**Stichele et al.** An integrated modelling methodology for estimating global incidence and prevalence of hereditary spastic paraplegia subtypes SPG4, SPG7, SPG11, and SPG15

Supplementary Material

**Supplementary Table 1.** Key model assumptions

| | | |
|---|---|---|
| **Incidence at birth per 100k** | SPG4 | 1.24 [a] |
| | SPG11 | 0.35 [b] |
| | SPG7 | 0.34 [c] |
| | SPG15 | 0.14 [c] |
| **Modifying factor: Founder effect** | Relative incidence ratio applied to SPG4 | 10 |
| | Risk factor assigned to each country/region | 2% |
| **Modifying factor: Consanguinity** | Relative incidence ratio applied to SPG7, SPG11, and SPG15 | 10 [d] |
| | Risk factor assigned to each country/region with an Arabic population | Refer to Supplementary table 4 & 5 |
| **Age at onset** | SPG4 | 24.8 [1] |
| | SPG11 | 13.1 [1] |
| | SPG7 | 37.2 [1] |
| | SPG15 | 14.7 [1] |
| | SPG4 - Caucasian | 21.88 [1] |
| | SPG4 - Asian | 28.85 [1] |
| | SPG4 - American | 30.97 [1] |
| **Mortality hazard ratio, SPG4 & SPG7** | All ages | 1.00 |
| **Mortality hazard ratio, SPG11 & SPG15** | Age: 0 – 35 years | 1.00 |
| | Age: 40 – 44 years | 1.20 |
| | Age: 45 – 49 years | 1.40 |
| | Age: 50 – 54 years | 1.60 |
| | Age: 55 – 59 years | 1.80 |
| | Age: 60+ years | 2.00 |

[a] *Calculated using weighted average prevalence from [16] and [17]*

[b] *Calculated using prevalence from [17]*

[c] *Calculated using relative mutation frequency (SPG7 to SPG11 & SPG15 to SPG11) from [1]*

[d] *halved for Arabic immigrant populations in non-arabic countries*

**Supplementary Table 2.** Evidence overview

| Study | Country | Prevalence | | | | | | | | | Patient Distribution | | | | Age at onset | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Prevalence | | | | | | | | | Mutation frequency | | | | Age at onset | | | |
| | | Sporadic | AD | AR | Total | By age | SPG4 | SPG11 | SPG7 | SPG15 | SPG4 | SPG11 | SPG7 | SPG15 | SPG4 | SPG11 | SPG7 | SPG15 |
| Ruano 2014 | Meta-analysis | X | X | X | X | | | | | | X | X | | | | | | |
| Chrestian 2016 | Canada | | | | | | | | | | X | X | X | | X | X | X | |
| Omidvar 2019 | Meta-analysis | | | | | | | | | | X | X | X | X | X | X | X | |
| Coutinho 2013 | Portugal (national) | | X | X | X | X | X | X | | X | X | X | | | X | X | | |
| Erichsen 2009 | Norway (southeast) | X | X | X | X | X | X | X | | | X | X | | | | | | |
| Filla 1992 | Italy (molise region) | | X | X | X | | | | | | | | | | | | | |
| Boukhris 2009 | Tunisia | | X | X | X | | | | | | | | | | | | | |
| Braschinsky 2009 | Estonia (national) | | X | X | X | X | X | X | | | X | | | | | | | |
| Hirayama 1994 | Japan (National) | | | | X | | | | | | | | | | | | | |
| Leone 1995 | Italy (Valle d'aosta region) | X | X | X | X | | | | | | | | | | | | | |
| McMonagle 2002 | Ireland (North Ir. & Irish rep.) | | X | | | | | | | | | | | | | | | |
| Polo 1991 | Spain (Cantabria region) | | | | X | | | | | | | | | | | | | |
| Silva 1997 | Portugal (Viano Do castelano) | | | | X | | | | | | | | | | | | | |
| Skre 1974 | Norway (Western) | | X | | | | | | | | | | | | | | | |
| Tsuji 2008 | Japan (National) | | | | X | | | | | | | | | | | | | |
| Werderlin 1986 | Denmark (Zealand) | | | | X | | | | | | | | | | | | | |
| Sridharan 1985 | Lybia | | | | X | | | | | | | | | | | | | |
| Brignolio 1986 | Italy (Turin province) | X | X | X | X | | | | | | | | | | | | | |
| Chen 1968 | China (Guam) | | | | X | | | | | | | | | | | | | |
| Fink 2013 | - | | | | | | | | | | X | X | | | | | | |
| Ishiura 2014 | Japan | | | | | | | | | | X | X | | | | | | |
| Liao 2014 | China | | | | | | | | | | | X | | | | | | |
| Martino 2019 | - | | | | | | | | | | X | | | | X | | | |
| Orsucci 2014 | Italy (Pisa town, Pisa province and Tuscany) | | | | X | | | | | | X | X | X | | X | X | X | |
| Park 2015 | Korea | | | | | | | | | | | | | | | | | |
| Racis 2014 | Italy (North-Western Sardinia region (province of Sassari) - insular) | | X | | X | X | | | | | X | X | X | | | | | |
| Schneider 2018 | Germany | | | | | | | | | | X | | | | | | | |
| Schule 2016 | Germany and France | | | | | | | | | | X | X | X | X | X | X | X | |
| Takiyama 2014 | Japan | | | | | | | | | | X | | | | | | | |
| Balicza 2016 | Hungary | | | | | | | | | | X | X | X | | X | X | X | |
| Loureiro 2013 | Portugal | | X | | | | | | | | X | | | | X | X | | |
| Lynch 2015 | Greece | | | | | | | | | | X | | X | | X | | | |
| Parodi 2018 | France | | | | | | | | | | | | | | X | | | |
| Coarelli 2019 | Europe | | | | | | | | | | | | | | | | X | |
| Choquet 2015 | Canada (Quebec) | | | | | | | | | | | | | | | | X | |
| Carasco-Salas 2020 | Spain (Huelva) | | | | | | | | | | X | X | X | | | | | |
| Stevanin 2008 | Multi-country (mainly France) | | | | | | | | | | | | | | | X | | |
| Hellberg 2019 | Sweden | | | | X | | | | | | | | | | | | | |

**Supplementary Table 3.** Ethnic composition per UN-defined regions

| UN Region | Base-case | Asian[a] | Founder effect | Arabic |
|---|---|---|---|---|
| **Sub-Saharan Africa** | 98.0% | 0.0% | 2.0% | 0.0% |
| **Northern Africa & Western Asia** | 39.9% | 2.1% | 2.0% | 56.0% |
| **Central & Southern Asia** | 98.0% | 0.0% | 2.0% | 0.0% |
| **Eastern & South-eastern Asia** | 0.0% | 97.3% | 2.0% | 0.7% |
| **Latin America & Caribbean** | 94.0% | 0.2% | 2.0% | 3.8% |
| **Australia/New Zealand** | 89.5% | 7.5% | 2.0% | 1.0% |
| **Oceania (excl. Australia & NZ)** | 98.0% | 0.0% | 2.0% | 0.0% |
| **Europe** | 92.3% | 0.8% | 2.0% | 4.9% |
| **North America** | 94.5% | 3.5% | 2.0% | 0.1% |

[a]*Modifying factor of Asian ethnicity is maintained in table above as it remained in the model's simulation. In the base-case, it was assumed to impact with a factor of 1 (no effect). 'Arabic' refers to consanguinity factor, which was conservatively applied to the proportion of Arabic subpopulations.*

**Supplementary Table 4.** Ethnic composition per country of interest

| Country | Base-case | Asian[a] | Founder effect | Arabic |
|---|---|---|---|---|
| **Belgium** | 92.6% | 0.1% | 2.0% | 5.3% |
| **France** | 90.1% | 1.2% | 2.0% | 6.7% |
| **Germany** | 96.3% | 0.3% | 2.0% | 1.4% |
| **Italy** | 96.3% | 0.6% | 2.0% | 1.1% |
| **Denmark** | 92.5% | 0.2% | 2.0% | 5.3% |
| **UK** | 96.8% | 0.8% | 2.0% | 0.4% |
| **US** | 95.9% | 2.0% | 2.0% | 0.1% |
| **Canada** | 93.0% | 5.0% | 2.0% | 0.0% |
| **Japan** | 0.0% | 98.0% | 2.0% | 0.0% |

**Supplementary Table 5.** HSP prevalence study details

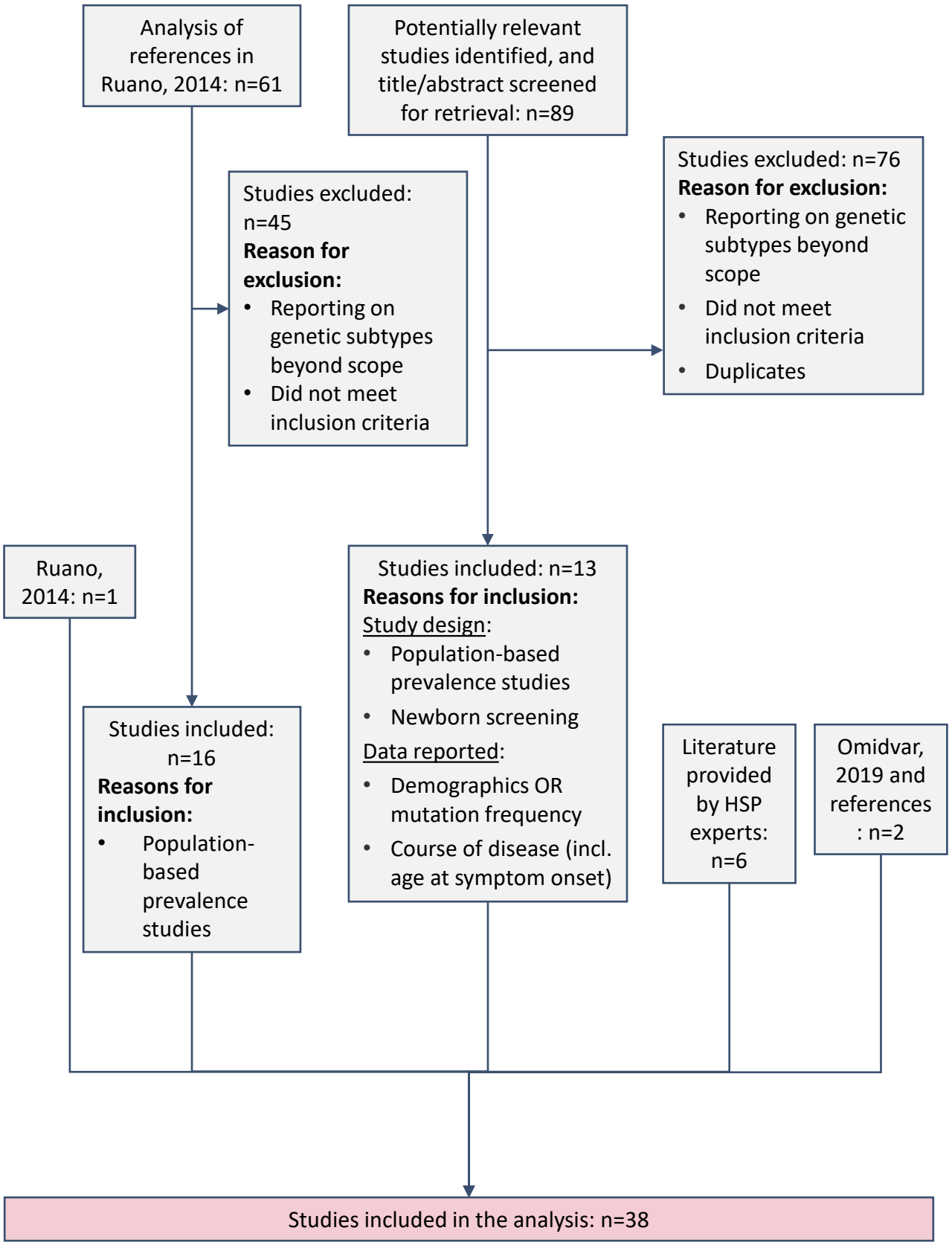
| Study | Country (Region) | Population | # Cases | Source of Data | Period Studied | Captured in Ruano, 2014 SLR |
|---|---|---|---|---|---|---|
| Sridharan, 1985 | Lybia | 519,000 | 11 | Multi | 1982-1984 | Yes |
| Brignolio, 1986 | Italy (Turin province) | 2,327,996 | 31 | Multi | 1945-1982 | Yes |
| Polo, 1991 | Spain (Cantabria region) | 510,000 | 49 | Hospitals + families | 1974-1986 | Yes |
| Filla, 1992 | Italy (Molise region) | 335,211 | 9 | Multi | 1979-1990 | Yes |
| Hirayama, 1994 | Japan (National) | 123000000 | 109 | Hospitals | - | Yes |
| Leone, 1995 | Italy (Valle d'aosta region) | 115,270 | 5 | Multi | 1981-1991 | Yes |
| McMonagle 2002 | Ireland (North Ir. & Irish rep.) | 5,436,000 | 69 | Hospitals + families | 2000 | Yes |
| Tsuji, 2008 | Japan (National) | 126,900,000 | 1103 | Registry | 2001-2002 | Yes |
| Braschinsky, 2009 | Estonia (National) | 1,340,000 | 59 | Multi | 2004 | Yes |
| Boukhris, 2009 | Tunisia | 869,700 | 50 | Hospitals | 1990-2007 | Yes |
| Erichsen, 2009 | Norway (Southeast) | 2,633,893 | 194 | Multi | 1996-2007 | Yes |
| Coutinho, 2013 | Portugal (National) | 10,322,000 | 418 | Multi | 1994-2004 | Yes |
| Silva 1997 | Portugal (Viano Do castelano) | 250,061 | 5 | Multi | 1994 | No |
| Chen, 1968 | China (Guam) | 37,975 | 7 | 1 Hospital | 1960-1966 | No |
| Skre, 1974 | Norway (Western) | 725,000 | 31 | 1 Hospital | 1960-1968 | No |
| Werderlin, 1986 | Denmark (Zealand) | 1,179,000 | 23 | Hospitals | 1961-1975 | No |
| Racis, 2014 | Italy (North-Western Sardinia region (province of Sassari) - insular) | 333,576 | 67 | Multi | 2000-2010 | No |
| Orsucci, 2014 | Italy (Pisa Town, Pisa province and Tuscany) | 1,311,953-20,173,732 | 45 | 1 Hospital | 2011-2012 | No |
| Loureiro, 2013 | Portugal | 9,958,333 | 239 | Population-based systematic survey | 1993-2004 | No |
| Hellberg 2019 | Sweden (national) | 9,640,000 | 235 | Registry | 2009-2013 | No |

*Multi: overlapping strategies*

*Families: systematic investigation of families of patients identified via previous sources*

**Supplementary Table 6.** Mean age at onset (Years)

| Reference | Region | Population | Number of cases | Not gene-specific | SPG4 | SPG11 | SPG7 | SPG15 |
|---|---|---|---|---|---|---|---|---|
| **Choquet, 2016** | Canada (Quebec) | N/A | N/A | N/A | N/A | N/A | 34.2 | N/A |
| **Chrestian, 2016** | Canada | 526 | 150 | N/A | 24.6 | 13.0 | 33.0 | N/A |
| **Coutinho, 2013** | Portugal | 10,322,000 | 418 | N/A | 33.0 | 14.0 | N/A | N/A |
| **Hellberg, 2019** | Sweden | 9,640,000 | 235 | | | | | |
| **Omdivar, 2019** | Global (Meta-analysis) | N/A | 13,570 | N/A | 24.8 | 13.1 | 37.2 | 14.7 |
| **Omdivar, 2019** | Caucasian (Meta-analysis) | N/A | N/A | N/A | 21.9 | 13.1 | N/A | N/A |
| **Omdivar, 2019** | Asian (Meta-analysis) | N/A | N/A | N/A | 28.9 | 12.8 | N/A | N/A |
| **Omdivar, 2019** | American (Meta-analysis) | N/A | N/A | N/A | 31.0 | 12.8 | N/A | N/A |
| **Racis, 2014** | Italy (Sardinian) | 333,576 | 67 | 36.6 | N/A | N/A | N/A | N/A |
| **Orsucci, 2014** | Italy (Pisa town, Pisa Province and Tuscany) | 1,311,953-20,173,732 | 45 | 37.4 | 38.7 | 26.0 | 39.0 | N/A |
| **Martino, 2019** | Italy | 41 | 21 | N/A | 28.4 | N/A | N/A | N/A |
| **Lynch, 2015** | Greece | 40 families | 54 | N/A | 27.5 | N/A | N/A | N/A |
| **Loureiro, 2013** | Portugal | 9,958,333 | 239 | 29.9 | 31.7 | N/A | N/A | N/A |
| **Ishiura, 2014** | Japan | N/A | 129 | 30.0 | N/A | N/A | N/A | N/A |
| **Schule, 2016** | Germany | 519 families | 608 | 30.8 | 35.0 | 17.0 | 9.0 | N/A |
| **Balicza, 2016** | Hungary | 58 | 19 | 28.6 | 21.0 | 13.0 | 37.6 | N/A |
| **Parodi, 2018** | France | N/A | 842 | N/A | 29.3 | N/A | N/A | N/A |
| **Coarelli, 2019** | Europe | N/A | 241 | N/A | N/A | N/A | 35.5 | N/A |
| **Stevanin, 2008** | Global | N/A | 76 | N/A | N/A | 14.0 | N/A | N/A |




**Supplementary Figure 1**