|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **No** | **Study** | **Country** | **Ethnicity** | **Disease group** | **No of cases** | **Repeat size in cases** | **No of controls** | **Repeat size in controls** | **Predominant haplotype** | **Repeat sizing method** | **Cut-off for expansion** | **Remarks** |
| 1 | Dobson-Stone et al, 2012 | Australia | Caucasian | Clinically diagnosed FTD | 89 (+3 with path data) | Mean (sd) 4.2 ± 0.2. Expansion in 10%  | 275 | Mean (sd) 4.4 ± 0.1 |  | Proband DNA: rp-PCR; Control DNA: genotyping PCR followed by rp-PCR | >30 | No difference in mean repeat length between expansion-negative FTD cases and controls (cases 4.2±0.2 vs controls 4.4±0.1 repeats). One healthy control with 38 repeats (not accurately sized) had normal MMSE score aged 89 with no family history of dementia or ALS. |
| Path-confirmed FTLD-TDP  | 22 | Expansion in 41%  |
| FTLD-Tau (PSP and CBD) | 16 | No expansions  |
| 2 | Ferrari et al, 2012 | USA | Diverse ethnicity | FTD spectrum | 53 | 4 cases had repeats in range 15-30 | 174 | 96.5% had <15 repeats | No cases had similar Finnish risk haplotype | rp-PCR | ≥30 | 5 controls had range of 15-30 repeats; 1 with 45. |
| 3 | Gomez-Tortosa et al, 2013 | Spain | Spanish | FTD spectrum | 135 | 100 cases (74%) ≤13 repeats; 4 cases with > 30; 5 cases with 20-22 repeats  | 216 | ≤14 | 5 cases with 20–22 repeats had at least one rs3849942 ‘A’ allele | rp-PCR | >30 | In 4 families, the 20- or 22-repeat alleles segregated consistently in all affected siblings; unaffected sibs had wild-type alleles (2-9 repeats); 20- or 22-repeat allele associated with surrogate marker of the founder haplotype in all cases. |
| 4 | Itcovitch et al, 2016 | Argentina | Latin American | FTD | 33 | <19 | 73  | <18 | Not studied | Fluorescent fragment lengthAnalysis; rp-PCR | Not specified  | Expansion in 6/33 FTD cases. No significant difference in allele frequencies between normal controls and FTD or ALS.  |
| 5 | Jiao et al, 2014 | China | Han Chinese | FTD (including 5 familial FTD) | 18  | Both groups combined: Mean (sd) 6.2 ± 4.8 (2-20) | 150 | Mean (sd) 6.0 ± 3.2(2-11)  | Proband from ALS-FTD family20-SNP risk haplotype | FAM fluorescent-labelled PCR then rp-PCR | Not specified | No significant difference in distributions of repeat numbers between patients and controls (p=0.23). |
| 6 | Lin et al, 2014 | Taiwan | Han Chinese  | Mixed disorders including FTD | 9 out of 482 cases had FTD | Range 2-25  | 485 | Range 2-25 | Not studied | 2-step rp-PCR  | >30, intermediate 20-29 | One young-onset typical PD case had 25 repeats, and 1 control with 21 repeats.  |
| 7 | Ogaki et al, 2013 | Japan | Japanese | FTLD (bvFTD, PPA, FTD-ALS) | 38 (2 are FTD-ALS) | For all cases, mean (sd) 3.77 ±2.56 (2-11 repeats) | None  | - | Not mentioned | rp-PCR | Not mentioned | No C9ORF72 expansion detected. Study was mainly focused on reporting MAPT and GRN mutation carriers. |
| 8 | Rutherford et al, 2012 | North American  | Not specified | FTD  | 580 | Range 1-25, with highest frequencies of 2, 5 and 8 repeats (supplementary material) | 1444 | ≤23, similar allele frequency distribution as cases | Not studied | 2-step PCR protocol | ‘Normal’ range defined as <30 repeats | Maximum repeat length within normal range was 25 in a patient and 23 in a control. No meaningful association between repeat length of normal alleles in 211 expansion carriers and disease phenotype or age at onset seen in C9ORF72 mutation carriers or non-mutation carriers. |
| FTD-ALS | 160 |
| 9 | Schottlaender et al, 2015 | UK | British | Path-confirmed CBD | 18 | 2-22 | 7579  | 11 with expanded repeats | Not mentioned | rp-PCR, followed by fragment length analysis. Southern blot for intermediate repeats. | Not specified | 1 typical PSP with 27 repeats had family history of dementia and PD. Unable to confirm segregation in this family. |
| Path-confirmed PSP | 177 |
| 10 | Simon-Sanchez et al, 2012 | Netherlands | Dutch | FTD | 363 (including 38 patients with FTD-ALS) | Mean (sd)13.9 ± 14.0 (1–64) | 522 | Mean (sd) 9.1 ± 6.8 (2–35) | Expansion carriers carried core risk haplotype | rp-PCR with fragment length analysis | >30 | Proband in an FTD-ALS family had 26 repeats; sequencing in family members revealed the expansion in an unaffected person and repeat range of 8-29 in affected persons. 1 affected individual of a family carrying the expansion had repeat length of 29. |
| 11 | Tang et al, 2016 | China | Han Chinese | FTD (bvFTD, PNFA, SD) | 52 (7 familial, 45 sporadic) | 2-13  | None | - | Not mentioned | rp-PCR | Not specified | Most frequent repeat length distribution of 2 (46.2%), 7 (19.2%), and 6 (15.4%). |
| 12 | Xi et al, 2012 | UK, Italy, Spain, North America | European and North American | FTLD | 520 | 2-30; most frequentallele: 2-, 5-, and 8-repeats, account for 75% of all alleles. | 602 | 2-30 | Not mentioned | 2-step PCR – fragment length analysis followed by rp-PCR | >30 | No intermediate or pathological number of repeats for the second allele (2-11 repeats) detected in expansion carriers. A trend toward association between the 10-repeat allele and risk for all 4 disorders (OR 1.72-2.14) seen. |
| 13 | Yeh et al, 2013 | Taiwan | Han Chinese | Sporadic FTD | 12 | Mean (sd) 4.5 ± 2.58 (1-10) | 100 | Mean (sd) 4.23 ± 3.08 (1-17) | Not studied | Fluorescent rp-PCR | Not specified |  |

Supplementary Table 1. FTD studies included. FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration; TDP = TAR DNA-binding protein; PSP = progressive supranuclear palsy; CBD = corticobasal degeneration; rp-PCR = repeat-primed polymerase chain reaction; MMSE = mini mental state examination; ALS = amyotrophic lateral sclerosis; SNP = single nucleotide polymorphism; PD = Parkinson’s disease; PPA = primary progressive aphasia; bvFTD = behavioural variant frontotemporal dementia; PNFA = progressive non-fluent aphasia; SD = semantic dementia; MAPT = microtubule associated protein tau; GRN = progranulin.