**Supporting information**

**Table S1.** **The** **primers used for cDNA amplification of** **CHIP.**

|  |  |
| --- | --- |
| wide-type or mutant CHIP | primers |
| W1: wide-type | F: atgaagggcaaggaggagaa |
| W2: wide-type | R: agggcagggaacctcagtag |
| M1: L165F | F: cctacttctccaggctcatt |
| M2: L165F | R: agtgcagctcgctct |
| M3: N130A- F | F: cggctgatcttcggggacgacat |
| M4: N130A-R | R: ctgctccttggccaggctgta |
| M5: W147C-F | F: aagcgctgtaacagcatt |
| M6: W147C-R | R: cttcttcgcgattcgaag |
| M7: Y207-F | F: aagtagatggcggacatggac |
| M8: Y207-R | R: gtcgtgcttggcctcaat |
| M9: S236T-F | F: acctttgagctgatgcgggag |
| M10: S236T-R | R: gatcttgccacacaggta |

**Table S2.** **The latest clinical features** **in the affected members of the three families (updated in Aug. 2013).**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Family 1 | | | | Family 2 | Family 3 |
|  | II:1 | II:2 | II:3 | II:5 | II:1 | II:1 |
| Gender | F | F | F | M | M | F |
| Age (yr) | 44 | 41 | 39 | 36 | 25 | 27 |
| Disease onset (yr) | 17 | 17 | 14 | 19 | 20 | 16 |
| Walking ability | w | U | U | U | I | U |
| Cognitive defect | + | + | + | + | - | - |
| Truncal/limb ataxia | +++/+++ | ++/++ | ++/++ | ++/++ | ±/+ | ++/+++ |
| Nystagmus | - | ++ | ++ | ++ | - | - |
| Saccade slowing | - | - | - | - | - | - |
| Ophthalmoplegia | +++ | - | + | - | - | - |
| Dysarthria | +++ | ++ | ++ | +++ | ± | + |
| Extrapyramidal signs | - | - | - | - | - | - |
| Position sense | D | D | D | D | N | N |
| Tendon reflex | N | ↑ | ↑ | ↑ | N | ↑ |
| Ankle tone | - | - | - | - | - | ± |
| Plantar responses | - | + | - | + | - | + |
| ICARS | 80 | 61 | 72 | 57 | 26 | 36 |
| SARA  MMSE | 35  6 | 21  18 | 24  10 | 20  29 | 8  29 | 15  29 |
| WAIS-RC | not done | 53 | 33 | 82 | not done | not done |
| ADL | 25 | 30 | 40 | 30 | 95 | 85 |
| Cerebellar atrophy on MRI | not done | severe | severe | severe | severe | severe |

Clinical signs are graded as follows: - = absent or subtle; + = mild; + + = moderate; + + + = severe; w = wheelchair; u = unilateral support; I =independent; N = normal; D = defect; WAIS-RC = Wechsler Adult Intelligence Scale (the Revised Chinese version); ADL = Activities of Daily Living scale. The cognitive abilities of these patients were evaluated by at least one cognitive scale, including the Mini-Mental State Examination (MMSE) ([Folstein *et al.*, 1975](#_ENREF_1)) and the Chinese Revised Wechsler Adult Intelligence Scale (WAIS-RC) (Gong YX. 1992).

**Table S3.** **Intelligence test scores of three patients from family 1 by** **the WAIS-RC.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Family 1** | **FSIQ** | **PIQ** | **VIQ** |
| **Patient II:2** | **53** | **49** | **62** |
| **Patient II:3** | **33** | **37** | **37** |
| **Patient II:5** | **82** | **74** | **92** |

Global cognitive functioning (Full Scale IQ) was assessed using the Chinese Revised Wechsler Abbreviated Scale of Intelligence

(WASI-RC) for both verbal (Verbal IQ [VIQ]) and nonverbal ability (or Performance IQ [PIQ]) (Gong XY. 1992; Wechsler, 1999).

**Table S4. Electrodiagnostic studies performed on three patients of Family 1.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | | | | **Family 1** | | | | |  | | | |
|  | **II:2** | | | | **II:3** | | | | | **II:5** | | | |
| **Nerve Conduction study** | Right/ Left | | | | Right/ Left | | | | | Right/ Left | | | |
| Motor nerve conduction | **median** | **ulnar** | **tibial** | **sural** | **median** | **ulnar** | **tibial** | | **sural** | **median** | **ulnar** | **tibial** | **sural** |
| Lantency (ms) | N/ N | N/ N | N/ N | N/ N | P/ N | N/ N | N/ N | | N/ N | N/ N | N/ N | P/ P | P/ P |
| Amplitude (mV) | N/ N | N/ N | Low/ Low | N/ N | Low/N | N/ N | N/ N | | N/ N | N/ N | N/ Low | N/ N | Low/N |
| NCV (m/s) | Slow/ N | N/ N | N/ N | N/ N | N/ N | N/ N | Slow/ Slow | | N/ N | N/ N | N/ Slow | Slow/ Slow | Slow/ N |
| Sensory nerve conduction | **median** | **ulnar** | **tibial** | **sural** | **median** | **ulnar** | **tibial** | | **sural** | **median** | **ulnar** | **tibial** | **sural** |
| Lantency (ms) | N/ N | N/ N | N/ N | N/ N | N/ Slow | N/ N | N/ N | | N/ N | N/ N | N/ N | N/ N | N/ N |
| Amplitude (uV) | N/ N | N/ N | N/ N | N/ N | Low/ N | Low/ Low | N/ N | | N/ N | N/ N | Low/ Low | low | Low/ Low |
| NCV (m/s) | Slow/ N | N/ N | N/ N | N/ N | N/ Low | N/ N | N/ N | | N/ N | N/ N | N/ N | Slow | N/ N |
| F-wave  Latency (ms)  Occurrence | Right  N  Ankle: 18% | | Left  N  Ankle: 100% | | Right  N  Wrist: 13% | | Left  N  Ankle: 100% | | | Right  N  Ankle: 100% | | Left  N  Ankle: 100% | |
| **Electromography** | N | | N | | N | | N | | | N | | N | |
| **Visual Evoked Response** | **Right** | | **Left** | | **Right** | | **Left** | | | **Right** | | **Left** | |
| Latency of P100 in visual half field | prolonged | | normal | | normal | | prolonged | | | normal | | normal | |
| Amplitude of P100 in visual half field | Low | | Low | | Low | | Low | | | Low | | Low | |
| Latency of P100 in visual whole field | prolonged | | normal | | prolonged | | nromal | | | normal | | normal | |
| Amplitude of P100 in visual whole field | Low | | Low | | Low | | Low | | | Low | | Low | |
| **Auditory Evoked Potential** | **Right** | | **Left** | | **Right** | | **Left** | | | **Right** | | **Left** | |
| Latencies (I, III and V) | prolonged | | normal | | normal | | normal | | | normal | | prolonged | |
| Amplitude (I, III and V) | Low | | Low | | Low | | Low | | | Low | | Low | |
| Peak interval of I-III | normal | | normal | | normal | | normal | | | normal | | prolonged | |
| Peak interval of III-V | normal | | normal | | normal | | normal | | | normal | | normal | |
| **Somatosensory Evoked Potential** | **Right** | | **Left** | | **Right** | | **Left** | | | **Right** | | **Left** | |
| median nerve |  | | | | | | | | | | | | |
| P15, N20, P25, N35, N20-N13, N20-N9 | disappeared | | disappeared | | disappeared | | disappeared | | | disappeared | | disappeared | |
| N13, N9 and N13-N9 | N | | N | | N | | N | | | N | | N | |
| tibial nerve |  | | | | | | | | | | | | |
| P40, N45, P40-LP, P40-PF | disappeared | | disappeared | | disappeared | | | disappeared | | disappeared | | disappeared | |
| LP, PF and LP-PF | N | | N | | N | | | N | | N | | N | |

**Note:** ‘N’ means normal; ‘P’ means prolonged.

**Table S****5.** **Summary of original Exome sequencing data.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Sample | Bases (MB) | Map Bases  (MB) | Map Bases  Rate (%) | Exon Map Bases  (MB) | Exon Map  Bases Rate (%) | Exon  Length  (MB) | Covered  Length  (MB) | Coverage (%) | Mean  Depth | Mode  Depth |
| II2 | 5782.88 | 4918.17 | 85.05 | 2376.96 | 48.33 | 37.62 | 36.78 | 97.66 | 55.76 | 38.45 |
| II3 | 6137.07 | 4851.29 | 79.05 | 2234.19 | 46.05 | 37.62 | 36.71 | 97.58 | 54.44 | 40.63 |
| Mean | 5959.98 | 4884.73 | 82.05 | 2305.58 | 47.19 | 37.62 | 36.75 | 97.62 | 55.10 | 39.54 |

**Table S6.** **Multi-point LOD scores between the disease locus and SNP polymorphism markers in Family 1.**

|  |  |  |  |
| --- | --- | --- | --- |
| Locus | Marker | Position from Peter(cM) | LOD |
| 16p13.3 | rs11248850 | 1.14 | 1.917 |
| 16p13.3 | rs8051485 | 1.30 | 1.917 |
| 16p13.3 | rs3752496 | 2.53 | 1.917 |
| 16p13.3 | rs12448639 | 2.78 | 1.917 |
| 16p13.3 | rs556179 | 3.04 | 1.917 |
| 16p13.3 | rs4984707 | 3.20 | 1.917 |
| 16p13.3 | rs4984727 | 3.34 | 1.917 |
| 16p13.3 | rs11248851 | 3.67 | 1.917 |
| 16p13.3 | rs1033466 | 4.88 | 1.917 |
| 16p13.3 | rs2437732 | 5.77 | 1.917 |
| 16p13.3 | rs2252523 | 6.26 | 1.917 |
| 16p13.3 | rs8057913 | 6.47 | 1.917 |
| 16p13.3 | rs26866 | 7.00 | 1.917 |
| 16p13.3 | rs26845 | 7.13 | 1.917 |
| 16p13.3 | rs4785919 | 8.74 | 1.917 |
| 16p13.3 | rs7194018 | 8.76 | 1.917 |
| 16p13.3 | rs6501170 | 9.63 | 1.917 |
| 16p13.3 | rs1218762 | 9.69 | -3.343 |

LOD＝logarithm of odds. LOD scores were calculated under an autosomal recessive mode of inheritance.

**Table S7.** **Prediction of the functional effects of mutantion in *CHIP.***

|  |  |  |  |
| --- | --- | --- | --- |
| Mutation in *CHIP* | Mutation taster | SIFT | polyphen-2 |
| c. 389 A>T (N130I) | disease causing | probably damaging | probably damaging |
| c. 441 G>T (W147C) | disease causing | probably damaging | probably damaging |
| c. 493 C>T (L165F) | disease causing | probably damaging | probably damaging |
| c. 621 C>G (Y207X) | disease causing | probably damaging | probably damaging |
| c. 4707 G>C (S236T) | disease causing | probably damaging | probably damaging |

Note: Mutation taster (www.mutationtaster.org/‎), SIFT (sift.jcvi.org/) and polyphen-2 (genetics.bwh.harvard.edu/pph2/‎).

Reference

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98.

Gong Y X. Manual of Wechsler Adult Intelligence Scale-Chinese version. Changsha: Chinese Map Press. 1992