The Largest Caucasian Kindred With Dentatorubral-Pallidoluysian Atrophy: A Founder Mutation in Italy

Silvia Grimaldi, MD,[1*] Chiara Cupidi, MD,[2] Nicoletta Smirne, BS,[2] Livia Bernardi, PhD,[2] Fabio Giacalone, MD,[1] Giuseppina Piccione, PsyD,[1] Salvatore Basiricò, DPT,[1] Giuseppe Donato Mangano, MD,[3] Rosaria Nardello, MD,[3] Laura Orsi, MD,[4] Enrico Grosso, PhD,[5] Valentina Laganà, PsyD,[2] Micaela Mitolo, PsyD,[6] Raffaele Giovanni Maletta, MD,[2] and Amalia Cecilia Bruni, MD[2]

[1]*Consorzio Siciliano di Riabilitazione - Associazione Italiana Assistenza Spastici (CSR-AIAS), Paceco, Trapani, Italy* [2]*Regional Neurogenetic Center (CRN), ASP Catanzaro, Lamezia Terme, Italy* [3]*Child Neuropsychiatry Unit, Department of Sciences for Health Promotion and Mother and Child Care "G. D'Alessandro," University of Palermo, Palermo, Italy* [4]*Neurology 1, Città della Salute e della Scienza University Hospital, Turin, Italy* [5]*Medical Genetics Unit, Città della Salute e della Scienza University Hospital, Turin, Italy* [6]*IRCCS Istituto delle Scienze Neurologiche di Bologna, Diagnostica Funzionale Neuroradiologica, Bologna, Italy*

ABSTRACT

Background: Dentatorubral-pallidoluysian atrophy is a hereditary neurodegenerative disease prevalently reported in Japan but rare in Caucasians. The objective of this study was to reconstruct the pedigree of Italian dentatorubral-pallidoluysian atrophy familial cases describing their clinical features.

Methods: We investigated 6 apparently unrelated dentatorubral-pallidoluysian atrophy families comprising a total of 51 affected individuals: 13 patients were clinically examined, and for 38 patients clinical data were collected from clinical sources. The dentatorubral-pallidoluysian atrophy diagnosis was genetically confirmed in 18 patients. Genealogical data from historical archives were analyzed.

Results: All 6 families were unified in a large pedigree deriving from a founder couple originating from Monte San Giuliano (Italy) in the late 1500s, with 51 affected subjects over the last 4 generations. Wide phenotypical variability in age at onset and clinical features was confirmed. Epilepsy was more frequent in juvenile cases than in late adults, with cognitive/psychiatric and motor disorders observed regardless of age at onset.

Conclusions: We have described the largest Caucasian dentatorubral-pallidoluysian atrophy pedigree from a single founder couple. The introduction of the dentatorubral-pallidoluysian atrophy gene in Italy could have arisen as a result of trade relationships between the Spanish or Portuguese and the Japanese in the 1500s. © 2019 International Parkinson and Movement Disorder Society

Key Words: *ATN1* gene; cerebellar cognitive-affective syndrome; dentatorubral-pallidoluysian atrophy; founder effect; genealogical method

Dentatorubral-pallidoluysian atrophy (DRPLA) is an autosomal-dominant neurodegenerative disease caused by the pathological expansion of the CAG triplet (>48 repeats) in the atrophin1 gene (*ATN1*).[1] Onset varies from infancy to adulthood, with few cases having onset older than 60 years of age,[2-6] and the disease exhibits wide clinical heterogeneity.[1] Four clinical syndromes have been described: epileptic, ataxic, choreoathetosic, and psychiatric (including cognitive decline). Myoclonic epilepsy is common in juvenile forms, whereas psychiatric and cognitive symptoms are prevalent in adults.[2] Individuals carrying small pathogenic expansions (49 to 55 CAG repeats) may exhibit mild cerebellar or behavioral symptoms at advanced ages,[7] mimicking other neurodegenerative diseases and making the disease underrated.

DRPLA is rare, and its worldwide prevalence is strongly related to ethnic background. The prevalence is greater in Japan (0.48:100,000 subjects),[8] and only 25 DRPLA families have been reported in the Caucasians population to date.[2-5,9-18]

The higher prevalence in Japan is associated with the presence of so-called normal expanded alleles in the Japanese population.[19] Normal expanded alleles are unstable alleles, having number of CAG repeats >17, at risk of expansion in pathological alleles during intergenerational transmission.[19]

*Correspondence to: Dr. Sivia Grimaldi, Consorzio Siciliano di Riabilitazione – Associazione Italiana Assistenza Spastici (CSR-AIAS), Via Campo Sportivo 5, 91027 Paceco (TP), Italy; silvgrim@libero.it

Silvia Grimaldi and Chiara Cupidi contributed equally to this work.

Relevant conflicts of interest/financial disclosures: All the authors disclose no conflicts of interest relevant to the article.

Funding agencies: The study was not sponsored by industries. This study was supported by current institutional resources.

Received: 3 May 2019; **Revised:** 1 August 2019; **Accepted:** 25 August 2019

Published online 00 Month 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27879

In Italy, all the described cases of familial DRPLA originated from western Sicily[20-22] except for one,[23] suggesting a single founder effect in the territory of Trapani.[22] However, affected Italian subjects have never been traced back to a single pedigree. This study aimed to reconstruct the pedigree of Italian DRPLA familial cases, describing the clinical features of the affected members and narrowing the date of the founder effect.

Materials and Methods

The study was carried out on 6 unrelated families affected by DRPLA, starting from the probands. All subjects were Caucasians and originated from western Sicily (Italy): 5 families originated from the territory of Trapani and 1 from Palermo. The study was performed in the hometowns of the probands and in the villages in which the affected branches lived, covering a geographical area of 7452 km^2.

Living relatives suspected of DRPLA were identified by clinical assessment. Patients were subjected to clinical examination, evaluation of cognitive, psychiatric, and behavioral symptoms (Mini Mental Status Examination [MMSE],[24] Mental Deterioration Battery,[25] Neuropsychiatric Inventory[26]), and brain CT or MRI.

Clinical data regarding suspected affected subjects who were dead or unavailable were obtained from interviews of relatives, from medical histories, from published clinical reports,[21] and from clinical records of the Psychiatric Hospital of Trapani.

Age at onset was defined as the age at which the first clinical symptoms were reported and could be identified for 21 patients. For another 16 patients, the age period in which onset occurred was inferred from available data. Patients were classified into 4 different groups according to age in period of onset: infantile (<36 months), juvenile (<20 years old), early adult (>20 years old), and late adult (>40 years old).

Genetic diagnosis was known in 8 subjects. In another 10 patients, genetic analysis of the trinucleotide repeat region in the *ATN1* gene was performed using genomic leukocyte DNA.[27]

Family trees were reconstructed through a systematic search of genealogical data from 11 municipal archives, 5 parish registers, 3 libraries, and 4 cemeteries, following the same methodology applied for genetic dementia[28,29] (Supplementary Fig. 1).

Records concerning birth, baptism, marriage, and death of relatives and ancestors of probands were examined. Individuals were linked to the pedigree through the transitive set of relationships (parent, offspring, spouse). To avoid biases, we followed both apparently unaffected and affected branches, as well as maternal or paternal ancestry or descent.

The collected data served as a database to identify links between families and the common ancestor.

Moreover, historical sources about the territory of Trapani in the 16th century were consulted.

Statistical analysis was performed on clinical and genetic data (Student t test, chi-square test, Pearson's and Spearman's correlations) using SPSS V21.0 statistical software (SPSS Inc., Chicago, IL). Ataxia, chorea, epilepsy, intellectual disability, cognitive decline or dementia, and psychiatric and behavioral disturbances were evaluated as clinical variables. Statistical significance was given by $P < 0.05$.

All living subjects or their legal representatives provided informed written consent for participation in the study. The study was approved by the local ethical committee and was performed in accordance with the Declaration of Helsinki.

Results

A genealogical link was established between all the affected subjects of the 6 investigated DRPLA families. A unique pedigree including approximately 7000 individuals from both affected and unaffected lineages was reconstructed over 16 generations, with a high rate of consanguinity (Fig. 1). A single couple considered the lone ancestors was identified living in the 1500s in Monte San Giuliano (now known as Erice), an ancient town belonging to the territory of Trapani. The branch from Palermo was linked to the Monte San Giuliano pedigree in 1819. We identified 51 affected subjects over 4 consecutive generations by personal examination (13 subjects), clinical records (3 subjects), medical history and interviews of relatives (26 subjects), or previous published reports (9 subjects). A dominant pattern of inheritance was proven, and the calculated segregation ratio was 0.59.

The mean age at onset was 31.4 ± 17.5 years (6–70 years), and mean age of death was 46.9 ± 16.9 years (10–77 years). Notably, age at onset was older than 60 years in 3 patients. Cases of infantile onset were not detected.

The main clinical features included ataxia (28 patients), epilepsy (24 patients), chorea (24 patients), cognitive impairment (18 patients), psychiatric/behavioral symptoms (18 patients), and intellectual disability (8 patients with juvenile age at onset); see Table 1. All clinical findings, including case reports, neuropsychological evaluation, and neuroimaging studies, are reported in the Supplementary materials (Supplementary case reports, Supplementary Fig. 2, Supplementary Tables 1 and 2).

Epilepsy was more frequent in juvenile cases than in late adult cases ($P < 0.05$). Psychiatric or cognitive disorders, ataxia, and chorea were equally distributed among the 3 onset age groups (Table 1).

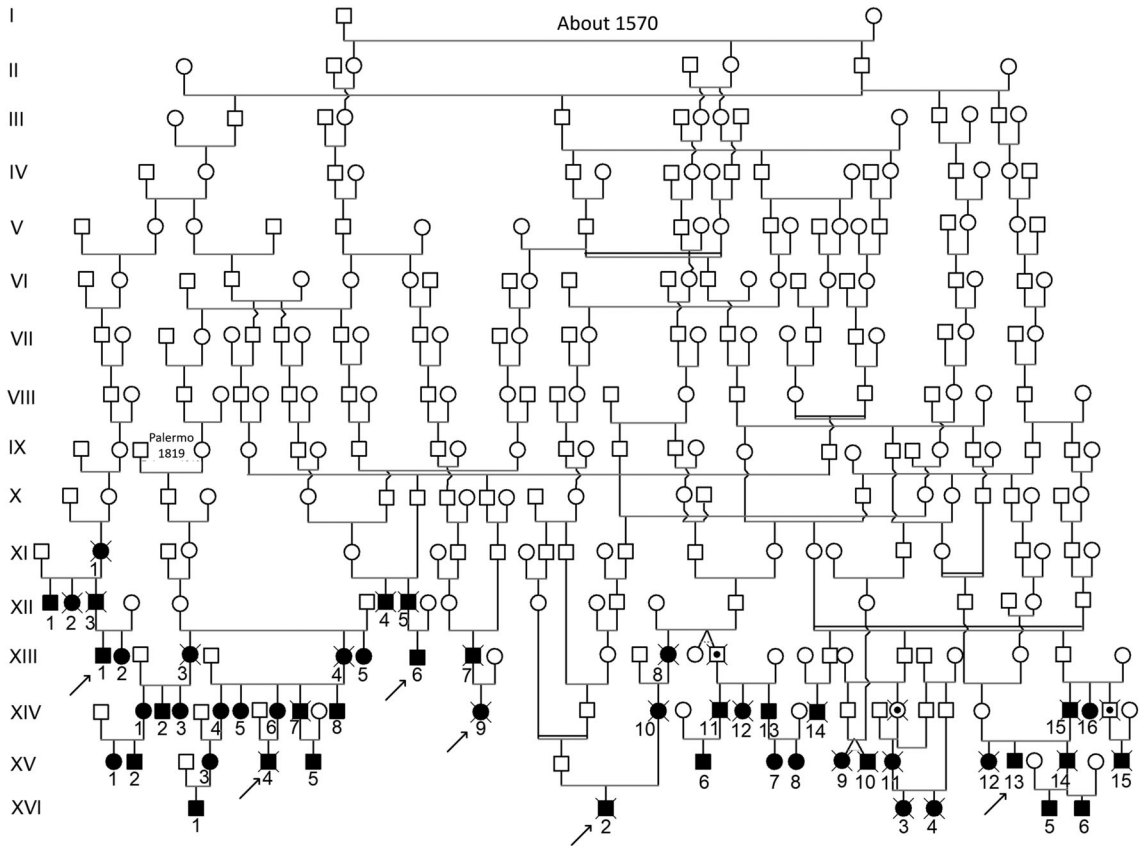

FIG. 1. Pedigree of the DRPLA families in Sicily. □ Male, ○ female, ■ ● affected, X deceased, ◘ ◉ obliged carrier. = consanguinity.

TABLE 1. Summary of clinical and genetic features in DRPLA patients

	n (%)	Juvenile	Adult	Late adult	Age at onset not known	*P*
n (%)	51	14 (27.5%)	10 (19.5%)	13 (25.5%)	14 (27.5%)	—
CAG size range	58–65	62–65	58–63	58–62	na	< 0.01
Sex	26 M, 25 F	8 M, 6 F	7 M, 3 F	7 M, 6 F	4 M, 10 F	ns
Age at onset	31.4 ± 17.5	11.6 ± 3.8	31.5 ± 7.7	48.8 ± 9.1	na	—
Age at death	46.9 ± 16.9	32.5 ± 11.9	51.3 ± 9.2	61.8 ± 9.8	26 ± 22.6	—
Ataxia	28 (54.9%)	9	9	9	1	ns
Epilepsy	24 (47.1%)	12[a]	6	4	2	< 0.05
Chorea	24 (47.1%)	4	7	9	4	ns
Cognitive impairment	18 (35.3%)	4	5	9	0	ns
BPS	18 (35.3%)	3	4	10	1	ns
Intellectual disability	8 (15.7%)	8	0	0	0	< 0.01
Parkinsonian symptoms	1 (2%)	0	0	1	0	—
Dystonia	3 (5.9%)	0	1	2	0	—
Myoclonus	2 (3.9%)	0	1	1	0	—
Ocular movements	7 (13.7%)	1	2	4	0	—
Postural Instability	24 (47.1%)	8	8	8	0	—
Neuropathy	1 (2%)	1	0	0	0	—

BPS, behavioral and psychiatric symptoms; na, not available; ns, not significant.
[a]$P < 0.05$ in juvenile cases vs late adult cases.

The number of CAG repeats was inversely related to the age at onset ($P < 0.01$) and to the age groups ($P < 0.01$) and was directly related to intellectual disability ($P < 0.05$). No significant correlations between CAG repeats and the other clinical features were identified.

Discussion

We reconstructed a large pedigree with DRPLA including 6 families and 51 affected members distributed over 4 generations. The families originated from

western Sicily, and the genealogical reconstruction across 16 generations led to the identification of a founder couple who lived in the ancient town of Monte San Giuliano at the end of the 1500s. The introduction of the mutated allele to the Italian population likely occurred from 270 to 600 years ago.[22] Our findings confirm the founder effect for DRPLA in Italy, narrowing the period to the 1500s, and identify the specific town of origin.

DRPLA is considered a very rare pathology in non-Asian populations, reported in single cases or small families[2-5,9-18] (Supplementary Table 3). The Italian pedigree described here counts the highest number of Caucasians subjects with DRPLA reported to date. In our subjects, the parental origin of the mutated gene may be dual (paternal or maternal) because of the high consanguinity rate in the pedigree, as demonstrated in case XVI.2 by the presence of both a normal expanded allele (42 CAG repeats) and a pathological allele (64 CAG repeats). Interestingly, this is the first report of a normal expanded allele with a very high number of CAG repeats in a DRPLA Caucasians pedigree.

The frequency of normal expanded alleles (ie, >17 CAG repeats) has been demonstrated to influence the prevalence of DRPLA in Japan[19] by inducing the generation of new pathological expanded alleles during intergenerational transmission.[19] We may speculate that the persistence of DRPLA in western Sicily from the 1500s to the present could be caused by a high frequency of expanded normal alleles in the population.

None of the branches in the present pedigree had any evidence of Asian ancestry. However, 7 subjects in the present pedigree (namely, subjects XIV.6, XIV.7, XIV.8, XIV.11, XV.4, XV.5, and XV.6) were previously examined[21] and shared a common haplotype with Japan and Portuguese families, supporting the hypothesis of an ancient common origin between European and Asian patients.

Historical research applied to the current territory of Trapani, including Monte San Giuliano (ie, the hometown of the founder couple of the pedigree), revealed that this region was under Spanish domination in the 1500s, and its port was a strategic hub for both commercial and military traffic. Citizens were obliged to so-called *posada*, offering free board and lodging to stationed Spanish soldiers,[30] facilitating unions and marriages between soldiers and Sicilian people. Remarkably, only Spanish and Portuguese kingdoms held trade relationships between Japan and Europe by sea in the 1500s. Therefore, historical reports and genetic analysis suggest that the introduction of the mutated DRPLA haplotype from Japan occurred in Italy by Spanish or Portuguese sailors at that time.

The present pedigree permitted the investigation of the clinical features in a large series of related DRPLA patients. Clinical findings confirmed the current understanding of DRPLA from Japanese populations could also be applied to Caucasians. The clinical manifestations were heterogeneous and often overlapped among the affected subjects, despite belonging to the same pedigree with a common genetic background. Age at onset spanned late infancy to older adults and inversely correlated with the number of CAG repeats. Interestingly, some patients had onset older than age 60 years with prominent cognitive and behavioral symptoms in addition to motor disturbances, misdiagnosed as aging-related neurological disease. Ataxia was the most frequently reported sign in all age groups. Intellectual disability was detected in half of juvenile cases, and it was directly related to the expanded CAG repeat size. Epilepsy significantly differed according to age. In juvenile cases epilepsy represented a cardinal symptom, showing generalized tonic-clonic seizures, whereas in late adults it was significantly less frequent, as previously reported,[7] and appeared in the advanced stages.

Cognitive, behavioral, and psychiatric disorders occurred equally in both juvenile and adult patients in this pedigree. Cognitive and behavioral impairment in DRPLA has not been specifically defined.[31] In the present clinical series, psychiatric and behavioral disturbances were accurately distinguished, with reports of delusions, hallucinations, depressed mood, apathy, loss of inhibitory control, poor judgment, impulsivity, irritability, and aggression.

Moreover, in this study, 2 patients underwent a complete neuropsychological battery, demonstrating moderate cognitive deterioration of attentive and executive functions, semantic fluency, and visuoconstructive abilities. Memory was relatively preserved in all its components (encoding, storage, and retrieval). The qualitative analysis of drawing indicated by the Qualitative Scoring MMSE Pentagon Test score of the MMSE pentagon copy task[32,33] also suggested semantic deficits related to the degradation of the mental representation of the figure, rather than graphic visuoperceptual difficulties.[34] The peculiar cognitive and behavioral profile in this DRPLA pedigree reflects "dysmetria of thought," which is a key element of cerebellar cognitive-affective syndrome.[35-38]

Neuroimaging in these DRPLA patients demonstrated atrophy of the cerebellum and midbrain at all ages, confirming the presence of cerebral Caucasians matter lesions only in adult and elderly patients[6] (Supplementary Table 4).

In conclusion, this study reported the largest Caucasians DRPLA pedigree arising from a single founder couple who lived in the late 1500s, suggesting the introduction of the DRPLA haplotype in Italy by Spanish or Portuguese trade with Japan in the 1500s. Broad phenotypical variability was confirmed, highlighting the

main effect of cognitive, psychiatric, and behavioral impairment on the clinical presentation. Our study provides evidence that DRPLA may be preserved over time in peculiar geographic areas, indicating that its prevalence could be higher than expected in non-Asian populations.

Acknowledgments: We thank Francesco Castelli, Fr. Piero Messana, Antonina Grammatico, Gabriele Tripi, Giustina Cannova, the staff of the Municipal Archives, and all subjects and families participating in the study.

References

1. Carroll LS, Massey TH, Wardle M, Peall KJ. Dentatorubral-pallidoluysian Atrophy: An Update. Tremor Other Hyperkinet Mov 2018;1:577.
2. Wardle M, Morris HR, Robertson NP. Clinical and genetic characteristics of non-Asian dentatorubral-pallidoluysian atrophy: a systematic review. Mov Disord 2009;24:1636–1640.
3. Nielsen JE, Sørensen SA, Hasholt L, Nørremølle A. Dentatorubral–pallidoluysian atrophy. Clinical features of a five-generation Danish family. Mov Disord 1996;11:533–541.
4. Warner TT, Williams LD, Walker RW, et al. A clinical and molecular genetic study of dentatorubropallidoluysian atrophy in four European families. Ann Neurol 1995;37:452–459.
5. Vinton A, Fahey MC, O'Brien TJ, et al. Dentatorubral-pallidoluysian atrophy in three generations, with clinical courses from nearly asymptomatic elderly to severe juvenile, in an Australian family of Macedonian descent. Am J Med Genet A 2005;136:201–2014.
6. Sugiyama A, Sato N, Nakata Y, et al. Clinical and magnetic resonance imaging features of elderly onset dentatorubral–pallidoluysian atrophy. J Neurol 2018;265:322–329.
7. Tsuji S. Dentatorubral–pallidoluysian atrophy. Handb Clin Neurol 2012;103:587–594.
8. Tsuji S, Onodera O, Goto J, Nishizawa M; Study Group on Ataxic Diseases Sporadic ataxias in Japan-a population-based epidemiological study. Cerebellum 2008;7:189–197.
9. Yiş U, Dirik E, Gündoğdu-Eken A, Başak AN. Dentatorubralpallidoluysian atrophy in a Turkish family. Turk J Pediatr 2009;5:610–612.
10. Warner TT, Lennox GG, Janota I, Harding AE. Autosomal-dominant dentatorubropallidoluysian atrophy in the United Kingdom. Mov Disord 1994;9:289–296.
11. Cox H, Costin-Kelly NM, Ramani P, Whitehouse WP. An established case of dentatorubral pallidoluysian atrophy (DRPLA) with unusual features on muscle biopsy. Eur J Paediatr Neurol 2000;4:119–123.
12. Wardle M, Majounie E, Williams NM, Rosser AE, Morris HR, Robertson NP. Dentatorubral pallidoluysian atrophy in South Wales. J Neurol Neurosurg Psychiatry 2008;79:804–807.
13. Muñoz E, Milà M, Sánchez A, et al. Dentatorubropallidoluysian atrophy in a Spanish family: a clinical, radiological, pathological, and genetic study. J Neurol Neurosurg Psychiatry 1999;67:811–814.
14. Destée A, Delalande I, Vuillaume I, Schraen-Maschke S, Defebvre L, Sablonnière B. The first identified French family with dentatorubral-pallidoluysian atrophy. Mov Disord 2000;15:996–999.
15. Vale J, Bugalho P, Silveira I, Sequeiros J, Guimarães J, Coutinho P. Autosomal dominant cerebellar ataxia: frequency analysis and clinical characterization of 45 families from Portugal. Eur J Neurol 2010;17:124–128.
16. Becher MW, Rubinsztein DC, Leggo J, et al. Dentatorubral and pallidoluysian atrophy (DRPLA). Clinical and neuropathological findings in genetically confirmed North American and European pedigrees. Mov Disord 1997;12:519–530.
17. Potter NT, Meyer MA, Zimmerman AW, Eisenstadt ML, Anderson IJ. Molecular and clinical findings in a family with dentatorubral-pallidoluysian atrophy. Ann Neurol 1995;37:273–277.
18. Connarty M, Dennis NR, Patch C, Macpherson JN, Harvey JF. Molecular re-investigation of patients with Huntington's disease in Wessex reveals a family with dentatorubral and pallidoluysian atrophy. Hum Genet 1996;97:76–78.
19. Takano H, Cancel G, Ikeuchi T, et al. Close associations between prevalences of dominantly inherited spinocerebellar ataxias with CAG-repeat expansions and frequencies of large normal CAG alleles in Japanese and Caucasian populations. Am J Hum Genet 1998;63:1060–1066.
20. Villani F, Gellera C, Spreafico R, et al. Clinical and molecular findings in the first identified Italian family with dentatorubral-pallidoluysian atrophy. Acta Neurol Scand 1998;98:324–327.
21. Aridon P, Tarantino P, Ragonese P, et al. Dentatorubral–pallidoluysian atrophy: haplotype of Asian origin in 2 Italian families. Mov Disord 2012;27:460–461.
22. Veneziano L, Mantuano E, Catalli C, et al. A shared haplotype for dentatorubropallidoluysianatrophy (DRPLA) in Italian families testifies of the recent introduction of the mutation. J Hum Genet 2014;59:153–157.
23. Le Ber I, Camuzat A, Castelnovo G, et al. A prevalence of dentatorubral-pallidoluysian atrophy in a large series of white patients with cerebellar ataxia. Arch Neurol 2003;60:1097–1099.
24. 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;12:189–198.
25. Carlesimo GA, Caltagirone C, Gainotti G. The Mental Deterioration Battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The Group for the Standardization of the Mental Deterioration Battery. Eur Neurol 1996;36:378–384.
26. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–2314.
27. Lesch KP, Stöber G, Balling U, et al. Triplet repeats in clinical subtypes of schizophrenia: variation at the DRPLA (B 37 CAG repeat) locus is not associated with periodic catatonia. J Neural Transm Gen Sect 1994;98:153–157.
28. Bruni AC, Bernardi L, Colao R, et al. Worldwide distribution of PSEN1 Met146Leu mutation: a large variability for a founder mutation. Neurology 2010;74:798–806.
29. Bernardi L, Frangipane F, Smirne N, et al. Epidemiology and genetics of frontotemporal dementia: a door-to-door survey in southern Italy. Neurobiol Aging 2012;33:2948.e1–2948.e10.
30. Favarò V. Sugli alloggiamenti militari in Sicilia tra Cinque e Seicento: alcune riflessioni. Mediterranea-Ricerche storiche 2010;20:459–478.
31. Lindsay E, Storey E. Cognitive Changes in the Spinocerebellar Ataxias Due to Expanded Polyglutamine Tracts: A Survey of the Literature. Brain Sci 2017;7:E83.
32. Caffarra P, Gardini S, Dieci F, et al. The qualitative scoring MMSE pentagon test (QSPT): a new method for differentiating dementia with Lewy Body from Alzheimer's disease. Behav Neurol 2013;27:213–220.
33. Mitolo M, Salmon DP, Gardini S, Galasko D, Grossi E, Caffarra P. The new Qualitative Scoring MMSE Pentagon Test (QSPT) as a valid screening tool between autopsy-confirmed dementia with Lewy bodies and Alzheimer's disease. J Alzheimers Dis 2014;39:823–832.
34. Farah MJ. The neurological basis of mental imagery: a componential analysis. Cognition 1984;18:245–272.
35. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain 1998;121:561–579.
36. Bruni AC, Takahashi-Fujigasaki J, Maltecca F, et al. Behavioral disorder, dementia, ataxia, and rigidity in a large family with TATA box-binding protein mutation. Arch Neurol 2004;61:1314–1320.
37. Gallo M, Frangipane F, Cupidi C, et al. The novel PSEN1 M84V mutation associated to frontal dysexecutive syndrome, spastic

paraparesis, and cerebellar atrophy in a dominant Alzheimer's disease family. Neurobiol Aging 2017; 56:213.e7–213.e12

38. Guell X, Hoche F, Schmahmann JD. Metalinguistic deficits in patients with cerebellar dysfunction: empirical support for the dysmetria of thought theory. Cerebellum 2015;14:50–58.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.