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REVIEW ARTICLE

FDG PET and the genetics of dementia

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Abstract Dementias are the most common neurodegenerative diseases and they are increasingly becoming a major public health problem. The most common form of dementia, affecting over 20 million people worldwide, is Alzheimer's disease (AD). AD is a neurodegenerative disease of the central nervous system mainly found in older adults, with an incidence that increases with age. With the development of newer technologies, including genetic screening technologies and PET/MRI scanning, the role of genetic studies and neuroimaging is being redefined; indeed, these approaches are able to provide support not only in the clinical diagnosis of dementia, but also in its presymptomatic evaluation. Many researchers agree that early identification of AD, before abnormal accumulation of amyloid and tau proteins, could provide an opportunity to hinder the progression of the disease. [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) PET studies have shown that decreased glucose metabolism in AD precedes clinical diagnosis and that the degree of clinical disability in AD correlates closely with the magnitude of the reduction in brain glucose metabolism. Data on presymptomatic mutation carriers from families with known early-onset autosomal dominant AD (familial AD) show reductions in the cerebral metabolic rate of glucose (CMRglc), consistent with the expected AD PET pattern, in the absence of severe atrophy on MRI. These results suggest that PET CMRglc measures have the potential to serve as preclinical biomarkers of dementia, useful also for tracking disease progression. This review highlights the role of genetics and FDG PET in understanding the pathogenesis of dementia.

Keywords FDG PET · Dementia · Gene · Alzheimer's disease

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Introduction

Dementias are the most common neurodegenerative diseases and they are increasingly becoming a major public health problem. These diseases are, in fact, one of the major causes of disability in the general population and it is estimated that their prevalence, currently standing at 35.6 million people worldwide, will increase to 115 million by 2050 [1].

The most common form of dementia, affecting over 20 million people worldwide, is Alzheimer's disease (AD). AD is a neurodegenerative disease of the central nervous system mainly found in older adults, with an incidence that increases with age. From a clinical point of view, it is characterized predominantly by initial deficits in episodic memory, followed by progressive involvement of semantic memory, attention, executive function and language skills. Disease progression, lasting an average of 10 years, leads to the death of the individual, usually due to intercurrent infections. The key features of the AD brain are neuronal and synapse loss, and the deposition of extracellular plaques composed of amyloid-β (Aβ) peptides and intraneuronal neurofibrillary tangles consisting of hyperphosphorylated tau protein.

Although the most frequent form is sporadic AD, the rare autosomal and dominant early-onset form of AD

(EOAD) has provided valuable insight into the disease pathogenesis.

Most dementia cases are late onset and are probably linked to both genetic and environmental factors. The most common risk factors include brain injury, diabetes, hypercholesterolemia and obesity. Moreover, recent studies seem to indicate an involvement of cerebrovascular risk factors in the development of a substantial proportion of dementia cases. With regard to the possible role of these risk factors in dementia, data (spanning 10 or 20 years) from large epidemiological studies conducted in Minnesota, Illinois and Indiana and from a US national study showed a substantial reduction in cognitive impairment in the general population, measured using neuropsychological tests, and thus justify cautious optimism over the possible impact of reducing cerebrovascular risk factors in dementia [2].

These data are also confirmed by the results of a Rotterdam study, which provided evidence of a reduction in the incidence of dementia between 1990 and 2005 [3].

Many experts agree that identifying AD early, before abnormal accumulation of amyloid and tau proteins, could provide an opportunity to hinder the progression of the disease.

A number of strategies under study were recently discussed at the 2012 annual meeting of the Society for Neuroscience. Several neuroimaging techniques have been included among the biomarkers of AD; however, scientific evidence is still under development [4].

To develop preventive treatments for AD, it is necessary to identify early biological markers that are predictive of AD. To date, the best-recognized in vivo markers are measures of brain structure and function, as obtained with neuroimaging. The distribution, in the brain, of the PET tracer [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) reflects regional glucose consumption, correlating with cerebral synaptic activity [5]. Since neurodegenerative dementias are characterized by synaptic and neuronal loss, FDG PET is able to consistently reveal significant hypometabolism in several cortical regions.

Brain volume loss as assessed on magnetic resonance imaging (MRI), and reductions in the cerebral metabolic rate of glucose (CMRglc) as measured with FDG PET are sensitive to AD-related brain changes. A crucial question is whether these brain measures can allow preclinical detection of dementia. To understand how AD starts and progresses, it is necessary to follow subjects through normal aging to the onset of clinical symptoms. Several studies have shown measures of brain atrophy directly assessed using MRI techniques, capable of capturing presymptomatic changes in familial forms of AD [6–8].

FDG PET studies have shown that decreased glucose metabolism in AD precedes clinical diagnosis and that the degree of clinical disability in AD correlates closely with the magnitude of the reduction in brain metabolism.

Recent studies have provided evidence of dynamic changes in PET amyloid and FDG imaging at different stages of AD [9]. In order to compare brain atrophy with hypometabolism as preclinical markers of AD, several studies have presented data on presymptomatic mutation carriers from families with known early onset, autosomal dominant AD, i.e. familial AD (FAD) [10]. Presymptomatic FAD individuals have been found to show CMRglc reductions consistent with the expected AD PET pattern, but in the absence of severe atrophy on MRI [11]. These results suggest that PET CMRglc measures could potentially serve as preclinical biomarkers of dementia, useful also for tracking disease progression.

New diagnostic criteria

A few years ago, the results of many years of research allowed an update of the clinical research criteria for dementia and the refinement of guidelines (originally conceived around two and a half decades earlier) for diagnosis of the various forms of dementia [12]. Meanwhile, 2011 saw the publication of recommendations, from the National Institute on Aging–Alzheimer's Association workgroups, on diagnostic guidelines for Alzheimer's disease [13]. These new recommendations are the result of acquisitions obtained through both laboratory and clinical research.

The new criteria proposed a common lexicon for the clinical and research sectors [12], which has generated much debate in the scientific community [14–16]. Developments in the field of biomarkers and the use, alongside traditional genetics, of new more specific and more sensitive techniques were crucial for the development of these new criteria, but also for redefining frontotemporal dementia (FTD) and its subtypes.

Guidelines on the diagnosis and management of dementia disorders recently developed by a European Federation of Neurological Societies (EFNS) study group on dementia, which took into consideration the canonical syndromes and molecular genetic aspects, identify a number of different clinical forms of dementia with different ages at onset and/or durations [17].

Moreover, in accordance with recent EFNS-ENS guidelines on the use of neuroimaging in the diagnosis of dementia [18], structural imaging should be performed to exclude other potentially treatable diseases, to detect vascular lesions, and to identify specific findings to help distinguish between different forms of neurodegenerative dementia.

Neuroimaging is recommended in cases in which the diagnosis remains in doubt. Amyloid imaging is likely to

prove clinically useful in several fields, including the evaluation of atypical AD presentations [18].

Biomarkers

Recent years have provided some important developments in the field of dementia, fundamental in furthering understanding of the pathogenetic mechanisms of the disease. It is now believed that AD pathophysiology started years before cognitive changes are detected and probably before the onset of clinical signs of dementia [19, 20]. Hence, there has emerged an urgent need for reliable diagnostic biomarkers able to detect the disease in a presymptomatic stage. Recent studies have focused on imaging markers or cerebrospinal fluid (CSF) and blood biomarkers for early diagnosis.

The biomarkers currently used for AD are both genetic, such as the pathogenetic mutations in three candidate genes (amyloid-β precursor protein, *APP*; presenilin 1, *PS1*; presenilin 2, *PS2*) and biochemical (amyloid-β and tau proteins in the CSF) [21]. Moreover, the biomarkers of neurodegeneration include neuroimaging correlates of hippocampal atrophy on structural MRI and symmetric decreased metabolism in the temporoparietal regions on FDG PET.

The ^{11}C Pittsburgh compound (PiB) has always been the most validated tracer for imaging amyloid pathology. However, there is now a new tracer, ^{18}F-florebetapir that, thanks to the longer half-life of the radioactive isotope ^{18}F (110 versus 20 min for the ^{11}C of ^{11}C-PiB), has the potential to be used even more extensively both for clinical and research purposes [22].

In a 2003 study involving a family carrying the T122R mutation in PS2 and showing an atypical presentation of dementia, all the biomarkers (the functional neuroimaging investigations, CSF levels of Aβ 1-42, and Tau protein) provided evidence indicating future dementia development [23].

Today, FDG PET has moved from the research arena into clinical practice. Amyloid imaging allows earlier diagnosis of AD and better differential diagnosis of dementia and it also provides prognostic information for mild cognitive impairment (MCI) [24].

The genetics of dementia

The genetic approach to the study of neurodegenerative diseases is undoubtedly the one that has provided and continues to provide the most significant contribution to understand the various aspects of these disorders: their pathogenesis and diagnosis, the therapeutic options, and the important ethical implications.

A search of the PubMed database using keywords such as "dementia" and "genetic" reveals, to date, more than 25,000 papers, almost half of which were published in the past 6 years. The earliest paper, published in 1952, concerns research into the genetics of AD and Pick's disease [25]; one of the most recent contributions is a large collaborative genome-wide association (GWA) study that highlights a new AD locus on chromosome 10 [26]. The list of genetic mutations associated with autosomal dominant forms of familial dementia is getting longer and longer [27].

The extensive study of the genetics of dementia led to the development of a molecular classification of different forms of dementia and now many groups are working to establish the possible diagnostic utility, in dementia, of the biological and genetic biomarkers developed [28].

The genetics of AD

Alzheimer's disease is a genetically complex, multifactorial disease involving many candidate genes [29]. From a genetic point of view, AD can be divided into two different forms: FAD and sporadic AD. Apart from the fact that FAD often has onset at an earlier age and can present some neurological characteristics not generally present in the sporadic form, the two subtypes are clinically indistinguishable. AD can also be divided into two groups by age at onset: early onset (onset <65 years; EOAD) and late onset (onset >65 years; LOAD).

In rare early-onset FAD, different disease-causing mutations have been described. At the time of writing, the Alzheimer Disease & Frontotemporal Dementia Mutation Database lists a total of 231 different fully penetrant autosomal dominant mutations in 517 families around the world (http://molgen-www.uia.ac.be/ADMutations/). These mutations are located in three genes (i.e. *APP*, *PS1*, *PS2*) that have been shown to cause 50 % of all FAD. In particular, 33 pathogenetic mutations for *APP*, 185 for *PS1* and 13 for *PS2* have been discovered [30, 31].

In the more common sporadic form, a locus on chromosome 19, coding for apolipoprotein E (ApoE), has been associated with increased susceptibility. In particular, genetic and epidemiological studies have identified the epsilon 4 (ε4) allele as a major risk factor for the disease, being associated with an increased risk of developing the disease and with a lower age at onset [32].

The ApoE ε4 allele is the only confirmed factor involved in genetic susceptibility to AD, but it is neither necessary nor sufficient to cause the disease [33]. Moreover, according to recent data, the ApoE could be a major gene with semi-dominant inheritance (individuals with a double dose of the ε4 allele have a 35-fold increased risk of developing the disease) [34].

The ApoE ε4 isoform is thought to interact with the mechanisms associated with aging, resulting in deposition in the brain, of aggregated deposits of abnormal proteins; this impairs neurotransmission, thereby hastening the disease process [35, 36]. However, over 70 % of all cases in the general population are associated with this gene, which suggests that numerous other factors, in addition to genetic predisposition, must together contribute to determining the disease [37].

In recent years, the search for other genetic factors has shown associations with polymorphisms in an increasing number of genes, all possibly involved, by interfering with the deposition and clearance of Aβ in the disease pathogenesis [38].

Recent progress in genomic methodology and the availability of large sample sizes have ushered in the era of GWA studies.

From 2005 to the present, many GWA studies have been published and thanks to these studies; several loci associated with various neurodegenerative diseases have been identified.

According to the AlzGene database, GWA studies have identified ten novel loci associated with an increased risk of developing AD, i.e. *BIN1*, *CLU*, *ABCA7*, *CR1*, *PICALM*, *MS4A6A*, *MS4A4E*, *CD33*, *CD2AP* and *EPHA1* [39–42].

The role of all the new genes in the pathogenesis of AD is supported by their involvement in the pathogenetic processes related to neurodegeneration, including the amyloidogenic cascade, tau hyperphosphorylation, apoptosis, oxidative stress, cholesterol and lipid metabolism, and immune inflammatory processes.

Despite these successes, this type of approach has many limitations because these associations do not have a high predictive value and may also lead to the identification of false positives and false negatives. For this type of approach, studying a very large number of subjects is necessary. In fact, whereas several thousand individuals are needed to describe an association with a rare, high-impact variant, the description of a common variant with a low effect requires many thousands of cases and controls [43].

For this purpose, international research groups have organized specific genetic consortia, thus making large collaborative studies feasible.

During 2011, thanks to a group of international researchers, the First International Collaboration on the Genetics of Alzheimer's Disease was established with a view to perform collaborative studies on large numbers of subjects (International Genomics of Alzheimer's Project).

Recent GWA studies have identified *CLU*, *CR1*, *ABCA7 BIN1*, *PICALM* and *MS4A6A/MS4A6E* in addition to the long-established ApoE as loci for AD [39–42, 44].

New findings have recently provided fresh insight into the genetic mechanisms underlying the development of AD.

Starting from the hypothesis that low-prevalence variants showing moderate to high effect may be associated with AD risk, two independent research groups [45, 46] have shown that a rare variant (rs 75932628 encoding an arginine to histidine substitution at residue 47, R47H) in the *TREM2* gene, encoding the triggering receptor expressed on myeloid cells on chromosome 6 (6p21.1-q15), is significantly associated with increased susceptibility to LOAD.

Another recent study has provided evidence that a low-frequency variant of the coding mutation (A673T) in the *APP* gene protects against AD and cognitive decline in the elderly without AD [47, 48]. The discovery of the protective effect of the A673T substitution against AD provides proof of the principle that reducing the β-cleavage of APP may protect against the disease, and supports the clinical usefulness of the current amyloid-directed therapeutic research efforts.

The recent important characterizations of the novel risk factor *TREM2* and the novel protective *APP*-related variant displaying a statistically significant association with AD provide grounds for cautious optimism regarding the results of genetic research.

It has been suggested that families need clinical guidelines to help them navigate the complexities of dementia (in particular AD and FTD) genetics and the processes of genetic testing and counseling [49].

In fact, the diagnosis of progressive disease in a clinically healthy individual is a new but increasingly frequent scenario for the neurologists and geneticists [50], and it is one that carries ethical implications [51] and underlines the importance of genetic counseling. The genetic approach, being able to shed light on the pathogenetic mechanisms of the disease and thus indicate possible therapeutic avenues, is important both from a research and a clinical perspective. For example, a recent study aiming to investigate whether treatment with human anti-Aβ monoclonal antibodies leads to a measurable reduction in the level of Aβ in the brain and to elucidate the mechanism of amyloid reduction provided data on the use of an amyloid-eating drug that removes plaque through phagocytosis [52].

As pointed out by a recent editorial in *Neurology* [53], it is recommended to start treating patients before the disease becomes symptomatic, i.e. to exploit the window, in the preclinical stages of the disease, in which CSF and PET biomarkers correlated with amyloidogenic and neurodegenerative processes are significantly altered.

FDG PET and the genetics of AD

The link between genetic susceptibility and AD could be elucidated by the association of AD candidate genes with alterations in brain functions, which can be assessed by FDG PET.

Several studies support the use of FDG PET as an AD biomarker and, furthermore, as an endophenotype for the assessment of genetic risk factors for AD.

FDG PET undoubtedly has many advantages; however, it could also have some limitations. First of all, metabolism studies are not able to provide information about the pathophysiological mechanisms linking genetic variability to AD susceptibility. In addition, CMRglc is also presumably subject to multiple genetic regulations and affected by environmental factors.

However, despite these limitations, FDG PET deserves to be considered a presymptomatic AD endophenotype, and several studies have already successfully used FDG PET to reveal CMRglc alterations in normal individuals who have a genetic risk of developing AD.

FDG PET and presymptomatic early-onset FAD

Studies of individuals from families with FAD with known genetic mutations have provided unique information about preclinical AD-related brain impairment and they constitute an ideal resource for exploring the relationship between genetic and phenotypic expression of the disease. Several FDG PET studies on presymptomatic FAD subjects showed the presence of regional parieto-temporal, posterior cingulate cortex (PCC) and medial temporal lobe hypometabolism on a background of wide-spread global CMRglc impairment (Fig. 1) [11, 54, 55].

In particular, a previous FDG PET study on presymptomatic at-risk individuals carrying the rare APP mutations (compared to individuals without mutations) reported the presence of parieto-temporal hypometabolism, with additional frontal deficits [56]. Similarly, a recent FDG PET study conducted on carriers of the PS2 mutation demonstrated CMRglc reductions in parietal and precuneus regions, showing progression at follow-up in parieto-temporal and frontal lobes [57].

Interestingly, an FDG PET study of presymptomatic PS1 mutation carriers provided definitive evidence that CMRglc reductions precede not only clinical symptoms but also structural brain changes, showing cortical and medial temporal lobe metabolic reductions, occurring before and exceeding structural brain atrophy observed on MRI. After partial volume correction, CMRglc reductions ranged from 13 % (whole brain) to 21 % (PCC), reflecting true reductions in brain glucose utilization per unit brain volume; after partial volume correction, the medial temporal lobe CMRglc values were reduced to 12 % in the hippocampus and 20 % in the entorhinal cortex [11].

These findings are consistent with and could be explained by the AD pathological cascade model: following the initial deposition of amyloid plaques, the dominant process is represented by neuronal and synaptic dysfunction, which could be studied using FDG PET. The neuronal loss that ultimately causes atrophy measurable with MRI appears only later [58].

FDG PET and ApoE-associated genetic risk

The ε4 allele of the ApoE gene is a widely recognized genetic risk factor for AD and the association between the ApoE ε4 allele and AD risk has been reported in hundreds of studies. The ApoE ε4 genotype is considered a risk factor since almost 40 % of LOAD patients have at least one ApoE ε4 allele; moreover, a copy of the ε4 allele is found in about 25 % of Americans and in 33 % of those with a reported family history of dementia in a first-degree relative. Two copies of the ε4 allele are found in 2–3 % of Americans and about 5 % of those with a reported history of dementia in a first-degree relative [59].

To date, many FDG PET studies have been published, examining the effect of the presence of the ApoE ε4 allele on CMRglc and confirming, study after study, the association between metabolic impairment, assessed by FDG PET, and AD genetic risk factors in cognitively normal subjects. FDG PET studies in non-demented individuals report that, as compared to ε4 non-carriers, ApoE ε4 homozygotes (therefore, with a particularly high risk of developing AD) have a significantly reduced CMRglc in the same brain regions as clinically affected AD patients, including the posterior cingulate/precuneus, parietal, temporal and prefrontal regions [59]. As compared to ε4 non-carriers, ApoE ε4 heterozygotes show similar, but milder, hypometabolism within the same brain regions found to be affected in AD patients and in ApoE ε4 homozygotes [59–62]. There is evidence that the metabolic reductions in ApoE ε4 carriers are more progressive (25 % decline in CMRglc over a two-year interval) and correlate with the reductions in cognitive performance [63].

Moreover, CMRglc abnormalities have been detected even earlier, in 20- to 40-year-old ApoE ε4 carriers [64], making them the earliest brain abnormalities yet found in living subjects at risk of AD, detected many years before the estimated median age of dementia onset in ε4 heterozygotes.

The ApoE ε4 allele also contributes to heterogeneity in MCI patients by regionally affecting brain metabolic activity, so that MCI ApoE ε4 carriers present a more extensive CMRglc impairment than non-carriers, reflecting the known ApoE ε4-related increased vulnerability to

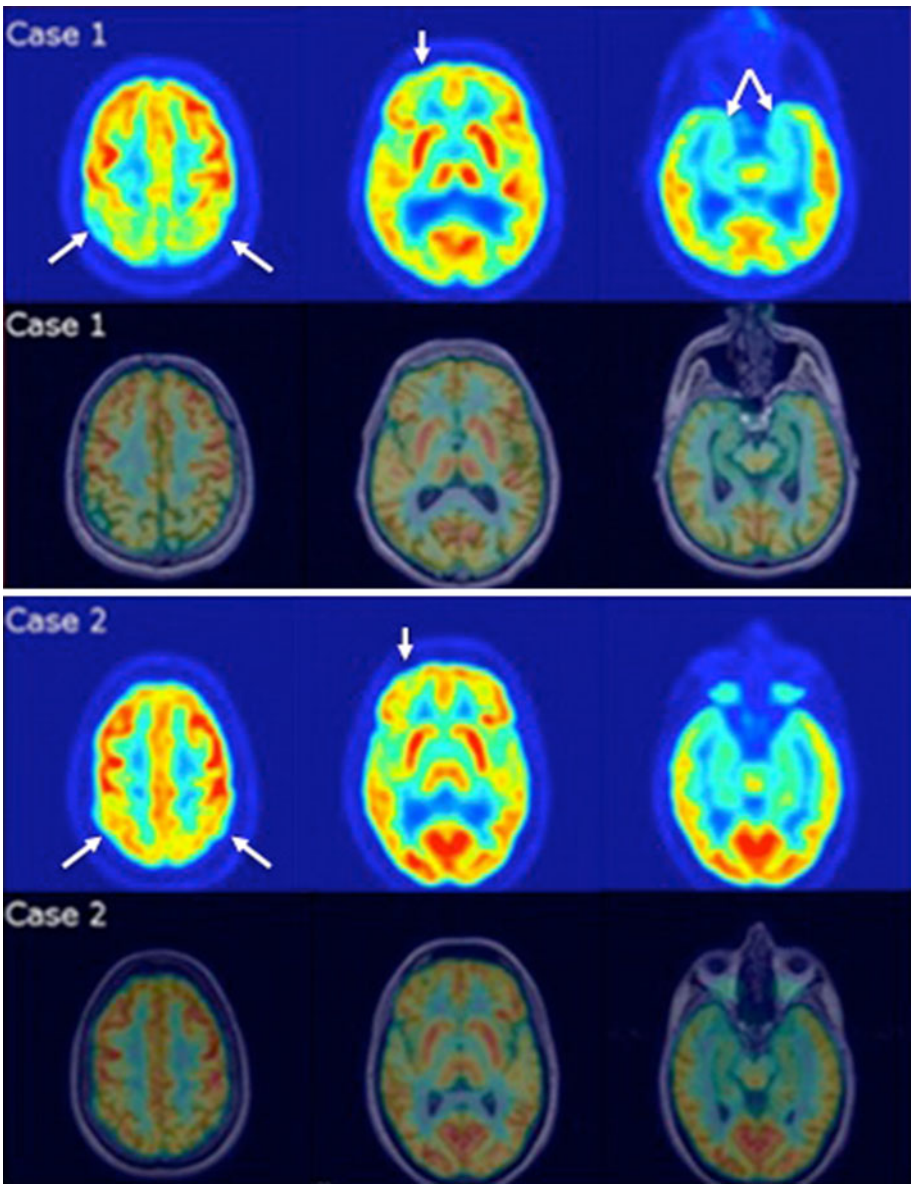

Fig. 1 FDG PET scans (*first row*) and MRI co-registration of two preclinical early-onset FAD siblings with the APP 717 Val-Ile mutation. *Case 1* a 60-year-old male with deficits in short- and long-term memory and in visuospatial and executive functions showed mild parietal and hippocampal atrophy associated with severe parietal hypometabolism and moderate CMRglc reductions in the frontal cortex and hippocampus. *Case 2* a 48-year-old female showed only long-term memory deficits and no significant atrophy on the MRI scan. However, the FDG PET scan demonstrated the presence of mild parietal and inferior frontal hypometabolism (*arrows* indicate the hypometabolism)

dementia [65]. In particular, the hypometabolism usually found in parietotemporal and temporal regions in MCI patients extended to the frontal and anterior cingulate cortex in MCI ApoE ε4 carriers. A recent study showed a differential effect of ApoE genotype on amyloid load and glucose metabolism in AD patients [66], confirming earlier reports.

FDG PET and maternal family history of AD

FDG PET studies have also proved to be useful in estimating the increased risk of future AD in another cognitively normal at-risk population, namely subjects with a maternal family history of AD. Indeed, recent reports provided evidence for phenotypic CMRglc differences between cognitively normal individuals with a maternal, paternal or negative family history of AD [67], even preceding the structural brain abnormalities observed on MRI [68]. In particular, individuals with a maternal history of AD were found to show CMRglc reductions in typically AD-vulnerable brain regions, namely the parietotemporal, posterior cingulate/precuneus, medial temporal and prefrontal cortices, as compared to individuals with no family history and those with an AD-affected father [67]. The hypometabolism occurred within the group of maternal AD subjects independently of the subject's age, gender, years of education and ApoE genotype.

Over a two-year follow-up, CMRglc impairment in maternal AD individuals was found to be progressive [69], with longitudinal CMRglc reductions in the posterior cingulate/precuneus, parietotemporal and frontal cortices. In contrast, individuals with an AD-affected father and those

with no family history of AD showed longitudinal CMRglc reductions only in the frontal cortex, which is a typical effect of aging.

FDG PET and the KIBRA gene

KIBRA is a cytoplasmic protein that is highly expressed in the brain and is a binding partner of dendrin, a putative modulator of synaptic plasticity. There are two allelic variants of the *KIBRA* gene (T and C), resulting in three possible genotypes: TT, CT and CC. GWA studies and several replication studies [70, 71] demonstrated that *KIBRA* T allele non-carriers (CC genotype) had lower episodic memory performance compared to *KIBRA* T carriers (CT and TT genotypes).

Since memory impairment is the cardinal clinical feature of AD, the next step was to investigate the possibility of an association between AD and *KIBRA*. Corneveaux and colleagues [72] tested this hypothesis using data from FDG PET, as an endophenotype. *KIBRA* T non-carriers showed significant CMRglc reductions, compared to *KIBRA* T carriers, in the same brain regions preferentially affected by AD, including the precuneus and PCC.

These FDG PET findings provide a foundation for a common molecular mechanism contributing not only to successful episodic memory performance but also to the predisposition to AD, opening possible future perspectives for memory-enhancing, AD-modifying and AD risk-reducing therapies.

Genetics of FTD

First described over 100 years ago, today we can refer to several clinical forms and at least 16 different pathological subtypes of FTD [73].

FTD refers to a disease spectrum including the behavioral variant FTD (bvFTD), primary progressive aphasia (PPA), progressive supranuclear palsy/corticobasal degeneration syndrome (PSP/CBDS), and FTD with amyotrophic lateral sclerosis (FTD-ALS).

The international consortia for the two main syndromes, bvFTD and PPA, have recently revised the diagnostic criteria and published consensus criteria [74, 75], including neuroimaging and genetics.

The first evidence of a genetic cause of familial FTD was provided 18 years ago with the demonstration of a linkage to chromosome 17 in a familial form with autosomal dominant parkinsonism [76]; the most recent evidence is a GGGGCC expansion in *C9orf72*, a major cause of FTD and ALS [77, 78].

To date, the familial forms of FTD [79] are explained by the seven genes (*C9orf72*, *CHMP2B*, *FUS*, *GRN*, *MAPT*, *TARDBP*, *VCP*), in which 193 pathogenetic mutations have been described (http://www.molgen.ua.ac.be/ADMutations). All the genes code for a protein including *C9orf72* [80], an open reading frame coding for a protein recently characterized and located on chromosome 9p21 [77, 78, 80]. The most revolutionary finding on the genetics of FTD is that these mutations and expansions concern a very high percentage of families in the world. Indeed, there are now more than 900 families in the world with mutations associated with FTD. A flow chart for FTD genetic testing was recently published [81].

There also exist phenotypic characterizations of FTD linked to the mutations in *GRN* and *C9orf72* and in which an important contribution is made by neuroimaging [82]. In particular, a study in monozygotic twins carrying a 4-bp deletion (c.388_391delCAGT) in exon 4 of *GRN* reported strong clinical, neuroimaging, and serum progranulin level similarities, demonstrating the importance of shared genetic profiles beyond environmental influences in the symptomatic expression of the disease [82]. In a recent case report, brain FDG PET demonstrated mild hypometabolism involving the medial frontal and lateral temporal lobes, the left more than the right, which progressed over time. This case was subsequently confirmed to have the *C9orf72* expansion, thus highlighting the need to consider mutations in the FTD-associated genes when a familial disorder is suggested and neuroimaging studies reveal findings atypical of an AD pathophysiological process, despite the typical anterograde amnesic syndrome [83].

Different research centers worldwide are involved in the genetic approach to FTD. The work of GENFI (http://www.ucl.ac.uk/drc/research/current-studies/genfi), a multicenter collaborative consortium for tracking the evolution of genetic FTD and its associated disorders from their earliest stages, is ongoing.

The main aim of GENFI is to recruit and follow a well-characterized and uniformly studied cohort of individuals affected with or at risk of developing the major genetic forms of FTD with mutations in the *MAPT* or *GRN* genes or expansions in the *C9orf72* gene.

The innovative aim of the consortium is to derive sample size estimates and outcome measures for future natural history studies and clinical trials of disease-modifying therapies.

Conclusions

Several studies describe the contribution made by FDG PET and genetics to understand the pathogenesis of dementia. The reported data on presymptomatic mutation carriers from families with known early-onset autosomal dominant AD (FAD) show reductions in the cerebral

glucose metabolism consistent with the typical AD PET pattern.

These reported results indicate that PET brain metabolic measures have a potential role to play as preclinical biomarkers for genetic dementia and for tracking disease progression.

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Conflict of interest B. Nacmias, V. Berti, I. Piaceri, S. Sorbi declare that they have no conflict of interest.

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