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Do depressive symptoms cause intellectual decline among elderly?

An 8-year longitudinal study

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This study examined the relationship between depressive symptoms and subsequent intellectual decline in Japanese elderly. Subjects (age=65-79 : n=805) comprised the first wave participants of the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA), and were tested 5 times and followed for about 8 years. Depressive symptoms at baseline were assessed using the Center for Epidemiologic Studies Depression scale (CES-D), and intellectual changes for 8 years were assessed with the Wechsler Adult Intelligence Scale-Revised Short Forms (WAIS-R-SF), including its Information test, Similarities test, Picture Completion test and Digit Symbol test. General linear mixed model analyses revealed that depressive symptoms at the time of the baseline measurement had affected 8 year changes of 'Information', 'Similarities' and 'Digit Symbol' test scores. In contrast, depressive symptoms were not associated with subsequent decline in 'Picture Completion' test scores. These results suggest that depressive symptoms among elderly may cause decline in levels of general factual knowledge, logical abstract thinking and speed of information processing.

Key words : depressive symptoms, intelligence, longitudinal study, general linear mixed model

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認知症の実態と予防の重要性

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第 18 回日本未病システム学会学術総会

●シンポジウム 4「認知症予防の最前線―現在そして将来，どこまでできるか―」

認知症の実態と予防の重要性

下方　浩史 [1)]
安藤　富士子 [2)]

1. はじめに

認知症にはまだ根本的な治療はなく，病状は長期にわたって慢性に進行して重症に至ることが多い．進行すると徘徊や暴力などの問題行動もみられ，末期には寝たきりとなり，誤嚥性肺炎や褥創などの合併症も生じて，経済的，社会的な負担がきわめて多い．認知症の出現頻度は高齢になるほど高くなるので，わが国の社会の高齢化に伴って今後急速に患者数が増大し，介護や医療への費用負担が急騰することが予想される [1-5]．このため，認知症罹患の実態を把握し，認知症の予防を目指すことはわが国にとっての緊急の課題となっている．

2. 認知症の有病率

認知症の有病率や罹患率に関しての疫学統計が，今後の医療費予測や高齢者の介護・福祉のあり方，医療政策に関して，重要な意味を持つと思われる．しかし，今まで認知症の疫学調査は十分には行われてこなかった．それは認知症という疾患の持つ特殊性により，調査に多くの困難を伴うためである [1-4]．

認知症の有病率は比較的低いので正確な統計データを得るためには対象人数を多くしなければならない．65 歳以上の高齢者は日本全体では現在約 3,000 万人であり，推定有病率の 1 %の違いが患者数推計では 30 万人の差となる．例えば，有病率 15 %を 14 ～ 16 %の信頼区間で得るためには 4,898 名の対象者が必要である．また，アルツハイマー病，血管性認知症，レビー小体型認知症，前頭側頭葉脳変性などの病型別有病率についての検討を加えるためには，さらに多くの対象者が必要である．

認知症の診断を行うためには専門的知識が必要であり，場合によっては MRI や PET などの検査や剖検が診断のためには必要となる．認知症患者やその家族は調査に対して消極的なことが多い．認知症は高齢者に多いため，身体機能の低下を認める者が少なくなく，訪問による検査などが必要で，実際の調査が思うようにいかないことも多い．また，認知症の有病率を調べる場合，調査地域の高齢者の年代分布によって有病率が異なる可能性がある．地域在住者を調査しても，問題行動のある認知症患者は施設に入所しているために，有病率が低く出てしまうことも考えられる．

認知症の有病率については 1970 年代から全国のさまざまな地域において疫学調査が行われてきたが，調査は県や市町村の地域ごとに行われており，最近まで全国規模での調査は行われていなかった．日本初の全国調査は，厚生労働省認知症対策総合事業「認知症の実態把握に向けた総合的研究」として実施された [6]．まず 2009 年から 2010 年にかけて全国 7 ヵ所で 65 歳以上の住民を対象として行われた（図 1）．訪問調査員による 1 次調査と専門医による 2 次調査を基本として，さらに頭部 MRI による脳萎縮や血管性病変の評価なども行い，精度の高い診断を目指した．全国での調査結果から 2008 年の日本の人口を基準にして推定された有病率は 12.4 ～ 20.2 %（平均 14.4 %）であった．2008 年度の 65 歳以上の全国人口 2,822 万人から，認知症患者数は 406 万人と推定された．しかし，施設入所者などを加えればこれよりも患者数はさらに多い可能性がある．従来の方法での患者数推計では 208 万人とされていたが，患者数は少な

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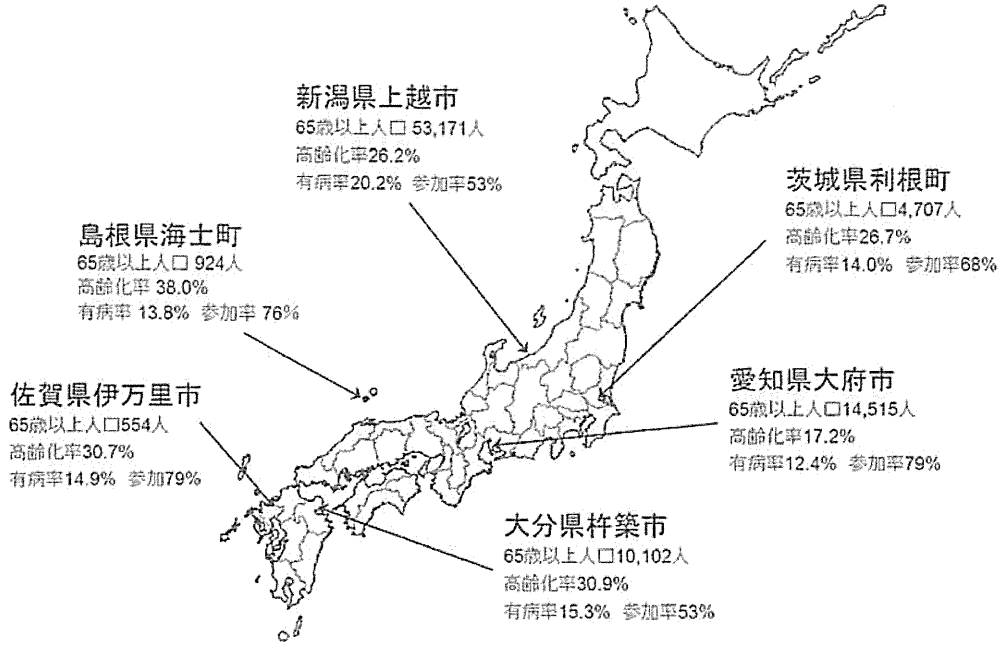
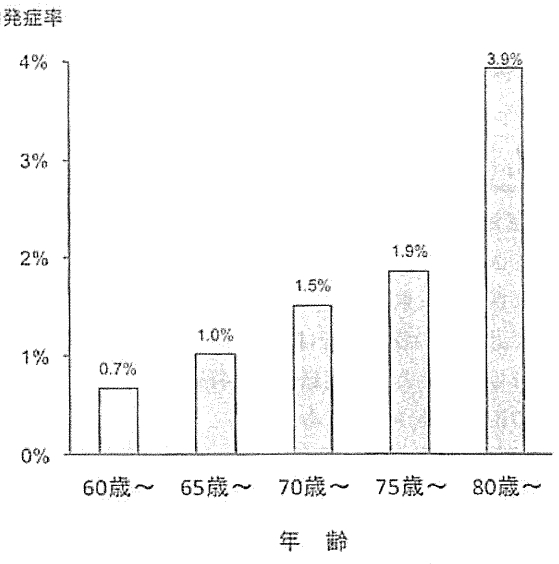


■図 1　認知症有病率全国調査結果（2008 年度日本全国の人口構成に基づく）

くともその約 2 倍存在することになる．

3. 認知症の発症率

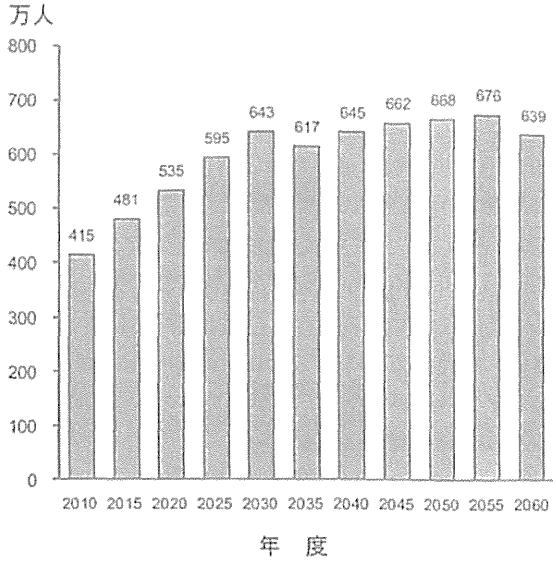
発症率を推定するためには，同一対象集団について複数年にわたっての繰り返しの調査が必要であり，有病率の推定よりも難しく，わが国の疫学調査の結果では認知症の発症率の推定はほとんど行われていない．われわれは，無作為抽出された地域住民を長期にわたって追跡した「国立長寿医療研究センター・老化に関する長期縦断疫学研究（NILS-LSA）」[7] のデータを用いて 8 年間の縦断的な検討から認知症の発症率の推定を行った（図 2）．その結果では，60 歳以上の地域住民の 1.5 %が毎年認知症となっていた．年齢が高くなるほど発症率は上昇し，80 歳以上では毎年 3.9% が認知症となっていたという結果であった．



■図 2　認知症の年間発症率（「国立長寿医療研究センター・老化に関する長期縦断疫学研究（NILS-LSA）」の 8 年間の縦断的観察から）

4. 将来推計

人口の高齢化に伴う認知症患者数の将来推計を行ってみた．性別・年齢別の認知症有病率は今回の全国調査の結果を用い，人口推計は国立社会保障・人口問題研究所の平成 24 年度 1 月推計を用いた．2010 年度の 65 歳以上の認知症推定患者数は全体として 415 万人で，



■図3 認知症患者数の将来推計（人口推計は国立社会保障・人口問題研究所の平成24年度1月推計を用いた）

有病率は約14.1パーセントであると推定される．今後，高齢者人口，特に後期高齢者の人口が急増し，患者数は2020年度に535万人，2030年度には643万人と，これからの20年間にアルツハイマー病の患者数は1.5倍に大きく増加すると予測される（図3）．

5. 認知症の経過と予後に関する統計

認知症は長期にわたって慢性に進行していくことが多い．このことが社会に大きな負担となる要因のひとつである．わが国の在宅認知症患者の5年後生命予後調査では，66％～86％の生存率が報告されており[3]，認知症の発症から死亡までの全経過は現在のところ7年から10年程度だと思われる．米国での認知症患者の大規模な追跡調査では，発症からの生存年数は10.5年，診断からの生存年数は5.7年であった[8]．他の研究でも認知症患者の診断後の生存年数は5年から9年であった[9-12]．米国の国立老化研究所（NIA）からの報告では，生存期間は年齢によっても大きく異なり，75歳までに診断されたアルツハイマー病患者の生存年数は診断後7年から10年であったが，85歳以降に診断された場合は3年未満の生存期間であった[13]．しかし今後，介護技術，医療の進歩により死亡までの期間は長くなっていくと思われる．

6. 認知症予防とのその重要性

世界有数の長寿の国であるわが国は急速に高齢化が進み，それとともに認知症患者の数も増大していく．今後15年間で認知症にかかわる介護費用は大きく増加し，年間10兆円に達するとも予想される．高齢化が進む一方で，少子化も進み，介護にかかわることのできる労働人口は激減する．このままでは認知症によって日本の社会が崩壊すると言っても過言ではない．認知症を予防していくことが，今後の日本にとっては極めて重要であろう．

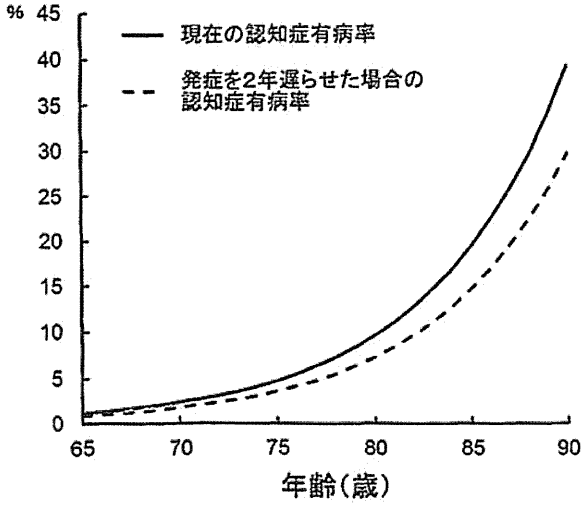
アルツハイマー病予防の切り札としてワクチンの開発が進められている．ワクチンはアルツハイマー病を引き起こすアミロイドβ蛋白の蓄積を予防するような作用を持つとされるが，脳炎などの重篤な副作用も報告されている[14]．また中年以降ではすでにアミロイドβ蛋白は蓄積されてしまっており，ワクチンは30歳以前に使用しなければ効果はないという．たとえワクチンが開発されたとしても，50年後の認知症発症を予防するために，有効性が不明でしかも脳炎などの副作用のリスクがあるワクチンを若者が使用するかどうかは疑問である．

認知症は生活習慣病でもあり，生活習慣の改善である程度の予防が可能である．生活習慣は血管性認知症だけでなくアルツハイマー病の発症と関連している可能性がある．特に食事は毎日の生活の中で繰り返され，影響が大きい．認知症の予防にはビタミンE，ビタミンC，カロテノイドのような抗酸化ビタミンが有用であり，中でも抗酸化作用を持つビタミンEが期待される[15,16]．葉酸やビタミンDの認知症予防作用も明らかにされてきている[17,18]．多価不飽和脂肪酸，特にn-3系のドコサヘキサエン酸（DHA），エイコサペンタエン酸（EPA）は認知症の予防に有用であり[19,20]，またアラキドン酸についても有用性の研究が進んでいる[21]．食事のパターンとしては野菜や魚類をバランス良く摂ることが重要である．適度な飲酒，特にワインが認知症の予防に有用であり[22]，喫煙は多くの研究で認知症の危険因子となることが報告されている[23]．運動によって認知症やアルツハイマー病のリスクを下げることは多くの論文で報告されている[24]．運動が糖尿病，脂質異常症，高血圧症を

予防し，その結果，動脈硬化の進行を遅らせて認知症の発症リスクを下げると考えられるが，運動自体が脳神経のネットワーク機能を強化し，認知症の発症を防ぐという直接的な効果も推測されている．

認知症の素因としての遺伝子多型の研究も進み始めている．しかし危険因子間の相互作用，特に遺伝子と生活習慣との相互作用についてはほとんど研究が進んでいない．例えば食塩の摂取により血圧が高くなる遺伝子多型は，塩分感受性遺伝子多型として知られている．特定の遺伝子多型を持つ人は塩分を多く摂ると高血圧症になりやすく，それが認知症のリスクとなる．このような遺伝子多型とライフスタイル，環境因子との相互作用は数多い．認知症に関連する遺伝子多型は直接に認知症を引き起こすわけではなく，むしろライフスタイルや環境因子の影響を修飾することで認知症の発症に関与するものと考えられる．特定の遺伝子多型の認知症発症寄与率は集団全体の生活習慣などによって異なると考えられ，このために集団が異なれば結果も異なることになり，遺伝子多型の影響について一定の結果が得られにくい．こうした，危険因子相互の作用について明らかにしていくには，大規模な一般住民で追跡を行い，生活習慣や認知機能の変化を継続的に観察する縦断的研究が必要である[25]．

医薬品の開発などで認知症の発症を完全に予防できなくても，仮に2年間だけでも遅らせるようなことが出来れば，各年齢の認知症の有病率は，2歳若い年齢に相当する有病率になると期待できる（図4）．65歳以上の全人口に対して，実際の年齢よりも2歳若い年齢の有病率を使って患者数を計算すると期待患者減少数は33万人，医療費削減効果は2,000億円，介護費用削減効果は7,700億円となる．さらに，家族が介護のために職につけなかったり，本人が病気のため社会参加が出来なかったりした損失も加えると合計の費用削減効果は，年間約2兆円にも達する．こうした経済的な効果を考えると，認知症性疾患の基礎研究，臨床研究へのわが国における研究費の支出は驚くほど少ない．



■図4　年齢別にみた認知症の有病率と認知症の発症を2年遅らせた場合の有病率
期待患者減少数は33万人，医療費削減効果は2,000億円，介護費用削減効果は7,700億円と推定される．

7. 最後に

世界でも類をみない速度で高齢化が進んでいるわが国にとって，認知症患者の増加は大きな社会問題である．今後15年間で認知症にかかわる介護費用は倍増し，年間10兆円に達するとも予想される[5]．高齢化が進む一方で，少子化も進み，介護にかかわることのできる労働人口は激減する．このままでは認知症によって日本の社会が崩壊すると言っても過言ではないかも知れない．一方で，認知症の発症を2年遅らせることができれば，それだけで年間2兆円もの費用が削減できる可能性がある．

日本人で比較的多いと言われる血管性認知症は，喫煙や高脂血症，高血圧，糖尿病などが要因となっており，禁煙や減塩，身体活動，食生活の改善などである程度予防することが可能である．最近ではアルツハイマー病も生活習慣病であると言われ始めており，生活習慣の改善である程度の予防が可能であろう．認知症の素因としての遺伝子多型の研究も進み始めている．こうした研究の推進により高齢者の知的機能を守り，高齢者の社会参画を可能にしていくことが是非とも必要であろう．

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Review Article

Aging-related Genes

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Abstract

Genetic factors affect an individual's maximum possible lifespan. In humans, the average lifespan is about 40 years shorter than the maximum lifespan. Any gene that influences the development of a disease is called a disease-susceptibility gene. The impacts of disease-susceptibility genes on aging and average lifespan would be much stronger than the impacts of aging genes on maximum lifespan. Multiple genes are associated with the aging process and age-related diseases, and gene-to-gene interactions are important, as are gene-environment interactions; the interactive effects of lifestyle are especially important. A broad-scale, long-term longitudinal study that includes detailed examinations of medicine, nutrition, physical activity, and psychology in a community-dwelling population is necessary for comprehensive genetic epidemiological study of aging and age-related diseases. Risk of disease to individuals can be more effectively assessed with data on genetic, lifestyle, and environmental factors. The most appropriate health education, lifestyle modifications, and health examination protocols could be then implemented in an individualized manner to prevent diseases and aging processes based on these personalized risk assessments.

KEY WORDS: aging, gene, epidemiology, longitudinal study, lifespan

Aging and genes

Japan is the world leading country with long living poeple. Nevertheless, until recently, few Japanese people lived more than 100 years. However, the number of centenarians has recently begun to increase rapidly; in 2012, there were 51,376 men and women aged 100 years or older in Japan. It is no longer inconceivable for a regular person to live for 100 years or more.

The lifespan of individual organisms varies based on species. The maximum lifespan for humans is currently 120 years, at most. The maximum lifespan in each species is determined by genes. Do longevity genes that increase maximum life-span exist? If such longevity genes exist, what is the function of these genes in the human body? Perpetual youth and longevity is a dream of people worldwide, and extensive research is currently being performed to clarify the mechanism of aging using new molecular and genetic methodologies [1)] to identify for longevity genes.

Search for an aging gene

Progeria (Hutchinson–Gilford progeria syndrome) is a rare genetic disease with symptoms that resemble the acceleration of the regular aging process [2)]. The first symptoms manifest in neonates and infants. In one year, a patient with progeria undergoes physical aging equivalent to that requiring over 10 years in an unaffected person. The average lifespan of patients with progeria is about 13 years. The incidence of progeria is very low, at only 1 person in every 4 to 8 million live births. The typical symptoms of progeria are growth insufficiency, a localized scleroderma-like skin condition, wrinkled skin, loss of eyesight, hair loss, atherosclerosis, cardiovascular disease, and renal failure. However, cognitive development and function are usually normal. A point mutation in position 1824 of the lamin A (LMNA) gene has been identified as the cause of progeria [3)].

Werner syndrome, also called adult progeria or progenoid syndrome, is another very rare genetic disease characterized by the appearance of premature aging. Symptoms of Werner syndrome are short stature, low body weight, absence of a teenage growth spurt, graying of hair, bilateral cataracts, hoarseness of the voice, and thickening of the skin. These symptoms appear after the age of 10. Patients with Werner syndrome generally die of atherosclerotic disease or cancer sometime between the ages of 40 and 60. In humans, Werner syndrome is an autosomal recessive disorder caused by a point mutation in the WRN gene on chromosome 8 [4)]. About 1,200 cases have been reported, and 80% of these patients are Japanese.

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The incidence of Werner syndrome is 3 per 100,000 live births in Japan.

The LMNA and WRN genes, which are responsible for progeria and Wener syndrome respectively, cause pathological aging processes, but do not regulate normal aging processes. The frequency of genotypes unrelated to lifespan did not differ between younger people and older people in a cross-sectional study [5] (*Fig. 1-A*). However, the frequency of certain genotypes changes with aging. A genotype with a high frequency among older people could represent a "longevity genes" that serves to prolong lifespan or to protect against age-related diseases (*Fig. 1-B*). In contrast, a genotype with a lower than average frequency among older people could represent an "aging gene" or a "gene resulting in shorter life expectancy" (*Fig. 1-C*).

Table 1 shows a list of genes associated with longevity based on the findings of a cross-sectional study of age difference in genotype frequency [5]. Most of these genes are related to a molecular pathway involved in nutrient metabolism, especially lipid or glucose metabolism, or in endocrine regulation.

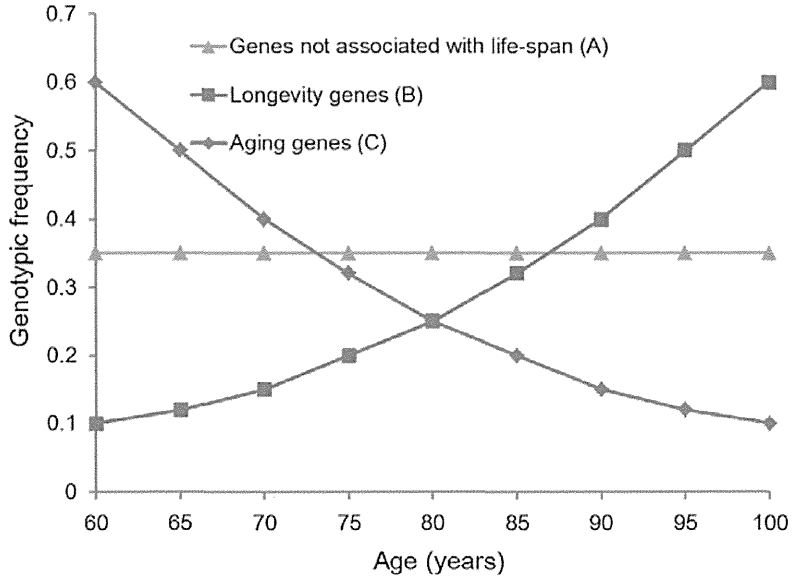

Fig. 1. **Genotypic frequency by age in genes not associated with lifespan (A), longevity genes (B), and aging genes (C) (Modified form Barzilai *et al.*, 2010 [5]).**

Table 1 Genes associated with longevity

Gene	Longevity	Relevant biological action	Chromosomal loci
Klotho (KL gene)	+	Insulin sensitivity, modulation of IGF-I and vitamin D	13q12
Silent mating type information regulation 2 homolog 1 (SIRT1)	+	Regulates epigenetic gene silencing and suppresses recombination of rDNA, associated with insulin action/sensitivity	10q21.3
Catalase (CAT)	+	Antioxidant that protects cells from hydrogen peroxide	11p13
Mammalian target of rapamycin (mTOR)	−	Modulates insulin, IGF, and mitogen function	1P36
IGF-I/insulin (FOXO)	−	Transcription factors that take part in cell growth and differentiation	12q23–23
GH	−	Stimulates growth, production of IGF-I	17 q22-q24
TSHβ	+	Production of TSH	1p13
Thyrotropin receptor (TSHR)	+	Production of T4 and T3	14q31
CETP	+	Facilitates the transport of cholesteryl esters and triglycerides between the lipoproteins	16q21
APOC-3	+	Inhibits lipoprotein lipase and hepatic lipase	11q23.1-q23.2
Adiponectin (AdipoQ)	+	Modulates glucose and fatty acid metabolism	3q27

Modified form Barzilai *et al.*, 2010 [5]

Aging genes and disease susceptibility genes

It is very rare for a human being to live 120 years; most people die from one of many diseases before reaching 120 years of age. Currently, the average human lifespan is thought to be about 40 years shorter than the maximum lifespan. Several lifestyle-related diseases, such as dyslipidemia, hypertension, diabetes, atherosclerosis, and cardiovascular disease, accelerate the aging process. The relationship between atherosclerosis and aging is particularly strong, as indicated by "a man is as old as his arteries". Susceptibility to lifestyle-related disease is influenced by genetic factors. Any gene that influences the development of disease is known as disease-susceptibility gene. The impact of disease-susceptibility genes on aging and average lifespan is thought to be much larger than the impact of aging genes on maximum lifespan.

Although disease-susceptibility genes determine the susceptibility of an individual to disease, including lifestyle-related diseases, a person with a specific disease-susceptibility gene does not always have the disease. Lifestyle or environmental factors might have much stronger effects on pathogenesis than any of the direct effects of the gene. For example, it should be possible to develop a new method for preventing a disease by investigating differences in lifestyle or environmental factors between individuals with and without disease in a group with a specific disease susceptibility allele. Moreover, investigation of longitudinal changes in modifiable risk factors such as lifestyle should be useful. A better understanding of changes in the incidence of a disease should be helpful for preventive genetic counseling; for example, a person with a specific disease-associated genotype may be able to reduce their personal risk of developing the respective disease if they double their physical activity.

Molecular epidemiology of aging

Genotypes related to aging or age-related disease are, in most cases, not single but multiple, and effects of genotypes are influenced by gene-to-gene interactions and gene-environment interactions. Thus, the analysis of genotypes is often difficult [6].

Case-control or association studies of genetic factors that affect aging or age-related diseases compare the frequency of genotypes in a group of cases with those in a control group. Usually, a relatively small number of cases and controls are examined in a case-control study. To date, many association studies have been conducted to identify genetic factors that affect or cause diseases and clinical condition. However, in most of these studies, gene-gene interactions and gene-environment interactions were not examined.

Affected sib-pair linkage analysis is a type of genome-wide analysis in which researchers study sib-pairs that are affected by a specific disease to identify disease-causing alleles [7]. Although significant linkage can be located in specific loci, identification of the actual disease-causing allele is usually difficult.

Calpain-10A, a member of the calpain-like cysteine protease family, was identified as a type 2 diabetes susceptibility gene in a genome-wide screen of affected sib-pairs of Mexican-American descent [8]. However, findings from other studies indicate that no association between the calpain-10 gene and diabetes exists in other population [9,10]. The results often differ based on the quality of the cohorts, especially for diseases such as diabetes, as numerous genes are related to glucose metabolism and obesity.

Findings based on affected sib-pair linkage analysis can be highly problematic. Collecting a large sample of sib-pair cases is often difficult, environmental factors are usually excluded, and the required genome-wide analyses are very costly. Association studies are better suited for the investigation of aging and age-related diseases because these involve many genotypes and many environmental factors. A large cohort is necessary for such analyses because each disease-related genotype may contribute a small amount to the onset of disease and because there are usually significant interactions with lifestyle and environmental factors. For example, in the analysis of dyslipidemia, contribution of genotype should be controlled for age, body size, diet, physical activity level, and among other factors. Multivariate and longitudinal analyses that account for changes in many examination results are essential in large cohort studies.

Epidemiologists and biostatisticians with experience in clinical medicine and human genome studies should develop methodologies for comprehensive and systematic assessments of many genotypes, lifestyles, and environmental factors in studies of molecular epidemiology. A large number subjects are necessary in epidemiological analyses of the associations between a disease and combinations of relevant genotypes. For example, in the case of combination of two genotypes with 10 percent mutation rate, the subject with both mutations is only 1 percent. To assess interactions between rare mutations at two different genes, a larger number of subjects are necessary than single mutation.

Based on whole-genome sequencing, the human genome encodes 30,000 genes, and in many cases, a single gene is highly pleiotropic because it has multiple roles and functions in multiple organs. For example, variants in the apolipoprotein ε4 gene are associated with lipid metabolism and atherosclerosis [11], and with Alzheimer's disease [12] and with osteoporosis [13]. A single allele of a gene may influence the aging process as well as the incidence of multiple age-related diseases, and the effect of the allele may be influenced by lifestyle, environmental factors, or both.

For the above-mentioned reasons, at least 2,000 middle-aged or elderly men and women should be selected, if possible, from a community-dwelling population as a basic cohort for a genetic epidemiological study of aging and age-related disease. Many alleles and candidate genes should be genotyped or, if possible, a genome-wide analysis of single nucleotide polymorphisms should be performed, and various life and environmental factors, medical findings, and disease markers should be assessed in a systematic way for each individual in the cohort. Moreover, for the assessment of time-dependent changes in lifestyle choices and environment factors, a comprehensive longitudinal study in which the subjects are observed repeatedly over time is desirable.

Research on the association of genotypes with common age-related diseases or disabilities that is controlled for many background factors can be accomplished with a nested case-control study design in which subjects with and without disease or disability are in the basic cohort. Research on genetic associations with differences in clinical parameters such as blood pressure, serum cholesterol level, and bone mineral density are also possible. For important geriatric diseases including Alzheimer's disease, Parkinson's disease, and femoral neck fracture, it is difficult to recruit enough affected patients from a single community-dwelling population to conduct a genetic association study. However, case-control study design is feasible if the patient group with the disease is recruited from collaborating hospitals and the control group without the disease is selected from the basic cohort.

Longitudinal epidemiological studies

Accumulation of basic data on aging is indispensable for the molecular epidemiological study of aging and age-related disease. The National Center for Geriatrics and Gerontology (NCGG) Research Institute (former National Institute for Longevity Sciences: NILS) is the leading national research center for aging and geriatrics; it is located in Obu City in the suburbs of Nagoya, Japan. In 1996, the Laboratory of Long-term Longitudinal Studies was established within the Department of Epidemiology, NILS; the initiative was focused on a new longitudinal study of aging in Japan. In October 1997, a trial run of the examinations was conducted, and in November 1997, we started the NILS-Longitudinal Study of Aging (NILS-LSA), a large-scale and comprehensive longitudinal study of aging in Japan [14]. Every day, six to seven participants were examined at the NILS-LSA Examination Center (***Fig. 2***). The first wave of the examinations finished in April 2000, and 2,267 participants (both male and female) had completed the examinations. The participants were examined every 2 years, and in July 2012, the seventh wave of examinations was completed.

The research area was defined as the neighborhood of NCGG, which included Obu City (population 79,000) and Higashiura Town (population 48,000). This area is located south of Nagoya, and is a bedroom town and also an industrial area of the Toyota group, and the area has many orchards and farms; therefore, the research area included both urban and rural characteristics. The research area is located at the center of Japan, and the climate is close to the average for all of Japan. We examined how representative this area is of Japan by conducting a national postal questionnaire of prefecture-stratified random samples of 3,000 households from all prefectures in Japan, and found that the lifestyle choices in the research were typical of all areas in Japan. Therefore, we expected that the results of the examinations in this area will be representative of Japan.

The participants in the baseline examinations of the NILS-LSA were males and females aged 40 to 79 years old. The population of Obu City and Higashiura Town was stratified by both age and gender, and participants were randomly selected from resident registrations in cooperation with the local governments. To test sex differences, the study cohort included equal numbers of males and of females; moreover, the numbers of participants within each decade (40s, 50s, 60s, 70s) were also to be equal. There are some dropout participants in each wave of the examination. These dropout participants were replaced newly recruited age- and sex-matched samples randomly selected from the resident registration except the participants over 79 years old. And, new participants, males and females aged just 40 years, were recruited every year. Recruitment and follow-up are expected to be much easier with volunteers than with randomly selected participants. However, because samples comprising volunteers generally tend to be interested in health, findings from samples comprising volunteers would produce biased results. Consequently, samples should comprise randomly selected participants in order observe the aging process of ordinary Japanese who live ordinary lives.

The participants were examined from 8:50 am to 4:00 pm at a special examination center within a facility at the NCGG. To examine 2,400 males and females in 2 years, that is, 1,200 males and females per year, six or seven participants were to be examined each day, 4 days a week, from Tuesday to Friday, 200 days (50 weeks) a year. We took advantage of the fact that all participants could be examined at the center; therefore, we could conduct detailed examinations that included medical evaluations as well as examinations of exercise physiology, body composition, nutrition, and psychology. Each examination was to be extensive and the most up-to-date, aiming at the internationally highest level in geriatrics and gerontology.

From the beginning of the study, blood samples for gene analysis were collected from almost all participants. There would be no other accumulation of DNA specimens with very detailed back ground information in a community-dwelling population in Japan and other countries. To date, 230 genotypes have been examined, and the associations between genotypes with age-related diseases and parameters of aging controlling for various background factors including nutrition and physical activity have been investigated.

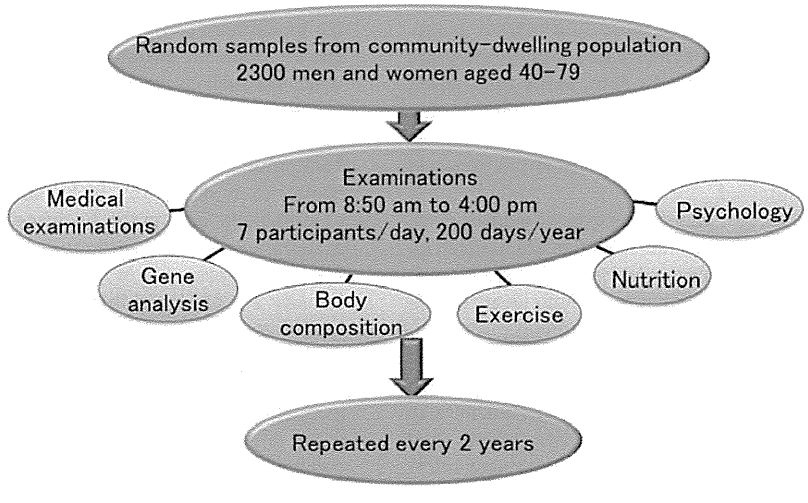

Fig. 2. **Implementation of the National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA).**

Genotype and bone mineral loss with aging

Age-related changes in bone mineral density (BMD) were examined via dual-energy x-ray absorptiometry (DXA) and a peripheral quantitative CT (pQCT) in the NILS-LSA. We found 31 genotypes that were associated with BMD (***Table 2***). These are results from association studies between genotypes of candidate genes and BMD by DXA or pQCT.

Fig. 3 shows the effects of the estrogen receptor (ERα) Xbal genotype on the relationship between BMD and lean body mass in post-menopausal women [30]. BMD tends to be higher with more muscle mass estimated as lean body mass, and the effect of lean body mass is larger in AG/GG type than in AA type of ERα Xbal genotype. We suspect that, for the purpose of preventing osteoporosis, an increase in muscle mass is more effective in people with the AG/GG type than in those with the AA type.

BMD is higher in AA type in a cohort with low muscle mass, but BMD is lower in AA type in a cohort with large muscle mass. Findings from analyses of cohorts with different muscle mass reveal that there may be an inverse association between genotype and BMD. Lack in analysis of interaction between gene and life-style would be one of the causes of poor reproducibility in genome research. Thus, comprehensive analyses of the interaction with detailed data from nutrition surveys and lifestyle examinations including smoking, alcohol drinking, and physical activity are essential in the study of Anti-Aging and disease prevention.

Gene and age-related cognitive impairment

Many genes are likely to influence cognitive function, but the associations between genetic polymorphisms and age-related cognitive impairment are unclear. There are significant differences in age-related cognitive decline among individuals.

Klotho is a type I membrane protein that shares sequence similarity with members of the glycosidase family [31], and it

Table 2 Newly found or confirmed associations between genotypes and bone mineral density (BMD) based on NILS-LSA findings

Genes and genotypes		Effects on BMD	Ref.
Calcium metabolism related hormones and receptors			
VDR	Vitamin D receptor (A-3731G)	Femoral neck BMD is high in men with CC type	15
ESR1	Estrogen Receptor α (PP/pp)	BMD is low in elderly women with CC type	16
ESR1	Estrogen Receptor α (XX/xx)	BMD is low in elderly women with GG type	16
OST	Osteocalcin (C298T)	BMD is low in premenopausal women with TT type	15
ADR	Androgen receptor (CAG repeat)	BMD is low in premenopausal women with frequent CAG repeat	17
CYP17A1	Cytochrome P450,family 17, subfamily A, polypeptide 1 (T-34C)	BMD is low in postmenopausal women with CC type	18
Cytokines growth hormones and receptors			
IL6	Interleukin-6 (C-634G)	Radial BMD is low in postmenopausal women with GG type	15
TGFB	Transforming growth factor-β1 (T29C)	Radial BMD is high in elderly women with CC type	19
OPG	Osteoprotegerin (T950C)	Radial BMD is low in premenopausal women with CC type	20
OPG	Osteoprotegerin (T245G)	Femoral neck BMD is low in pastmenopausal women with GG type	20
CCR	Chemokine receptor 2 (G190A)	BMD is high in postmenopausal women and middle-aged men and with AA type	21
Bone matrix related protein			
MMP1	Matrix metalloproteinase-1 (1G/2G at-1607)	Radial BMD is low in postmenopausal women with 2G/2G type	22
MMP9	Matrix metalloproteinase-9 (C-1562T)	BMD is low in men with CT/TT type	23
COL	Collagen type1 (G-1997T)	BMD is low in postmenopausal women with GG type	24
ICAM1	Intercellular adhesion molecule-1 (Lys469Glu)	BMD is low in postmenopausal women with AA type	25
PLOD1	Procollagen-lysine 2-oxyglutarate 5-dioxygenase (Ala99Thr)	BMD is low in pre and postmenopausal women with GA/AA type	25
CX37	Connexin 37 (Pro319Ser)	BMD is low in men with TT type	25
Others			
KLOT	Klotho (G-395A)	BMD is low in pre and postmenopausal women with GG type	17
MTP	Microsomal triglyceride transfer protein (G-493T)	BMD is high in premenopausal women with TT type	18
VLDLR	VLDL receptor (triplet repeat)	BMD is high in men with more than 8 CGG repeat	18
ALAP	Adipocyte-derived leucine aminopeptidase (Lys528Arg)	BMD is high in premenopausal women with GG type	25
LIPC	Hepatic lipase (C-514T)	BMD is low in postmenopausal women with TT type	25
CNR2	Cannabinoid receptor 2 gene (A/G, rs2501431)	BMD is low in pre and postmenopausal women with AA/AG type	25
PON1	Paraoxonase-1 (Gln192Arg)	BMD is low in postmenopausal women with GG type	26
PON1	Paraoxonase-1 (Met55Leu)	BMD is low in postmenopausal women with TT type	26
PON2	Paraoxonase-2 (Cys311Ser)	BMD is low in postmenopausal women with CC type	26
DRD4	Dopamine D4 Receptor (C-521T)	BMD is low in men with CC type	27
FOXC2	Forkhead box C2 (C-512T)	BMD is low in men and women with T allele	28
PLN	Perilipin (C1243T)	BMD is low in men with C allele	28
MAOA	Monoamine oxidase A (uVNTR)	BMD is low in women with repeat less than 4	29
SH2B1	Src-homology-2-B (Ala484Thr)	BMD is low in women with A allele	29

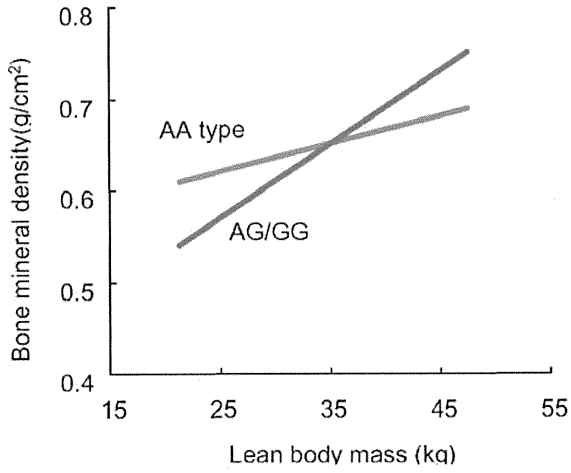

Fig. 3. **The effects of the estrogen receptor (ERα) XbaI genotype on the relationship between BMD and lean body mass in post-menopausal women. The BMD tends to be higher in women with more muscle mass as estimated as lean body mass, and the effect of lean body mass is larger in AG/GG type than in AA type of ERα XbaI genotype (modified from Kitamura *et al.*, 2007 [30]).**

is a fundamental regulator of aging in mice [32]. Mice lacking this protein exhibit multiple aging phenotypes and age-related disorders, including a shortened lifespan, reduced spontaneous activity, arteriosclerosis, infertility, skin atrophy, premature thymic involution, pulmonary emphysema, and osteopenia, although the function of klotho remains to be determined [31,33]. A human homolog of the mouse klotho gene was isolated and its structure was determined [34]. Cognitive impairment was previously shown in klotho gene mutant mice aged seven weeks or over [35]. The klotho gene may be mediate age-related changes in cognitive function in humans.

The effects of klotho gene genotype on cognition were examined in the NILS-LSA [36]. The subjects comprised 2,234 participants in the NILS-LSA aged 40 to 79 years. The klotho gene promoter polymorphism G-395A was identified, and cognitive function was assessed using the Japanese Wechsler Adult Intelligence Scales - Revised Short Forms (JWAIS-R SF) and Mini Mental State Examination (MMSE). The differences in cognitive function were compared between the GG type and GA/AA type of the klotho gene G-395A polymorphism. There was no significant difference in IQ between the GG type and GA/AA type in the subjects aged 40 to 59 years. However, the IQ level was significantly different in terms of the klotho genotype for subjects aged 60 to 79 years (p=0.004). The mean and SE of IQ levels of the subjects with the GG type and the GA/AA type at nucleotide –395 were 99.8 ± 0.5 and 102.6 ± 0.8, respectively. There were also significant differences in three subtests within the JWAIS-R SF: Information, Similarities, and Picture Completion for subjects aged 60 to 79 years. Also, the MMSE score was slightly lower for the GG type than for the GA/AA type (p=0.099).

There were statistically significant differences in cognitive function for klotho gene promoter polymorphism G-395A only in subjects aged 60 or over. This polymorphism may be associated with age-related cognitive impairment, and not associated with cognitive development during childhood to adolescence.

A new genetic strategy for Anti-Aging and prevention of age-related disease

The impact of genetic surveys could be enormously helpful for preventive treatments of geriatric disease as well as Anti-Aging. Previously, associations between disease and genotype were usually investigated by association studies of a specific genotype and a specific disease in molecular epidemiology research. However, we should clarify the following to apply results of epidemiological study to Anti-Aging medicine and preventive medicine: 1) the penetration rates of the genotypes in Japanese; 2) contribution rate to incidence of disease by each susceptibility genotype; 3) factors associated with development of disease in carriers of disease susceptibility genotype; 4) interactive effects with other genotypes; and 5) other physiological effects of the genotype.

These can be investigated in community-dwelling populations and patient cohorts that have detailed background data. Risk of disease can be estimated with the aid of accumulated data. The best-suited education and modification of lifestyles and the content and frequency of examinations for each individual can be determined based on the risk estimation can be applied for disease prevention and Anti-Aging.

Conflict of interest statement

The authors declare no financial or other conflicts of interest in the writing of this paper.

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Visual-Statistical Interpretation of ^{18}F-FDG-PET Images for Characteristic Alzheimer Patterns in a Multicenter Study: Inter-Rater Concordance and Relationship to Automated Quantitative Evaluation

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ABSTRACT

BACKGROUND AND PURPOSE: The role of ^{18}F-FDG-PET in the diagnosis of Alzheimer disease is increasing and should be validated. The aim of this study was to assess the inter-rater variability in the interpretation of ^{18}F-FDG-PET images obtained in the Japanese Alzheimer's Disease Neuroimaging Initiative, a multicenter clinical research project.

MATERIALS AND METHODS: This study analyzed 274 ^{18}F-FDG-PET scans (67 mild Alzheimer disease, 100 mild cognitive impairment, and 107 normal cognitive) as baseline scans for the Japanese Alzheimer's Disease Neuroimaging Initiative, which were acquired with various types of PET or PET/CT scanners in 23 facilities. Three independent raters interpreted all PET images by using a combined visual-statistical method. The images were classified into 7 (FDG-7) patterns by the criteria of Silverman et al and further into 2 (FDG-2) patterns.

RESULTS: Agreement among the 7 visual-statistical categories by at least 2 of the 3 readers occurred in >94% of cases for all groups: Alzheimer disease, mild cognitive impairment, and normal cognitive. Perfect matches by all 3 raters were observed for 62% of the cases by FDG-7 and 76 by FDG-2. Inter-rater concordance was moderate by FDG-7 ($\kappa = 0.57$) and substantial in FDG-2 ($\kappa = 0.67$) on average. The FDG-PET score, an automated quantitative index developed by Herholz et al, increased as the number of raters who voted for the AD pattern increased ($\rho = 0.59$, $P < .0001$), and the FDG-PET score decreased as those for normal pattern increased ($\rho = -0.64$, $P < .0001$).

CONCLUSIONS: Inter-rater agreement was moderate to substantial for the combined visual-statistical interpretation of ^{18}F-FDG-PET and was also significantly associated with automated quantitative assessment.

ABBREVIATIONS: AD = Alzheimer disease; J-ADNI = Japanese Alzheimer's Disease Neuroimaging Initiative; MCI = mild cognitive impairment; NC = cognitively normal subject

PET can visualize regional glucose metabolism by using ^{18}F-FDG; and hypometabolism in the posterior cingulate/precuneus and temporoparietal cortices is regarded as a typical uptake pattern of Alzheimer disease (AD).[1] These findings are considered useful for differentiating AD from other disorders presenting with dementia as well as for predicting conversion from mild cognitive impairment (MCI) to AD.[2,3]

Three approaches for evaluating brain PET images are visual interpretation alone, visual interpretation with adjunctive statis-

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The Research Group of the Japanese Alzheimer's Disease Neuroimaging Initiative comprised investigators from 38 different facilities. The investigators contributed to the design and implementation of J-ADNI and/or provided data but did not participate in the analyses of this report.

T. Yamane contributed to concept and design, analyzed data, and wrote the manuscript. Y. Ikari and T. Nishio acquired and analyzed PET data. Kazunari Ishii, Kenji Ishii, T. Kato, and K. Ito acquired and interpreted PET data. D.H.S. Silverman critically revised the manuscript and enhanced its intellectual content. M. Senda critically revised the manuscript, enhanced its intellectual content, and approved the final content of the manuscript. T. Asada, H. Arai, M. Sugishita, and T. Iwatsubo acquired clinical data and approved the final content of the manuscript.

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tical tools (visual-statistical), and automated quantitative analysis, but the relationship between the latter 2 of these approaches has been little explored, to our knowledge. Visual interpretation features comprehensive and flexible assessment of the qualitative radioactivity distribution by the reader, who may look into all features across the brain. This approach appears effective because patients with AD typically present with characteristic temporoparietal hypometabolism known as the "AD pattern." However, inter-rater variability inevitably occurs because each rater has his or her own experience and criteria, especially for borderline cases, and this variability can potentially be increased or decreased when the reader also takes into account statistical information provided by various software display tools.

On the other hand, quantitative analysis traditionally extracts radioactivity uptake values of the region of interest, placement of which is a subjective matter requiring experience. Although a recently developed anatomic standardization technique can define ROIs automatically and further allows voxelwise statistical analysis to generate *Z*-maps, standardization may not always be accurate and may require adjustment by a human observer. Although these region-of-interest values can be processed into a numeric indicator such as an FDG-PET score[4,5] and a cutoff level can be determined, a single indicator may not be as accurate as complex and comprehensive evaluation by expert readers. As a result, a "combined" approach of visual and quantitative evaluation is often used during image interpretation, in which the readers examine both the tomographic PET images and the result of region-of-interest analysis and/or a *Z*-map.

Inter-rater variability and comparison between visual reading and software-based evaluation have been studied by some investigators on brain ^{18}F-FDG-PET. Ng et al[6] studied the inter-rater variability of 15 patients with AD and 25 cognitively normal subjects (NCs) and reported that visual agreement between 2 readers was good ($\kappa = 0.56$). Tolboom et al[7] studied the variability of 20 patients with AD and 20 NCs and reported that agreement between 2 readers was moderate ($\kappa = 0.56$). Rabinovici et al[8] also reported the inter-rater agreement of ^{18}F-FDG ($\kappa = 0.72$). However, the data of these preceding studies were acquired with a single scanner in a single site and were evaluated by the readers belonging to the institution who were used to the scanner and its image quality. In addition, the studied subjects did not include patients with MCI, in whom PET findings featuring AD, if any, are mild and may make the discrimination challenging. Furthermore, inter-rater variability for combined interpretation of visual and statistical analysis has never been reported, to our knowledge.

In the present study, we analyzed the baseline scans of ^{18}F-FDG in a multicenter clinical project named Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI)[9] and evaluated the inter-rater variability among 3 independent expert raters who were blinded to the clinical information and interpreted the PET images to evaluate the characteristic AD pattern in ^{18}F-FDG-PET on the basis of a combined visual-statistical evaluation. The raters looked at the 3D stereotactic surface projection *Z*-map of ^{18}F-FDG-PET visually as well as the ^{18}F-FDG tomographic images because it is considered the standard means of human interpretation of ^{18}F-FDG-PET images in Japan and therefore was adopted as the official interpretation method in J-ADNI. Images were also assessed by automated quantitative analysis by using an FDG-PET score, which was derived from ADtsum,[4,5] and were compared with the visual-statistical rating by the 3 raters and with their consensus.

MATERIALS AND METHODS

Subjects

Data used in the present study were obtained from J-ADNI.[9] This project was approved by the ethics committee of each site in which J-ADNI data were acquired, and written informed consent was obtained from each subject before participating in J-ADNI. All subjects were native Japanese speakers, 60–84 years of age, and were registered as 1 of 3 clinical groups (mild AD, MCI, or NC). Subjects of the mild AD group scored 20–26 in Mini-Mental State Examination-Japanese and 0.5–1.0 in the Clinical Dementia Rating-Japanese and were compatible with the probable AD criteria in the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association.[10] Subjects of the MCI group scored 24–30 in the Mini-Mental State Examination-Japanese and 0.5 in the Clinical Dementia Rating-Japanese. Subjects of NC group scored 24–30 in the Mini-Mental State Examination-Japanese and 0 in the Clinical Dementia Rating-Japanese. The exclusion criteria were depression (Geriatric Depression Scale-Japan $\geq$ 6), cerebrovascular disorders (Hachinski Ischemic Score $\geq$ 5), and other neurologic or psychiatric disorders.

Enrollment in each clinical group for J-ADNI was primarily determined by the referring physician, and 303 consecutive subjects entered the study to undergo ^{18}F-FDG-PET scanning. A thorough central review of the clinical and behavioral data by expert psychiatrists and psychologists excluded 29 cases that had erroneous assessment of the cognitive test results, depression or cerebrovascular disorders that had been overlooked, prohibited concomitant medications, or other deviations from the criteria. As a result, 274 baseline ^{18}F-FDG-PET scans (67 mild AD, 100 MCI, and 107 NC) were analyzed in the present study.

PET Imaging

As a quality assurance measure necessary for the multicenter study, all PET sites in J-ADNI were qualified for the PET scanner and other devices, resting-state environment, quality of the on-site-produced PET drugs, and so forth before scanning of the first subject. Intersite differences were minimized by standardizing the imaging protocol, and interscanner differences were addressed with the Hoffmann 3D phantom data.[11] The data used for the analysis in the present study were acquired with 14 types of PET or PET/CT scanners in 23 PET centers.

In the ^{18}F-FDG-PET scans, all subjects fasted for at least 4 hours and their preinjection blood glucose levels were confirmed to be <180 mg/dL. Intravenous administration of ^{18}F-FDG (185 $\pm$ 37 MBq) was followed by a resting period of 30 minutes in a dimly lit and quiet room. Dynamic scans (300 seconds $\times$ 6 frames) were obtained starting 30 minutes postinjection in the 3D mode. Attenuation was corrected for by a transmission scan with segmentation for dedicated PET and by a CT scan for PET/CT.

All the PET images acquired in each PET site went through the J-ADNI PET quality control process,[11] in which head motion between frames was corrected for and bad frames were removed to create sum frame images. Then the images were reoriented to the anterior/posterior commissure line with the same matrix size and

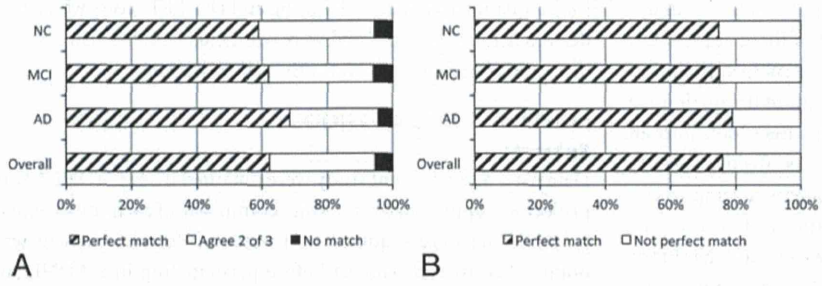

FIG 1. Breakdown of the ^{18}F-FDG-PET cases into degree of match by 3 raters in a combined visual-statistical human classification into 7 (FDG-7) (*A*) or 2 (FDG-2) (*B*) categories. A perfect match by the 3 raters is observed for 62% of the cases for FDG-7 and 76% for FDG-2 in total. The AD group shows the highest concordance followed by the MCI and NC groups, in this order, both for FDG-7 and FDG-2.

voxel size so that all camera models presented images of similar orientation and appearance to the viewer and were then passed on to image interpretation.

The ^{18}F-FDG-PET images that had passed through the quality control process above were also treated with a 3D stereotactic surface projection technique to generate *z* score maps (displayed with upper = 7 and lower = 0) by using iSSP software, Version 3.5 (Nihon Medi-physics, Tokyo, Japan). The normal data base used for generating the *Z*-maps was made by a method of leave-one-out cross-validation based on 25 healthy subjects of J-ADNI (11 men and 14 women; mean age, 66.0 ± 4.8 years) who were interpreted as having a normal pattern by one of the coauthors of the study. The *Z*-maps were used not for the automated quantification but for a part of the information for human raters in the visual-statistical interpretation.

Human Interpretation

Those ^{18}F-FDG images generated through the quality control process above were independently interpreted with the combined visual-statistical method by 3 expert raters blinded to the clinical group and other clinical and laboratory data. The raters were provided with the ^{18}F-FDG tomographic images on the viewer as well as the *Z*-map images in PDF format. Information about the age and sex was also provided to the raters. Moreover, T1-weighted MR images acquired in 3D mode by using MPRAGE or its equivalent and reformatted in axial sections were also provided together with axial T2WI and proton-attenuation images, in which the MR imaging sections did not correspond to the PET section positions. The experience of the 3 raters as physicians specializing in nuclear neuroimaging was 17, 19, and 19 years, respectively, when this project started.

After independent interpretation, consensus reads were performed by the 3 raters and 2 other discussants who are experienced nuclear medicine physicians specialized in neuroimaging. The experience of both discussants as physicians specializing in nuclear neuroimaging was 20 years. The same images and information as that in the independent interpretation were also provided for the discussants in the consensus reads. The 7 sessions of consensus reads lasted for 1.5 years in the order of subject enrollment in J-ADNI. In the consensus reads, the cases in which the evaluations by the 3 raters did not completely match were discussed, and the unified visual-statistical interpretation was determined as an official judgment by the J-ADNI PET Core.

For classification of ^{18}F-FDG-PET, the criteria of Silverman et al[1] were adopted for classifying the uptake pattern in J-ADNI. All 3 expert raters and the 2 discussants had attended a training course for the criteria organized by Silverman et al before starting the J-ADNI project. In the criteria of Silverman et al, ^{18}F-FDG uptake patterns were classified into 7 categories: progressive patterns: P1, P1+, P2, and P3, in which P1 represents the characteristic AD pattern and P1+ represents AD-variant pattern, including the characteristic Lewy body dementia pattern; and nonprogressive patterns: N1, N2 and N3, in which N1 represents the characteristic normal pattern. In addition to these original 7 categories (FDG-7), the present study defined a binary criteria (FDG-2) in which the 7 categories were dichotomized into posterior-predominant hypometabolism (AD and AD-variant) patterns (P1, P1+) and the other patterns (N1, N2, N3, P2, and P3).

Automated Quantitative Evaluation

In the automated quantitative analysis, the FDG-PET score, as a measure of the AD pattern, was calculated from ADtsum[4] by using the Alzheimer's Discrimination Tool in PMOD, Version 3.12 (PMOD Technologies, Zurich, Switzerland)[4,5] by using the following equation: FDG-PET score = log2 {(ADtsum / 11,089) + 1}. The FDG-PET score was not calculated in 1 case because no significant clusters were determined for the image.[4] This case was excluded from the quantitative analysis.

Statistical Analysis

Concordance among the 3 raters was evaluated by Cohen κ statistics. As comparisons between human and automated evaluation, the association between the FDG-PET score and the number of the raters who interpreted the case as P1 (AD pattern) in FDG-7 was evaluated by the Spearman rank correlation coefficient. Likewise, association between the FDG-PET score and the number of the raters who interpreted the case as N1 (normal pattern) was evaluated. The association was also examined between the FDG-PET score and the number of raters in FDG-2 classification (ie, how many raters judged the case as the AD and AD-variant patterns [P1, P1+] versus the other patterns [N1, N2, N3, P2, and P3]). A P value $< .05$ was considered significant. In addition, the FDG-PET score was compared with the final combined visual-statistical interpretation determined by the consensus read and with the clinical group. Receiver operating characteristic analysis was used to obtain the optimum cutoff level for the quantitative index for discrimination.

Neither iSSP nor the PMOD Alzheimer's Discrimination Tool was approved for clinical use by the US Food and Drug Administration.

RESULTS

Figure 1 summarizes concordance rates among the 3 raters. Agreement among the 7 visual-statistical categories by at least 2 of the 3 readers occurred in >94% of cases for all groups: NC, MCI,

and AD. The κ statistic $\pm$ SE for each pair of the 3 raters was 0.59 $\pm$ 0.04, 0.54 $\pm$ 0.04, and 0.58 $\pm$ 0.04 in FDG-7 (average, 0.57), and 0.73 $\pm$ 0.04, 0.65 $\pm$ 0.0, and 0.64 $\pm$ 0.05 in FDG-2 (average, 0.67), respectively.

Figure 2 illustrates the relationship between the FDG-PET score and the number of raters who visually-statistically interpreted the ^{18}F-FDG-PET image as P1 (Fig 2*A*) and N1 (Fig 2*B*). A significant positive association was observed between the FDG-PET score and the number of P1 interpretations ($\rho = 0.59$, $P < .0001$). The mean FDG-PET score was 0.46 $\pm$ 0.37 ($n = 103$) for the scans no raters interpreted as P1, but it increased to 0.723 $\pm$ 0.39 ($n = 34$) for those that 1 rater interpreted as P1, to 0.99 $\pm$ 0.45 ($n = 31$) for 2 raters, and to 1.21 $\pm$ 0.73 ($n = 105$) for all 3 raters. Likewise, a significant negative association was observed between the FDG-PET score and the number of N1 interpretations ($\rho = -.64$, $P < .0001$). The FDG-PET score was 1.15 $\pm$ 0.69 ($n = 146$) for the scans no raters interpreted as N1, but it decreased to 0.80 $\pm$ 0.39 ($n = 28$) for those 1 rater interpreted as N1, 0.50 $\pm$ 0.25 ($n = 40$) for 2 raters, and 0.34 $\pm$ 0.22 ($n = 59$) for all 3 raters. A similar association was observed between the FDG-PET score and the number of raters who interpreted the case as AD and AD-variant patterns, including the Lewy body dementia pattern (P1, P1+) or the other patterns (N1, N2, N3, P2, and P3); and both showed significant positive and negative associations ($\rho = 0.60$, $P < .0001$; and $\rho = -0.60$, $P < .0001$).

Figure 3 illustrates scatterplots of the FDG-PET scores as contrasted to the combined visual-statistical interpretation determined by the consensus read of ^{18}F-FDG-PET for each clinical group. For each group as well as for all subjects, cases with P1 interpretation showed higher FDG-PET scores than those with N1. Receiver operating characteristic analysis on P1 and N1 cases led to a cutoff FDG-PET score of 0.67 for discrimination between P1 and N1. As was expected, NC cases with P1 interpretation had lower FDG-PET scores than MCI and AD cases with P1 interpretation, and the ratio of the cases above-to-below the cutoff level was also lower. As for the cases with other patterns, a large fraction of the cases with N2 interpretation had FDG-PET scores above the cutoff level, though most were below 1.0. The FDG-PET scores of the cases with P1+ and P2 were variable.

DISCUSSION

Matches among 7 visual-statistical categories by at least 2 of 3 readers occurred in >94% of cases for each clinical group, and perfect matches among the 3 raters were observed for 62% of the cases for FDG-7 and 76% for FDG-2 categorization schemes in total. The mild AD group showed the highest concordance, followed by MCI and NC, in order, for both FDG-7 and FDG-2. The AD pattern in ^{18}F-FDG-PET is usually seen in the early stage of AD and is expected to predict the onset of AD.[1,12] Because most of the subjects who are clinically diagnosed as having AD may have had an established AD pattern in ^{18}F-FDG-PET, it is reasonable for these results that AD showed the highest concordance.

Based on the classification of κ values described by Landis and Koch,[13] agreements were considered to be moderate for FDG-7 and substantial for FDG-2. Inter-rater variability is one of the indices that are often used to evaluate the validity of methods of image interpretation, and it facilitates comparison with the other studies. The κ index of FDG-2 ($\kappa = 0.67$) of the present study showed values similar to those of the other studies ($\kappa = 0.56$-$.72$) evaluated by the bi-

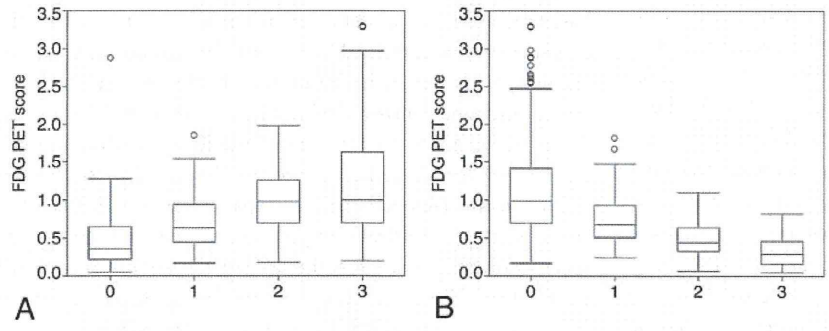

FIG 2. Boxplots of the FDG-PET score against the number of raters who interpreted the ^{18}F-FDG-PET images as P1 (*A*) and N1 (*B*) based on the FDG-7 criteria. The FDG-PET score gradually increases as the number of P1 (AD pattern) interpretations increases (Spearman rank correlation coefficient: $\rho = 0.59$, $P < .0001$). On the other hand, FDG-PET score gradually decreases as the number of N1 (normal pattern) interpretations increases ($\rho = -.64$, $P < .0001$).

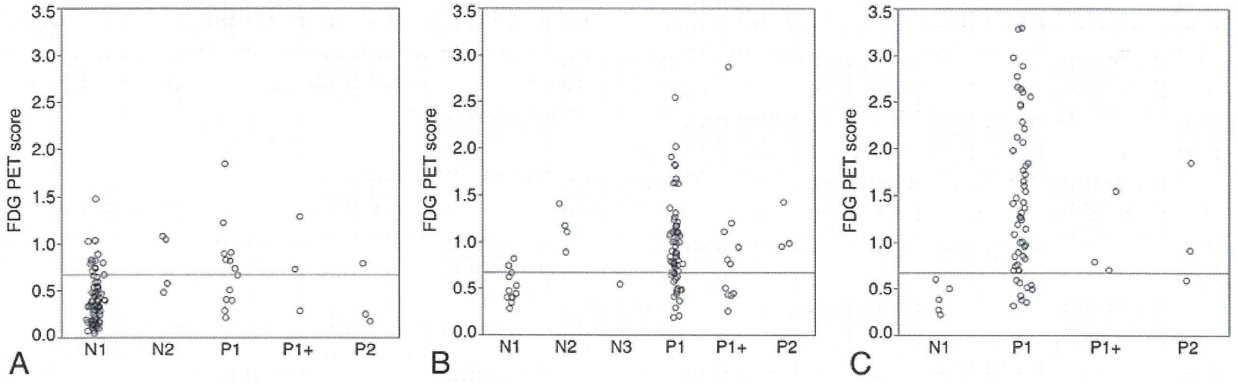

FIG 3. Scatterplot of the FDG-PET score as contrasted with the combined visual-statistical interpretation determined by the consensus read of ^{18}F-FDG-PET for each clinical group (*A*, NC; *B*, MCI; and *C*, AD). The horizontal line indicates the cutoff level of 0.67 derived by receiver operating characteristic analysis on P1 and N1 cases.