterswijk M,2012[34] | Netherlands | European | PB | RP-PCR  | 30 | 35/97  | 87/1422 | 0/748  | rEEC                | No       |   |
| Chester C,2013[101]         | Portuguese  | European | HB | RP-PCR  | 30 | 1/9    | -       | -      | AC                  | No       |   |
| Debray S,2013[36]           | Belgium     | European | HB | RP-PCR  | 30 | 32/62  | 45/471  | 0/384  | rEEC/AC<br>def/pro  | Probable | Mutation in SOD1, TARDBP, FUS also screened   |
| Harms MB,2013[37]           | USA         | European | HB | RP-PCR1 | 30 | 22/51  | 55/797  | 2/526  | rEEC def/pro        | Probable | Mutation in SOD1, TARDBP, FUS also screened   |
| Kenna KP,2013[38]           | Irish       | European | PB | HTS     |    | 15/50  | 24/394  | 311    | rEEC<br>def/pro/pos | Possible | Mutation in SOD1, TARDBP, FUS also screened   |
| Liu R,2013[39]              | Chinese     | Asian    | HB | RP-PCR  | 30 | 0/61   | -       | 0/100  | rEEC                | No       | Mutation in SOD1, TARDBP, FUS also screened   |
| Garcia-Redondo A,2013[102]  | Spanish     | European | HB | RP-PCR2 | 30 | 42/155 | 25/781  | 0/507  | rEEC def/pro        | Probable |   |
| Jang JH,2013[103]           | Korean      | Asian    | HB | RP-PCR  | 30 | 0/8    | 0/246   |        | rEEC def/pro        | Probable |   |
| Williams KL,2013[104]       | Australian  | European | HB | RP-PCR2 | 30 | 72/187 | 21/606  | -      | rEEC def/pro        | No       |   |
| Alavi A,2014[40]            | Iranian     | Asian    | HB | RP-PCR2 | 30 | 1/17   | 1/61    | 0/10   | rEEC def            | Possible |   |
| Borghero G,2014[42]         | Sardinian   | European | HB | RP-PCR  | 30 | 39/100 | 20/275  | 0/262  | rEEC<br>def/pro/pos | Possible | Mutation in SOD1, TARDBP, FUS also screened   |
| Fogh I, 2014[105]           | British     | European | HB | RP-PCR  | 30 | -      | 43/534  | -      | rEEC                | -        | Sample of Italian and Dutch was deleted due to duplicated with van Blitterswijk M,2012 and Ratti A,2012 |
| Jiao B,2014[106]            | Chinese     | Asian    | HB | RP-PCR1 | 30 | 1/10   | 0/100   | 0/150  | rEEC                | No       |   |
| Liu ZJ,2014[43]             | Chinese     | Asian    | HB | NGS     |    | 0/8    |         | -      | rEEC                | No       | Mutation in SOD1, FUS, TARDBP also screened   |
| Soong BW,2014[44]           | Chinese     | Asian    | HB | RP-PCR  | 30 | 5/30   | 2/131   | -      | rEEC def/pro        | Possible | Mutation in SOD1, FUS, TARDBP also screened   |
| Abramycheva NY,2015[107]    | Russian     | European | HB | RP-PCR1 | 30 | 3/20   | 6/238   | 0/223  | rEEC def            | Possible |   |
| He J,2015[108]              | Chinese     | Asian    | HB | RP-PCR1 | 30 | -      | 3/1092  | 0/1062 | rEEC                | -        |   |
| Özoğuz A,2015[47]           | Turkey      | European | HB | RP-PCR2 | 30 | 15/82  | 11/361  | 200    | rEEC                | NO       | Mutation in SOD1, FUS, TARDBP also screened   |
| Vrabec K, 2015[50]          | Slovenian   | European | HB | RP-PCR  | 30 | -      | 5/85    | -      | rEEC                | -        | Mutation in SOD1, FUS, TARDBP also screened   |
| Chen Y,2016[109]            | Chinese     | Asian    | HB | RP-PCR2 | 30 | -      | 8/918   | 632    | rEEC def/pro        | -        |   |
| Murphy J,2016[110]          | USA         | European | HB |         |    | -      | 15/274  |        | rEEC<br>def/pro/pos | -        |   |
| Van Mossevelde S,2016[111]  | Belgium     | European | HB | RP-PCR  | 30 | -      | 3/147   | -      | rEEC<br>def/pro/pos | Possible |   |



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AC, Awaji criteria; EEC, El Escorial criteria; rEEC, revised El Escorial criteria; def, definite ALS; pro, probable ALS; pos, possible ALS; sus, suspect ALS; Probable FALS, ALS patient with one first or second- degree relative with ALS; Possible FALS, ALS patient with a distant relative with ALS (more distant than first or second- degree), or ALS patient with a family member with frontotemporal dementia; HB, hospital based study; PB, population based study; DHPLC, denaturing high-performance liquid chromatography; HRM, high-resolution melting; HTS, high-throughput sequencing; NGS, next-generation sequencing; SSCP, single-strand conformation polymorphism. RP-PCR1, RP-PCR2.

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