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ORIGINAL ARTICLE

Rediscovery of the case described by Alois Alzheimer in 1911: historical, histological and molecular genetic analysis

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ABSTRACT

In 1911, Alois Alzheimer published a detailed report (*Zbl. ges. Neurol. Psych.* 4: 356–385) on a peculiar case of the disease that had been named after him by Emil Kraepelin in 1910. Alzheimer describes a 56-year-old male patient (Johann F.) who suffered from presenile dementia and who was hospitalized in Kraepelin's clinic for more than 3 years. Post-mortem examination of the patient's brain revealed numerous amyloid plaques but no neurofibrillary tangles in the cerebral cortex, corresponding to a less common form of Alzheimer disease which may be referred to as 'plaque only'. We have identified well-preserved histological sections of this case and performed mutational screening of exon 17 of the amyloid precursor protein gene and genotyping for apolipoprotein E alleles. The patient was shown to be homozygous for apolipoprotein allele ε3 and lacked APP mutations at codons 692, 693, 713 and 717. This case is of historical importance as it may have convinced Kraepelin to name the disease after his co-worker, Alois Alzheimer.

Keywords: Alzheimer disease, amyloid plaques, amyloid precursor protein gene, apolipoprotein E gene, neurofibrillary tangles

INTRODUCTION

In 1907, Alzheimer published his now famous report on a 51-year-old woman who had come under his care in 1901 while he worked as an attending physician in the Frankfurt Asylum (1). The original case file of this patient, Auguste D., was discovered recently, and it has been speculated that the patient's dementia was not caused by the typical neurodegeneration of Alzheimer disease but by arteriosclerosis of the brain (2). Alzheimer's report on Auguste D. is not a full-size research paper but an abstract summarizing the presentation he gave at the *37. Versammlung südwestdeutscher Irrenärzte* (37th Meeting of the Southwest German Psychiatrists) in Tübingen on November 3, 1906 (1). Therefore, the first report by Alzheimer on the morphology of the disease that was named after him by Emil Kraepelin in 1910 (3) does not contain any illustrations. Yet numerous figures, mainly drawings, which include several examples of the histopathology of his first case were published by Alzheimer in 1911 together with a second case report (4). Both publications are available in English (5,6).

In the report on his second published case, Alzheimer gives a detailed description of the clinical history of a 56-year-old demented man (Johann F.). According to Alzheimer's notes (4), the patient was admitted to the psychiatric clinic on November 12, 1907. There was no history of excessive drinking. In the previous 6 months he had become forgetful, could not find his way, could not perform simple tasks or carried these out with difficulty. He stood around, did not

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bother about food, but ate greedily whatever was put in front of him. He was not capable of buying anything for himself and did not wash. He was admitted by the service for the poor (4,6). After 3 years of hospitalization and repeated clinical examinations, Johann F. died on October 3, 1910, in the Royal Psychiatric Clinic in Munich showing features of pneumonia. Neuropathological examination of his brain revealed the widespread presence of amyloid plaques but not a single neuron showing neurofibrillary change (4). Alzheimer provides ample clinical, biographic and neuropathological data of this patient which have allowed us to identify histological sections found among archival material at the Institute of Neuropathology of the University of Munich. Using recently established methods for the molecular genetic analysis of neuropathological tissue (7–9), we have been able to perform mutational screening of exon 17 of the amyloid precursor protein (APP) gene and genotyping for apolipoprotein E (APOE) alleles. The history of this discovery will be detailed elsewhere.

MATERIALS AND METHODS

Selection of tissue sections

Histological sections belonging to this case were identified as described below. All tissue sections to be used for molecular genetic analysis were first studied under the light microscope. The following tissue sections were selected for DNA extraction: no. 28 cerebral cortex (Mann's stain?); no. 35 spinal cord (Mann's stain?); no. 45 cerebral cortex (Mann's stain?); no. 67 cerebral cortex (Mann's stain?); no. 43 cerebellum (Mann's stain?); no. 8 cerebellum (Nissl's stain); no. 18 cerebral cortex (Nissl's stain).

DNA extraction

All sections were processed separately. Glass coverslips were removed by overnight incubation in 100% xylene at room temperature. Tissue sections were then transferred to fresh Eppendorf tubes under sterile conditions and washed with 95 and 70% ethanol for 30 min each, followed by brief centrifugation in an Eppendorf centrifuge. Pellets were dried at 68°C in a TRIO-Thermoblock (Biometra) and resuspended in 1× TE. Digestions were performed in 200 µl aliquots containing 0.2 M Tris, pH 8.0, 10 mM EDTA, 10% SDS, and 4 mg/ml proteinase K (Cat. no. 161519, Boehringer Mannheim) at 50°C for 16–24 h (8).

For purification of DNA, digested tissue was extracted twice with phenol-chloroform-isoamylalcohol (25:24:1) and once with chloroform. Volumes obtained after extraction were concentrated using either ethanol precipitation at –20°C overnight or using a Microcon-30 concentrator (Cat. no. 42409, Amicon) as described (8). 'Mock' DNA extractions were included for control.

Polymerase Chain Reaction (PCR)

PCR reactions were performed in 50 µl volumes using thin-walled reaction tubes and GeneAmp reagents (Perkin-Elmer) following the manufacturer's recommendation. A quantity of 200 µM of each deoxynucleotide, 200 ng of each primer, and 1.25 U of *Taq* DNA polymerase were used in each PCR reaction. Samples were covered with 20 µl of mineral oil, and 1 µl of the concentrated DNA solution was finally added. Primer sequences and PCR reaction conditions for amplification of exon 17 of the APP gene and for genotyping of APOE alleles were essentially as described (7,9).

Genomic amplification of exon 17 of the APP gene was performed with primers *Aint3* 5′-TAAGAAATGAAATTCTT-CTAATTGC-3′ and *Aint4* 5′-GCAGTCAAGTTTACCTACC-TCCACC-3′ after denaturation for 3 min at 94°C, and 32 cycles at 91°C for 30 s, 55°C for 30 s and 72°C for 1 min, followed by a 10 min final extension step at 72°C on a TC 480 thermal cycler (Perkin-Elmer). GeneAmp nucleotides were used in the buffer supplied with *Taq* polymerase (Perkin-Elmer) or a buffer containing 300 mM Tris–HCl, pH 9.0, 75 mM $(NH_4)_2SO_4$, and 10 mM $MgCl_2$ (Invitrogen).

For the determination of APOE alleles, a new polymerase chain reaction assay was employed which allows genotyping of archival neuropathological tissue (9). Primer pairs were Rup1 and Rup2 (5′-CTGGGCGCGGACATGGAG-3′, 5′-GC-AGGTGGGAGGCGAGGC-3′) resulting in a 115 bp amplification product, and Rup3 and Rup4 (5′-GGCCAGAGC-ACCGAGGAG-3′, 5′-GCCCCGGCCTGGTACACT-3′) amplifying a 119 bp DNA fragment. Reaction conditions were denaturation at 94°C for 5 min, followed by 43 cycles at 94°C for 30 s, 68°C for 30 s and 72°C for 1 min, and final extension at 72°C for 10 min. The reaction buffer contained 300 mM Tris-HCl, pH 9.5, 75 mM $(NH_4)_2SO_4$, and 10 mM $MgCl_2$ (Invitrogen).

*Hha*I digestion of the Rup 1/2 and Rup 3/4 amplicons distinguishes between 3/4 and 2/3 alleles, respectively (9). For control, the primers described by Wenham *et al.* (10) were used. Following digestion with *Hha*I (Boehringer), DNA fragments were separated on a 5% intermediate melting temperature agarose gel (Metaphor, Biozym) containing 0.15 µg/ml ethidium bromide. Fragment sizes generated by *Hha*I digestion are given in the legend to Figure 3b. Negative ('no DNA') PCR samples were always run in parallel to control for contamination.

Non-radioactive direct sequencing of PCR products

The genomic sequence of exon 17 of the APP gene was determined between nucleotides 2065 and 2211 (11), encompassing codons 692, 693, 713, and 717, where point mutations have been described in some individuals (12–16). Cycle sequencing of PCR products was performed using 5′-digoxigenin end-labeled oligonucleotide primers 5′-TAAGAAATG-AAATTCTTCTAATTGC-3′ and 5′-GCAGTCAAGTTTA-CCTACCTCCACC-3′, followed by separation of the sequencing reactions on an 8% denaturating polyacrylamide gel (7,17). PCR reaction conditions were 3 min at 94°C, followed by 32 cycles at 91°C for 30 s, 55°C for 30 s and 72°C for 1 min, with 10 min final extension at 72°C. Sequencing bands were visualized using immunological detection with alkaline phosphatase conjugated Fab fragments and nitroblue tetrazolium/X-phospate as an enzymatic substrate (17).

RESULTS

Identification of the case

Entry no. 784 in the autopsy book of Kraepelin's clinic identifies a male patient bearing the last name 'Feigl' who died on October 3, 1910, and who came to autopsy from the

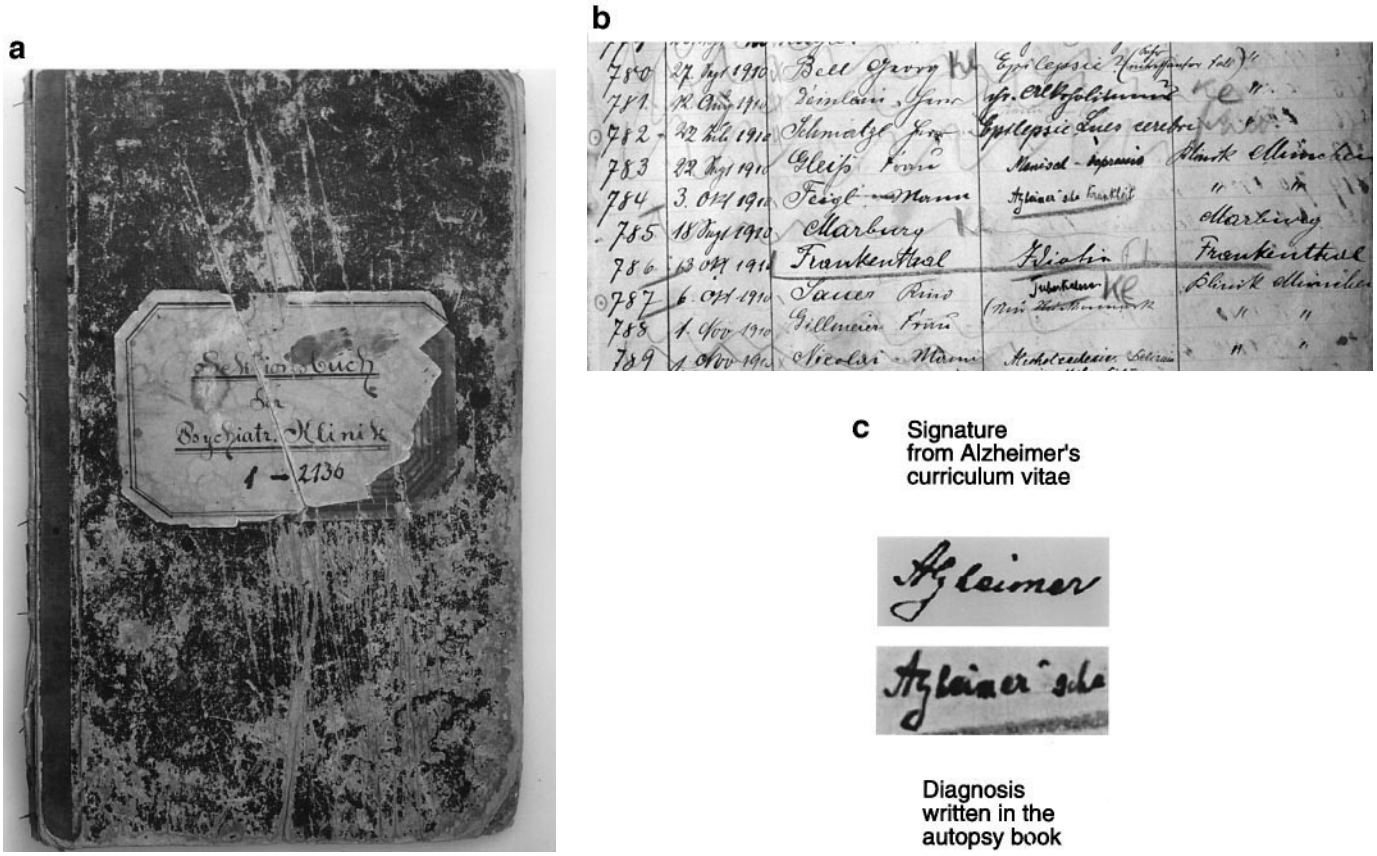


Figure 1. (**a**) Autopsy book ('Sektionsbuch') of the psychiatric clinic in Munich. (**b**) Entry no. 784 lists a male individual ('Mann') bearing the name 'Feigl' who died on October 3, 1910, in the psychiatric clinic ('Klinik München'). The diagnosis reads 'Alzheimer'sche Krankheit' (Alzheimer's disease). (**c**) Alzheimer's signature (upper part of figure) taken from his curriculum vitae which was written after he had joined Kraepelin's clinic (31). For comparison, the diagnosis written in the autopsy book has been enlarged (lower part of figure).

Munich psychiatric hospital (Fig. 1a, b). Based on the case number in the autopsy book and the family name of the patient, we were able to identify histological sections, found on December 30, 1992, among archival material at the Institute of Neuropathology of the University of Munich. Many of these sections are labeled by both the case number and the last name of the patient (Fig. 2a). The admission report of Johann F. (Fig. 4) shows his first and his last name together, several important dates as well as clinical information which appear in Alzheimer's paper (4). The autopsy book states 'Alzheimer'sche Krankheit' (Alzheimer disease) as the patient's diagnosis with the handwriting closely resembling that of Alois Alzheimer (Fig. 1c).

Histological examination

Examination of the histological sections in the light microscope yielded morphological results which are in complete agreement with Alzheimer's paper (4). Although many amyloid plaques were present in the cerebral cortex of this patient (Fig. 2b–d), we did not find neurofibrillary tangles. It should be noted that sections of the hippocampus and the entorhinal region were not available. Silver impregnations performed over 2 days in Alzheimer's laboratory using Bielschowsky's method (Fig. 2a) were found together with a number of Nissl stained specimens. In addition, numerous sections apparently prepared according to the methods of Mann, Herxheimer and Weigert were present but we have not yet completed our morphological analysis of all tissue sections since some of the stains require verification. Therefore, a detailed report on the extensive histology of this case will be published elsewhere.

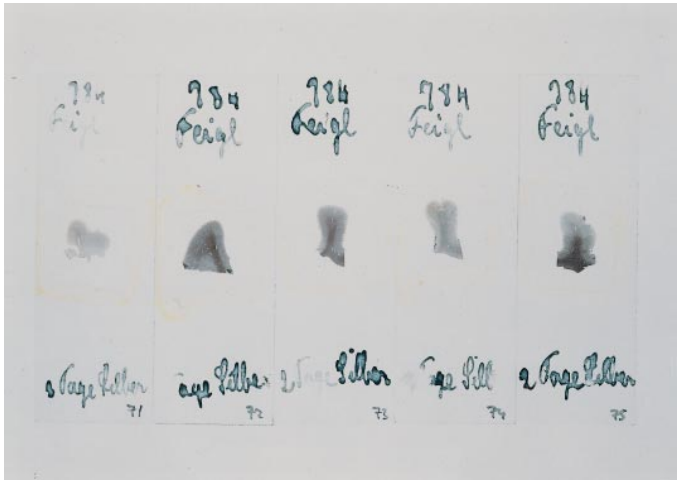
Molecular genetic analysis

At the time when this case was rediscovered, the frequency of APP mutations in Alzheimer disease was just being established. Using direct non-radioactive sequencing of polymerase chain reaction (PCR) products (7,17), we did not detect mutations at codons 692, 693, 713, and 717 or at other nucleotides within exon 17 of the APP gene (Fig. 3a). Consequently, a pathogenic role of exon 17^{APP} mutations in this case of severe amyloid deposition can be excluded. The apolipoprotein E genotype of Alzheimer's patient was found to be ε3/ε3 (Fig. 3b). We have also started screening for mutations in the presenilin genes. Yet, given the limited amount of tissue available, this study was postponed in order to save material for additional histological analyses and until our knowledge on genetic defects in Alzheimer disease is more complete.

DISCUSSION

Alzheimer gives a very detailed description of his patient, Johann F. (4). Starting with this information, we were able to

a



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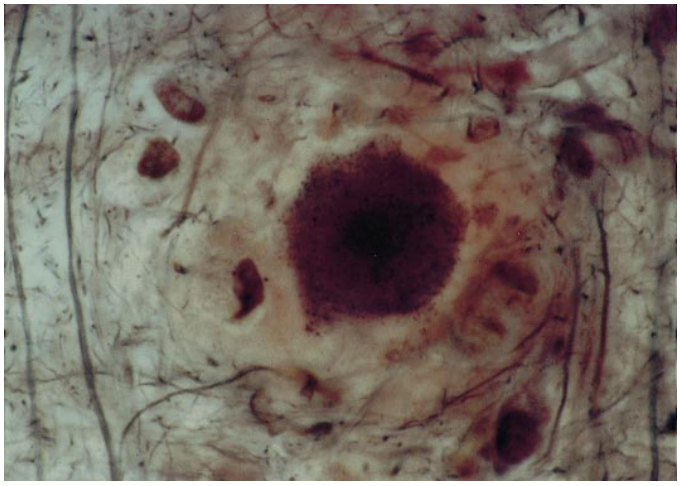

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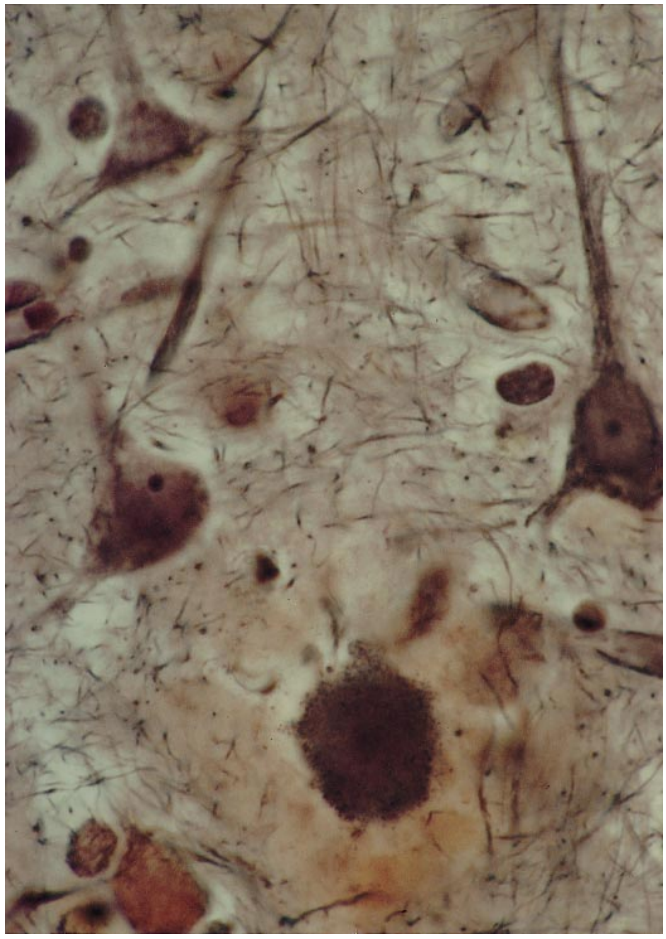

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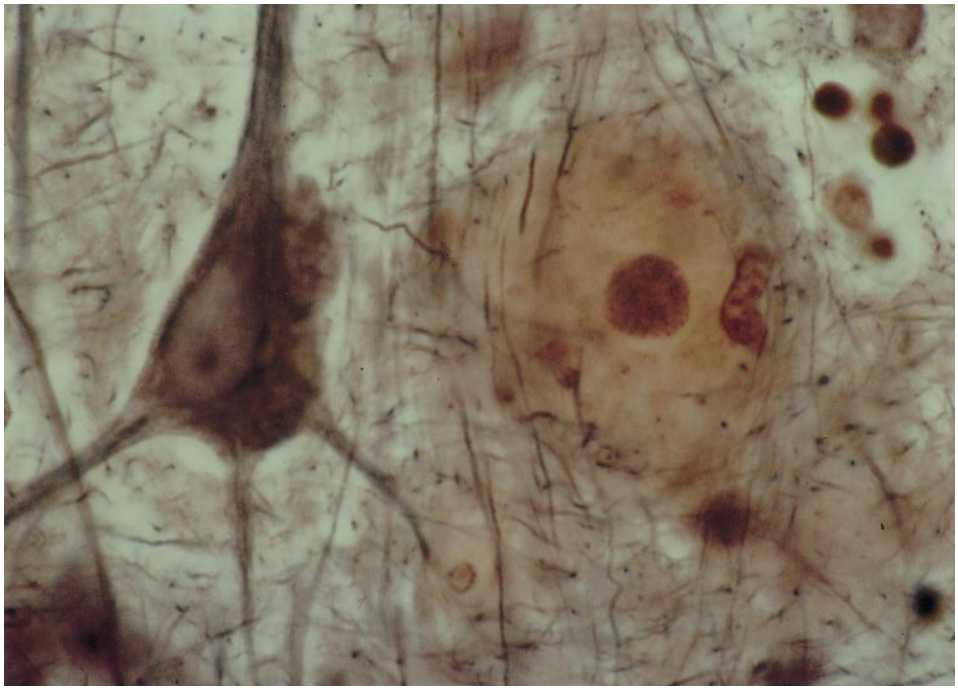


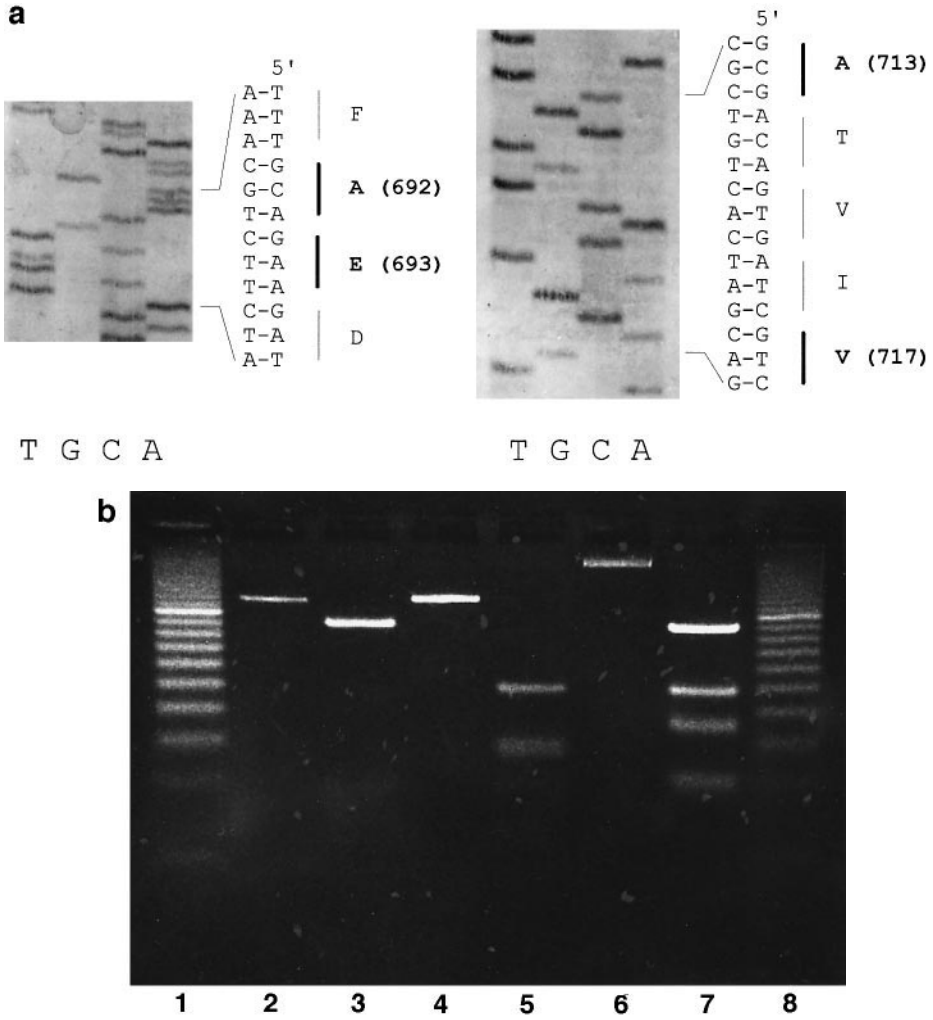
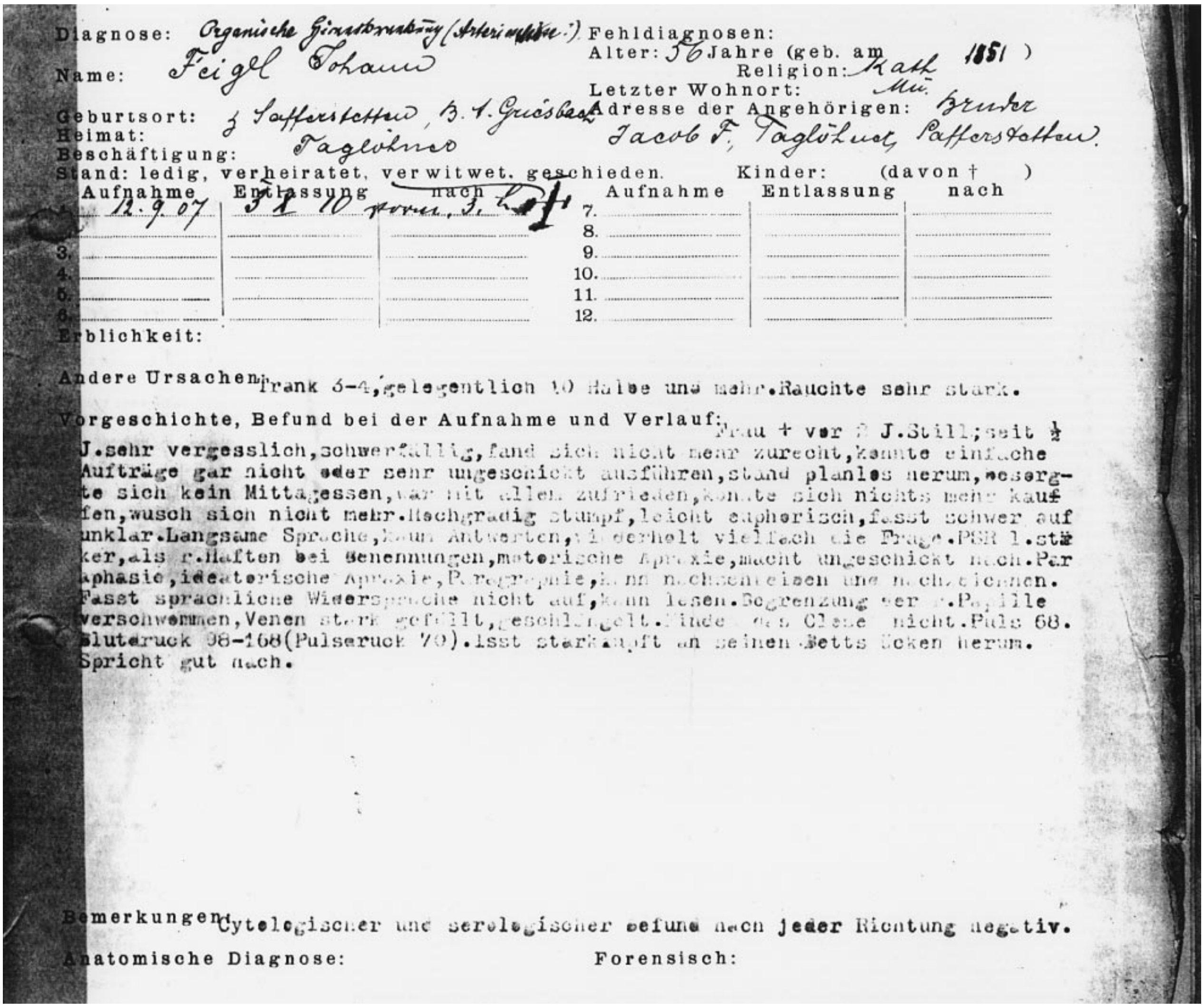


Figure 3. (a) Genomic sequence of part of exon 17 of the APP gene. Known mutation sites, codon numbers and the corresponding peptide sequence are set in bold type. No mutations were found. (**b**) APOE genotyping. Gel electrophoresis of PCR amplicons obtained with the primers Rup 1/2, Rup 3/4, and Wbp 1/2 before (lanes 2, 4, and 6) and after (lanes 3, 5, and 7) *Hha*I digestion. A 10 bp DNA ladder was loaded on lanes 1 and 8. The presence of an ε4 allele would create a 72 bp restriction fragment in lanes 3 and 7, whereas the presence of an ε2 allele would result in a 72 bp and 81 bp restriction fragment in lanes 5 and 7, respectively. As can be seen in lanes 3, 5 and 7, the patient shows homozygosity for apolipoprotein allele ε3.

identify tissue sections which belong to this case based on the matching dates and on the first and the last name of the patient in Alzheimer's paper as well as in the autopsy book, on the tissue sections and in the patient's admission report. The latter document (Fig. 4) contains additional interesting information. Although most of its data match exactly, there are two exceptions. The first difference concerns the date of the hospital admission of the patient which was September 12, 1907 (Fig. 4), and not November 12, 1907, as reported by Alzheimer. On reading the clinical history of the patient, this typographical error in Alzheimer's publication (4) is readily apparent. The second discrepancy concerns the misspelling of the name 'Feigl' in the admission report as there is an additional 'e' (Feigel). However, 'Feigl' is a common Bavarian name of which several different spellings exist without an associated difference in pronunciation. In addition, the clinical history given in the admission sheet also appears in Alzheimer's paper, confirming the identity of the case. Finally, the ink used by Alzheimer's laboratory to label the tissue sections was compared to that of three other cases listed in the autopsy book, and they were shown to be of identical origin (opinion from the Bavarian State Bureau of Criminal Investigation, data not shown). Thus, the tissue sections were confirmed to be older than 80 years.

It is unknown whether Kraepelin ever saw Auguste D., Alzheimer's first patient, who died in the Frankfurt asylum (1,2). However, Kraepelin was most likely familiar with Johann F. as Kraepelin and Alzheimer used to work together very closely which is gratefully acknowledged by Kraepelin in the introduction to the second volume of his textbook (3).

Figure 2. (**a**) Bielschowsky-stained tissue sections processed for two days ('2 Tage Silber'). (**b–d**) Staining of classical amyloid plaques (with core) in the cerebral cortex of Alzheimer's patient. Pyramidal neurons and neurites within the plaque do not show neurofibrillary change. Magnification: ×700 (b), ×1000 (c), ×500 (d).


Diagnose: Organische Hirnerkrankung (Arteriosklerose?) Fehldiagnosen:
Alter: 56 Jahre (geb. am 1851)
Name: Feigl Johann Religion: Kath
Letzter Wohnort: Mü.
Geburtsort: Adresse der Angehörigen: Bruder
Heimat: Jacob F., Taglöhner, Pfaffenstetten
Beschäftigung: Taglöhner
Stand: ledig, verheiratet, verwitwet, geschieden. Kinder: (davon †)

Aufnahme	Entlassung	nach		Aufnahme	Entlassung	nach
12.9.07	3.1.10		7.			
			8.			
			9.			
			10.			
			11.			
			12.			

Erblichkeit:

Andere Ursachen: Trank 3–4, gelegentlich 10 Halbe und mehr. Rauchte sehr stark.

Vorgeschichte, Befund bei der Aufnahme und Verlauf: Frau + vor ? J. Still; seit ½ J. sehr vergesslich, schwerfällig, fand sich nicht mehr zurecht, konnte einfache Aufträge gar nicht oder sehr ungeschickt ausführen, stand planlos herum, besorgte sich kein Mittagessen, war mit allem zufrieden, konnte sich nichts mehr kaufen, wusch sich nicht mehr. Hochgradig stumpf, leicht euphorisch, fasst schwer auf, unklar. Langsame Sprache, kaum Antworten, wiederholt vielfach die Frage. PSR l. stärker, als r. Haften bei Benennungen, motorische Apraxie, macht ungeschickt nach. Paraphasie, ideatorische Apraxie, Paragraphie, kann nachschreiben und nachzeichnen. Fasst sprachliche Widersprüche nicht auf, kann lesen. Begrenzung der r. Papille verschwommen, Venen stark gefüllt, geschlängelt. Findet den Stuhl nicht. Puls 68. Blutdruck 98–168 (Pulsdruck 70). Isst stark, zupft an seinen Betts Ecken herum. Spricht gut nach.

Bemerkungen: Cytologischer und serologischer Befund nach jeder Richtung negativ.

Anatomische Diagnose: Forensisch:

Figure 4. The admission report of Johann F. provides the missing link between the first name ('Johann') and the initial of the last name ('F.') given in Alzheimer's paper. The clinical history ('Vorgeschichte') also appears in the publication. Interestingly, Johann F. was admitted with a diagnosis of possible vascular dementia. The initial clinical diagnosis probably written by Alzheimer reads 'Organische Hirnerkrankung (Arteriosklerose?)', i.e., organic brain disease (arteriosclerosis?).

Accordingly, Alzheimer acted as head of the hospital when Kraepelin was not in Munich which occurred frequently when Kraeplin was working on his textbook. It is well known that Kraepelin was the first to use the term Alzheimer disease in the 8th edition of his famous '*Psychiatrie*' which he was revising at the time. However, much speculation exists (18) as to why Kraepelin so readily accepted Alzheimer's clinical and histopathological description. One reason may have been the competition between Munich and the group in Prague headed by Arnold Pick whose co-worker Fischer had published interesting findings on amyloid plaques (19). However, the case of Johann F. may provide a better explanation. Alzheimer submitted his report on this patient together with a detailed description of the cellular pathology of Alzheimer disease in January of 1911, i.e., only a few months after the autopsy. This suggests that the studies on Johann F. became part of a long planned manuscript which eventually comprised 30 printed pages. It also implies that Johann F. who was admitted with a diagnosis of possible vascular dementia (Fig. 4) was observed very closely during his stay in the psychiatric clinic. Finally, publication of the new eponym 'Alzheimersche Krankheit' by Kraepelin (3,4) practically forced Alzheimer to write his own name as the patient's diagnosis in the autopsy book (Fig. 1b, c), only 3 years after his first description of the disease.

As already stated by Alzheimer himself (4), the case of Johann F. is remarkable from a histopathological point of view since numerous plaques but no neurofibrillary tangles are detectable in the cerebral cortex of this patient. A substantial fraction of Alzheimer cases may belong to this type, and it has been suggested that 'plaque dementia' (6) may comprise a separate subgroup of the disorder (20). Yet, having to rely on the stains from Alzheimer's time we did not detect any Lewy bodies (21).

From a molecular genetic point of view it is interesting to note that Alzheimer's patient lacks the common Alzheimer disease susceptibility allele, apolipoprotein E ε4 (22–23). This allele represents a well-established genetic risk factor for the development of Alzheimer's disease (see A. Roses, this issue), and approximately two-thirds of all Alzheimer patients carry

one or two copies of this allele. Some authors have found that presence of the ε4 allele is associated with an increased deposition of amyloid. Yet, influence of apolipoprotein E genotype on neuropathology is lacking in familial Alzheimer cases (24). Unfortunately, pedigree data are presently unavailable in the case of Johann F. who was affected by a presenile form of the disease. While exon 17^{APP} mutations are absent, we cannot exclude mutations in the presenilin-1, presenilin-2, or other Alzheimer disease genes that could have caused the amyloid pathology in this patient (25–28). Thus, the case of Johann F. may belong to a subgroup of Alzheimer disease not only from a clinical and histopathological but also from a molecular genetic point of view. This fits well with the emerging concept of Alzheimer disease not representing a single disease entity but a heterogeneous group of disorders (29). The finding that neuropathological tissue which has been stored for more than 80 years can be used successfully for molecular genetic analysis may be of general relevance in this context as the results of our study strongly support the concept that epidemiologically relevant data may be obtained using retrospective genotyping of archival brains (30).

The tissue sections reported on in this paper are likely to represent the only histological material which is left from Alzheimer's own research on the disease that was named after him. The material and the stains are well-preserved and of high quality, documenting once again Alzheimer's high technical standards (31). We anticipate that the study of the case of Johann F. may serve as a source of inspiration not only to those working in the Alzheimer field.

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