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# The role of historical medical archives in the genealogical rebuilding of large families affected by neurodegenerative diseases.

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## ABSTRACT

Starting from a proband for whom a family history of neurodegenerative disorder has been reported, clinical and genealogical methods are often used together to reconstruct the pedigree of many large families affected by hereditary diseases.

This approach was fundamental in the rebuilding of the N family, the kindred originated from southern Italy affected by early onset autosomal dominant Alzheimer's disease (AD), that has given an important contribution to the discovery of Presenilin 1, the main gene responsible for AD.

The identification of several patients in this pedigree, encompassing 11 generations with several hundred of affected subjects, was achieved through the meticulous study of medical records in the archives of the Provincial Psychiatric Hospital of Girifalco in Italy and in the municipal and parish archives of many towns belonging to the same geographical area. The research on N family triggered several other studies on hereditary neurodegenerative disorders in Southern Italy. Investigation focusing on antique archives and the analysis of phenotypes allowed to reconstruct and clinically detail large pedigrees of hereditary diseases, such as frontotemporal dementia and spinocerebellar ataxia 17, even before the discovery of their causative genes.

Neuroscience community is familiar with the case of Auguste D., a 56 years old woman affected by early onset dementia, whose clinical and neuropathological features were described by Alois Alzheimer in the seminal paper in 1907[1]. It is equally intriguing to know the story of an Italian pedigree (N Family) that lead to the discovery of Presenilin 1, the main gene causative for familial Alzheimer's disease (AD) in 1995[2].

Alzheimer's Disease (AD) is the most frequent cause of neurodegenerative dementia and it is characterized by progressive loss of memory and other changes in cognition and behaviour. According to the age at onset, AD was classified in early onset AD (EOAD), before 65 years, and the more common form, late onset AD (LOAD). Most of AD cases are sporadic and the aetiology is largely unknown, whereas in 5% of cases the disease is familial and linked to genetic mutations, mainly for EOAD.

The genetics of AD is now largely understood with a clear pattern of autosomal dominant inheritance associated to mutations of one of the three causative genes: Amyloid Precursor Protein (APP)[3] or Presenilin genes (PSEN1, PSEN2)[2,4]. Mutations in PSEN1 gene are more frequent compared to PSEN2 and APP genes. To date, more than 216 private mutations have been identified worldwide in PSEN1 gene affecting about 476 families (www.molgen.ua.ac.be/ADMutations ).

In the 70's, the familial form of AD was only presumed, because several subjects affected by dementia had clustered in the same family. However, the evidence of a mendelian inheritance of autosomal dominant type was not yet achieved. In 1972, the neuropathologist Jean Francois Foncin (Salpetriere Hospital, Paris) disclosed the histopatological features of AD in the brain biopsy of a 42-years-old woman affected by dementia. Many relatives of the patient had also exhibited the same symptoms and Foncin supposed a familial form of AD, undertaking a clinical and genealogical study in the Southern Italy, where the family originated[5]. In particular, the archives of the Provincial Psychiatric Hospital of Girifalco, where several affected members were institutionalized, had provided the biggest bulk of information to rebuild the pedigree tree. These archives included 16000 clinical records collected since 1881 and the accurate clinical descriptions of the indoor patients allowed researchers to retrospectively make AD diagnosis.

The earliest clinical record belonged to the patient Angela R. and dated back to 1904, three years before Alois Alzheimer's first description of the disease[6]. Even if the diagnosis was generically indicated as "bulbar palsy" at the time, the clinical record of Angela R represent the oldest medical document describing in detail the clinical features of a person suffering from Alzheimer's Disease.

Angela R was a farmer born in 1865 in a small village called Nicastro. In 1904, she was admitted to the Psychiatric Hospital. Psychiatric examination was highly accurate in exploring mental functions, allowing to define the clinical phenotype. Angela R was affected by a familial form of dementia with a non-amnestic presentation, matching the dysexecutive clinical pattern[7]. No neuropathological study was made on Angela R's brain. However, the pathological hallmarks of AD were clearly demonstrated in her direct descendants, as well the genetic cause of the disease, namely the mutation PSEN1-Met146Leu[8].

The retrieval of Angela R's medical record was crucial in linking to the same kindred two different still unrelated branches: the Italian-French N family studied by Foncin[5] and another AD family, previously described by Feldman[9] in United States in 1963.

Hence, the application of the genealogical method led to the rebuilding of the largest pedigree known to be affected by familial AD[10,11]. Apart from the Girifalco archives, many other sources were contemporaneously used in order to reduce biases to a minimum, as well as to obtain information before the opening of the Hospital. A systematic search of genealogical data was performed from municipal documents (Civil status or Register office, available from 1800 to nowadays) and parish registers, taken by the priests from the XVII$^{th}$ century. In addition, the Status Animarum registers (a kind of census taken by parish priests dating back up to the XVI$^{th}$ century) enabled reconstitution of nuclear families. The research was performed in the village from which the family originated and in other villages of the same geographical area where the affected branches of the families lived. To rebuild the different branches of the pedigrees the examined data concerned birth, baptism, marriage and death certificates of relatives and ancestors of probands. To avoid bias in the collection of data, the research followed both apparently unaffected and affected branches, as well as maternal or paternal ancestry or descent. The collected data finally served as database used to identify the links between the families and the common ancestor, to detect instances of consanguinity and to generate a control population matched with the affected branches.

The N family was broadly descripted in 1985[5], then updated[8,12], and it encompassed 11 generations with several hundred of affected members[8]. It expanded both geographically (in Europe, North and South America and Australia), and temporally, with ancestors traced to the XVII$^{th}$ century and the earliest known obligated carrier (a woman named Vittoria who died at 43 years) born in 1715[5]. The full work on N family (also called FAD4) was instrumental to propose a mendelian model of inheritance for AD genetics[13], to map the gene for familial AD to chromosome 21[12] and then to clone Presenilin 1 gene in 1995[2]. Then, the *PSEN1-Met146Leu* mutation, causing the disease in N family, was defined as private and founder[8].

Moreover, the research on N family triggered several other studies on hereditary neurodegenerative disorders in Southern Italy. It became clear that Calabrian region represented an area with a low genetic heterogeneity and a high level of consanguinity because of the geographic isolation over the centuries, allowing rare mutations to be preserved[8,14].

In 2002, a kindred originating from a small Calabrian village (Biv) was reconstructed for 15 generations back to 16th century, including about 8,000 persons[15]. Thirty-four affected subjects over four consecutive generations have been identified and the autosomal dominant transmission was evident. The homogeneous behavioural pattern of dementia characterised by an insidious onset, loss of social awareness and absence of insight in the affected members was consistent with the clinical diagnosis of Frontotemporal Dementia[15]. In that time, MAPT gene was the only gene associated to FTLD but no mutations were disclosed in this kindred. Only in 2006 the discovery of PGRN gene allowed to identify the causative gene in the Biv pedigree[16]. After ten years, a door-to-door population study in the same village showed an unusual higher incidence of FTD compared to AD and a high prevalence of GRN mutations, confirming the genetic peculiarity of this geographical area[17].

Another large autosomal dominant family (57 affected members in 5 generations) affected by dementia with ataxia, extrapyramidal features, and epilepsy originated from Nicastro (the same village of Angela R.) was studied, but the screening of 26 different genes, including PS1, did not lead to any results in 2002[18]. After 2 years, the TATA box-binding protein gene was recognized as the causative one in this family, broadening the clinical picture of spinocerebellar ataxia type 17 including dementia with behavioral symptoms[19].

In conclusion, applying the genealogical method associated to the analysis of clinical phenotypes, large pedigrees of many hereditary diseases had been described even before the discovery of the causative genes. The work on this kind of families has been inestimable to investigate the biological basis of Alzheimer's disease and other neurodegenerative disorders. Moreover, the accurate clinical description of the pedigree was essential to understand the relationship between phenotype and genotype, and to highlight the heterogeneity of the clinical expression of the disease in the same family, giving the chance to explore both environmental and genetic modifying factors.

## References


1. Alzheimer A, Stelzmann RA, Schnitzlein HN, et al. An English translation of Alzheimer's 1907 paper, "Uber eine eigenartige Erkankung der Hirnrinde". Clin Anat. 1995; 8: 429-31.
2. Sherrington R, Rogaev EI, Liang Y, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature. 1995; 375: 754-60.
3. Goate A, Chartier-Harlin MC, Mullan M, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature. 1991; 349: 704-6.
4. Rogaev EI, Sherrington R, Rogaeva EA, et al. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. Nature. 1995; 376: 775–8.
5. Foncin JF, Salmon D, Supino Viterbo V, et al. Demence presenile d'Alzheimer transmise dans une famille etendue. Rev Neurol Paris. 1985; 141: 194-202.
6. Borrello L, Cupidi C, Laganà V, et al. A familial Alzheimer's disease case in the days of Auguste D. J Neurol. 2016; 263(12): 2494-2498.
7. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7: 263-9.
8. 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.
9. Feldman RG, Chandler KA, Levy LL, et al. Familial Alzheimer's Disease. Neurology. 1963; 13: 811-24.
10. Foncin JF, Salomon D, Bruni AC. Notes on the methods for the study of kindreds with familial Alzheimer's disease. In: Familial Alzheimer's disease. Molecular Genetics and Clinical Perspectives. Winters-Miner eds Marcel Dekker Inc New York and Basel. 1989.
11. Bruni AC, Montesi MP, Rainero I, et al. The power of systematic genealogical study in familial Alzheimer disease. Ital J Neurol Sci. 1993; 14(3): 239-44.
12. St George-Hyslop PH, Tanzi RE, Polinsky RJ, et al. The genetic defect causing familial Alzheimer's disease maps on chromosome 21. Science. 1987; 235(4791): 885-90.
13. Bruni AC, Montesi MP, Salmon D, et al. Alzheimer's Disease: a model from the quantitative study of a large kindred. J Geriatr Psychiatry Neurol. 1992; 5: 126–131.
14. Cizza G, Bernardi L, Smirne N, et al. Clinical manifestations of highly prevalent corticosteroid-binding globulin mutations in a village in southern Italy. J Clin Endocrinol Metab. 2011; 96(10): E1684-93.
15. Curcio SA, Kawarai T, Paterson AD, et al. A large Calabrian kindred segregating frontotemporal dementia. J Neurol. 2002; 249(7): 911-22.
16. Bruni AC, Momeni P, Bernardi L, et al. Heterogeneity within a large kindred with frontotemporal dementia: a novel progranulin mutation. Neurology. 2007; 69(2): 140-7.
17. 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(12): 2948.e1-2948.e10.
18. Filla A, De Michele G, Cocozza S, et al. Early onset autosomal dominant dementia with ataxia, extrapyramidal features, and epilepsy. Neurology. 2002; 58(6): 922-8.
19. 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(8): 1314-20.