**Supplementary Information: Identifying schizophrenia patients who carry pathogenic genetic copy number variants- the importance of the neurodevelopmental history.**

Supplementary table 1. Proportions of missing data in the Irish cohort for the phenotypes included in the analysis (discovery dataset).

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **N (Total)** | **N (Data available)** | **% Complete** |
| Early age of onset of symptoms | 1215 | 1199 | 98.7 |
| History of learning difficulties | 1215 | 1195 | 98.4 |
| History of specific learning disorder | 1215 | 1192 | 98.1 |
| History of school supports | 1215 | 1195 | 98.4 |
| Primary school attainment only | 1215 | 1204 | 99.1 |
| History of developmental delay | 1215 | 1162 | 95.6 |
| Comorbid neurodevelopmental diagnosis | 1215 | 1195 | 98.4 |
| Family history of neurodevelopmental disorder | 1215 | 1087 | 89.5 |
|  | | | |

Supplementary table 2. Proportions of missing data in the Cardiff cohort for the phenotypes included in the analysis (replication dataset).

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **N (Total)** | **N (Data available)** | **% Complete** |
| History of developmental delay | 479 | 337 | 70.4 |
| Comorbid neurodevelopmental diagnosis | 479 | 417 | 87.1 |
|  |  |  |  |

Supplementary table 3. Schizophrenia-associated risk CNVs.

|  |  |
| --- | --- |
| **Locus** | **Position in Mb** |
| 1q21.1 del | chr1:146,57-147,39 |
| 1q21.1 dup | chr1:146,57-147,39 |
| NRXN1 del | chr2:50,15-51,26 |
| 3q29 del | chr3:195,73-197,34 |
| WBS dup | chr7:72,74-74,14 |
| VIPR2 dup | chr7:158,82-158,94 |
| 15q11.2 del | chr15:22,80-23,09 |
| AS/PWS dup | chr15:24,82-28,43 |
| 15q13.3 del | chr15:31,13-32,48 |
| 16p13.11 dup | chr16:15,51-16,30 |
| 16p11.2 distal del | chr16:28,82-29,05 |
| 16p11.2 dup | chr16:29,64-30,20 |
| 17p12 del | chr17:14,16-15,43 |
| 17q12 del | chr17:34,81-36,20 |
| 22q11.2 del | chr22:19,02-20,26 |
| Note: Copy number variant loci listed in Rees et al. (1) with previous evidence for associations with schizophrenia. Copy number variation positions are in UCSC Build 37. Del, deletion; dup, duplication; WBS, Williams-Beuren Syndrome; AS/PWS, Angelman/Prader-Willi syndrome. | |

Supplementary table 4. Copy number variants identified in individuals in discovery dataset.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Case** | **Locus** | **CNV** | **Chr** | **Position in Mb** | |
|  | | | | **Start** | **Stop** |
| Case 1 | 1q21.1 | Del | 1 | 145932468 | 147831184 |
| Case 2 | 1q21.1 | Del | 1 | 146330584 | 147825662 |
| Case 3 | 1q21.1 | Del | 1 | 146717564 | 146970946 |
| Case 4 | NRXN1 | Del | 2 | 50870373 | 50971478 |
| Case 5 | 15q11.2 | Del | 15 | 22751094 | 23487547 |
| Case 6 | 15q11.2 | Del | 15 | 22770994 | 23236972 |
| Case 7 | 15q11.2 | Del | 15 | 22770994 | 23236972 |
| Case 8 | 15q13.3 | Del | 15 | 30755047 | 32489254 |
| Case 9 | 17p12 | Del | 17 | 14098277 | 15475088 |
| Case 10 | WBS | Dup | 7 | 72732833 | 74142105 |
| Case 11 | AS/PWS | Dup | 15 | 24727231 | 25107593 |
| Case 12 | 16p13.11 | Dup | 16 | 14929751 | 16396513 |
| Case 13 | 16p13.11 | Dup | 16 | 15481934 | 18314234 |
| Case 14 | 16p13.11 | Dup | 16 | 15481934 | 17296550 |
| Case 15 | 16p13.11 | Dup | 16 | 15481934 | 16340441 |
| Case 16 | 16p11.2 | Dup | 16 | 29517711 | 30177808 |
| Case 17 | 16p11.2 | Dup | 16 | 29517711 | 30306969 |
| Case 18 | 16p11.2 | Dup | 16 | 29580034 | 30191908 |
| Case 19 | 16p11.2 | Dup | 16 | 29595483 | 30017620 |
| Note: Copy number variation positions are in UCSC Build 37. Del, deletion; dup, duplication; WBS, Williams-Beuren Syndrome; AS/PWS, Angelman/Prader-Willi syndrome. | | | | | |

**Supplementary table 5. Proportion of individuals with positive history of phenotypic variables**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Discovery Sample** | | | **Replication Sample** | | |
| **Phenotypic Variable**  **(References)** | CNV  (n = 19) | No CNV  (n = 1196) | Total  (n = 1215) | CNV  (n = 8) | No CNV  (n = 471) | Total  (n = 479) |
| Early onset of symptoms  (2, 3) | 6 (31.6%) | 270 (22.6%) | 276 (22.7%) | - | - | - |
| History of learning difficulties  (4-6) | 8 (42.1%) | 181 (15.1%) | 189 (15.6%) | - | - | - |
| Specific learning disorder  (4-6) | 2 (10.5%) | 15 (1.3%) | 17 (1.4%) | - | - | - |
| Remedial school support  (4-6) | 1 (5.3%) | 36 (3.0%) | 37 (3.0%) | - | - | - |
| Low educational attainment  (4-6) | 4 (21.1%) | 150 (12.5%) | 154 (12.7%) | - | - | - |
| History of developmental delay  (7-9) | 5 (26.3%) | 77 (6.4%) | 82 (6.7%) | 3 (37.5%) | 92 (19.5%) | 95 (19.8%) |
| Comorbid neurodevelopmental diagnosis  (7-9) | 3 (15.8%) | 43 (3.6%) | 46 (3.8%) | 4 (50.0%) | 40 (8.5%) | 44 (9.2%) |
| Family history of Neurodevelopmental disorder  (10, 11) | 5 (26.3%) | 343 (28.7%) | 348 (28.6%) | - | - | - |
| Note: Proportions of individuals with positive history of phenotypic variables and SCZ-associated pathogenic CNV status. | | | | | | |

Supplementary table 6. Multiple logistic regression model using two phenotypic variables to model SCZ-associated CNV carrier status in Irish data set.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **β** | **SE** | **Wald statistic (Z)** | **P** | **OR (95% CI)** |
| Comorbid neurodevelopmental disorder | 1.76 | 0.67 | 2.63 | 0.009 | 5.81 (1.28-19.29) |
| History of developmental delay | 1.72 | 0.55 | 3.13 | 0.002 | 5.60 (1.73-15.74) |
| Note: Predictor coefficients were tested using Wald tests and confidence intervals obtained using the Wald method. Nagelkerke pseudo R Square = 0.172). | | | | | |

Supplementary table 7. ROC curve results for modelling SCZ-associated CNV status using two phenotypic variables in the Irish dataset.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Cutoff Value** | **Sensitivity (%)**  **(95% CI)** | **Specificity (%)**  **(95% CI)** | **AUC (%)**  **(95% CI)** | **PPV (%)**  **(95% CI)** | **NPV (%)**  **(95% CI)** |
| 0.05 | 47.1 (23.0-72.2) | 90.1 (88.3-91.8) | 68.6 (56.3-80.9) | 6.7 (5.5-17.3) | 99.1 (97.4-99.3) |
| Note: Optimal Cutoff Value, Sensitivity, Specificity, Area Under The Curve, and Predictive Values using two independent variables (“History of developmental delay”, “Comorbid neurodevelopmental disorder”) to model for SCZ-associated CNV status in Irish cohort (discovery dataset).CI, confidence interval; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value | | | | | |

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