Genetic Testing in Dementia – A Medical Genetics Perspective

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Abstract:

Objective

When a genetic cause is suspected in a person with dementia, it creates unique diagnostic and management challenges to the treating clinician. Many clinicians may be unaware of the practicalities surrounding genetic testing for their patients, such as when to test and what tests to use and how to counsel patients and their families. This review was conducted to provide guidance to clinicians caring for patients with dementia regarding clinically relevant genetics.

Methods

We searched PubMed for studies that involved genetics of dementia up to March 2020. Patient file reviews were also conducted to create composite cases.

Results

In addition to families where a strong Mendelian pattern of family history is seen, people with younger age of onset, especially before the age of 65 years were found to be at an increased risk of harbouring a genetic cause for their dementia. This review discusses some of the most common genetic syndromes, including Alzheimer disease, frontotemporal dementia, vascular dementia, Parkinson disease dementia/dementia with Lewy bodies and some rarer types of genetic dementias, along with illustrative clinical case studies. This is

followed by a brief review of the current genetic technologies and a discussion on the unique genetic counselling issues in dementia.

Conclusions

Inclusion of genetic testing in the diagnostic pathway in some patients with dementia could potentially reduce the time taken to diagnose the cause of their dementia. Although a definite advantage as an addition to the diagnostic repository, genetic testing has many pros and cons which need to be carefully considered first.

Key Words: Dementia Genetics, Next Generation Sequencing, Genetic Counselling in Dementia, Clinical Genetics, Early Onset Dementia

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Key Points/Highlights:

- This review gives a broad overview of the types of genetic dementias, clinically pertinent genetic tests and when to use them, with some case examples
- The pros and cons of the different types of commercially available genetic tests are outlined
- This article also discusses aspects of the complex genetic counselling issues in this progressive condition without current cure

- A brief discussion of relevant clinical trials is also covered

Introduction

Dementia causes a progressive decline in one or more cognitive domains which include complex attention, executive function, learning and memory, language, perceptual-motor function and social cognition [1]. Cognitive decline in dementia leads to a reduction in the ability to perform their activities of daily living, with ongoing regression over time. People with dementia suffer a 30% mortality rate and a 73% nursing home admission rate compared to <10% mortality rate and <5% nursing home admission rate in age matched controls [2].

Although a mix of genetic and environmental risk factors are known to contribute to dementia in general, some of the strongest genetic causes for dementia are identified in those who have a strong Mendelian pattern of family history as well as those with a younger age of onset, especially when accompanied by a suggestive family history [3, 4].

This article details the types of dementias where the chance of identifying a genetic cause is high. In this review, early onset dementia (EOD) is used to mean onset of dementia under the age of 65 years, “familial dementia” is used to represent cases where one or more first or second degree relatives are also affected and “genetic dementia” is used where a genetic cause is identified as the underlying reason for dementia in an individual.

Genetic Dementias:

Although genetic causes can be responsible for many types of dementias at various ages of onset, recent studies report that a younger age at onset (typically under 65 years) as well as family history are highly predictive of a chance of finding clinically meaningful genetic

mutation(s). Koriath et al, in their recent study, demonstrated ~ 15 to 20% chance of finding a pathogenic mutation in patients with dementia onset between 20 and 64 years, with this rate steadily decreasing with increasing age [5]. A strong family history (corresponding to ≥3 affected family members over two generations connected by a first degree relative) equated to a 45% chance of finding a pathogenic mutation in their study [6, 7].

Even in the absence of a reported family history, a very young age of onset (i.e. younger than 51 years) has been shown to result in ~12.3% chance of finding a pathogenic mutation, especially in the *PSEN1* gene [8-18]. Whilst not all EOD has a genetic basis and not all people with dementia onset over the age of 65 years are "non-genetic", the chances of finding a clinically meaningful genetic diagnosis remains higher in EOD (especially when combined with a family history), as well as those with a strong Mendelian type of family history regardless of age of onset.

EOD is defined variably as dementia occurring under the age of 60 or 65 years, although the arbitrary cut-off of 65 years is more widely used [19]. Worldwide estimates from the years 2000 to 2013 suggest that ~40-100 per 100,000 people suffer from EOD [20-23]. The differential diagnoses to consider in EOD are broad and need to include the genetic types of dementias. The underlying causes of dementia in those with EOD differ slightly in different studies, but progressive neurodegenerative disorders underlie most EODs, with Alzheimer disease (AD), fronto-temporal dementia (FTD) and vascular dementia (VaD) featuring as the most common causes [22, 24-26]. In a UK based study of 185 EOD patients aged between 30 and 64 years, the most common diagnosis was AD (34%) followed by vascular dementia (VaD) (18%), FTD 12%, alcohol related dementia (10%) and dementia with Lewy bodies (DLB) (7%) [20]. A Japanese study reported VaD to be the most common cause in those with

EOD (42.5%) followed by AD (25.6%), head trauma (7.1%), DLB/Parkinson disease dementia (PDD) (6.2%), FTD (2.6%), and other causes (16.0%) [23]. An Australian study of 86 participants with EOD showed a predominance of AD (47%), followed by FTD (14%) and smaller numbers of other types of dementias [27].

Standard diagnostic steps in a patient with dementia include detailed history, collateral history from family members, physical examination for signs of neurodegenerative disorders, detailed cognitive and neuropsychological assessment, relevant blood and urine tests to investigate for any underlying systemic illness causing cognitive decline and structural brain imaging such as magnetic resonance imaging (MRI). Based on the results of these initial investigations, further directed investigations such as cerebrospinal fluid (CSF) analysis, electroencephalogram (EEG), more specific nuclear neuroimaging such as positron emission tomography (PET) scan or single-photon emission computed tomography (SPECT) scan or in some cases computerised tomography (CT) or MRI based cerebral angiograms are undertaken.

In cases where an underlying genetic cause is suspected either due to investigations suggesting a genetic neurodegenerative disorder or due to the presence of a suggestive family history, genetic testing forms an important adjunct to the above investigations. Finding a genetic cause in such cases can provide diagnostic certainty, inform risk for other family members and may also open up opportunities for certain therapeutic trials in selected cases. Next generation sequencing (NGS) methods (also known massively parallel sequencing) such as whole exome analysis now enables testing of almost all of the known major genetic causes of dementia simultaneously [28]. Recent studies using these newer gene sequencing methods have shown diagnostic benefit in dementia and demonstrated that significant proportion of

clinical diagnoses are inaccurate, highlighting overlap between AD, FTD, VaD, prion disease and other neurodegenerative conditions [29]. There are many issues including technical limitations and family implications to consider before offering such tests to patients and their families. Moreover, access to testing as well as pre- and post- test counselling varies greatly across jurisdictions.

The following review will detail the most common genetic dementia syndromes, genetic diagnostic approaches, a discussion of utility, access, pros and cons and limitations of genetic testing from a clinical perspective, illustrated by composite case examples.

Genetic Diagnoses in Dementia

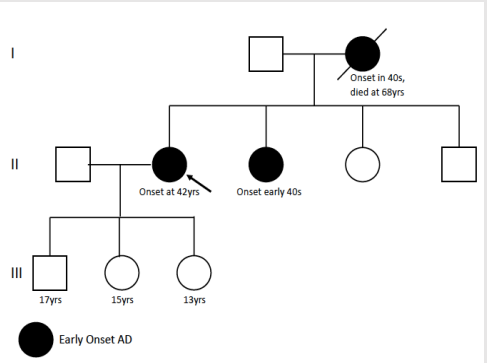
The most common dementia syndromes where a clinically meaningful genetic cause can be found are AD, FTD, PDD and DLB, and specific types of vascular dementia such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Other rarer genetic causes include Niemann Pick type C (NPC), genetic prion diseases, dementia co-occurring with other neurodegenerative disorders such as Huntington disease (HD), spino-cerebellar ataxias (SCA).

Alzheimer disease (AD)

AD is the commonest and most widely studied type of dementia. Genetic causes for AD in those with early onset can be either monogenic, i.e. driven by a single gene or polygenic, with contributions from multiple genetic variants throughout the genome. Later onset AD is mostly polygenic or driven by genetic risk factor variants in addition to environmental and lifestyle risk factors.

A. Monogenic AD (Fig 1):

Case example 1:
A 42 y.o. social worker, mother of three was referred from a tertiary neuropsychiatry clinic with a 6-12 month history of cognitive decline, likely early onset AD and a strong family history of the same. She had no past history of depression or other mental illness and was not on any regular medications. Neuropsychology assessment was indicative of AD. No abnormalities were detected in standard blood and CSF analysis. MRI Brain, brain SPECT imaging and 18-Fluorodeoxyglucose PET scan were all suggestive of AD.



Genetics Consultation: Based on the history and investigations, likelihood of monogenic AD was thought to be high. After pre-test counselling family decided to undergo research based genetic testing and receive results in the future when relevant to children for family planning decisions.

Genetic Results: NM_000021.3 (***PSEN1***) c.737C>A p.Ala246Glu

Pertinent counselling issues: Families may not wish to know the results immediately given implications for children in a condition with no current cure. Appropriate pre-test genetic counselling is therefore important in ensuring that families understand and prepare for the potential psychological implications of finding out if there is an inherited cause.

Fig 1: Monogenic Alzheimer disease

Early onset AD (EOAD), defined as dementia onset under 65 years, forms ~5% of all AD and when combined with a Mendelian family history, may have an identifiable monogenic cause in ~60-80% of cases [30]. Familial early onset AD (FEOAD) represents <2% of AD [30]. FEOAD cases are predominantly due to mutations in one of the three autosomal dominantly inherited genes: *APP*, *PSEN1* and *PSEN2*. Pathogenic mutations in these genes are known to disrupt the amyloid beta (Aβ) pathway in the brain, resulting in processing of the amyloid precursor protein into longer isoforms of the Aβ peptide, which are less soluble compared to the normal shorter isoforms, leading to toxic deposits on the cerebral surface, termed amyloid plaques [31, 32]. Progressive microscopic deposition of Aβ neuritic plaques leads to synaptic disruption and is thought to be the predominant neuropathologic basis for AD [33].

a. APP

In 1984 it was shown that Aβ could be isolated from the cerebral vasculature of adult patients with Down syndrome (trisomy 21) with a hypothesis that the gene responsible for Aβ may reside in chromosome 21 and with increased protein product predicted as the underlying mechanism [34]. The gene *APP* (OMIM 104760), located in chromosome 21q, was isolated by Kang et al in 1987 [35]. The protein product APP is a membrane spanning protein that is converted into smaller sub-units, including Aβ, by sequential proteolytic processing facilitated by beta and gamma secretases [36]. Defects in this processing can lead to excessive production of Aβ or increase in the toxic, amyloidogenic long isoforms of Aβ [37].

Pathogenic mutations in the *APP* gene contribute to 10-15% of FEOAD with onset of symptoms occurring typically in the 50s and ranging from 45 to 60 years old [38]. Most pathogenic mutations in *APP* occur in exons 16 and 17, the area of the gene encoding transmembrane domain which is the gamma secretase cleavage site [39, 40]. *APP* mutations can also cause cerebral amyloid angiopathy resulting in cerebral haemorrhage, ischaemia leading to dementia [41]. Interestingly, variants protective against dementia or only causing disease in autosomal recessive inheritance pattern have also been described in this gene. The A673T substitution is believed to protect against AD due to decreased production of Aβ resulting from reduced beta secretase activity; and A673V substitution destabilises the Aβ aggregates in the heterozygous form (dominant-negative effect), therefore only causing AD in biallelic i.e. autosomal recessive form [42, 43].

b. PSEN1 and PSEN2

PSEN1 (OMIM 104311) encodes presenilin-1 which is part of the gamma secretase complex. The gene was isolated in 1995 [44] and contributes to 30-70% of cases of FEOAD [30].

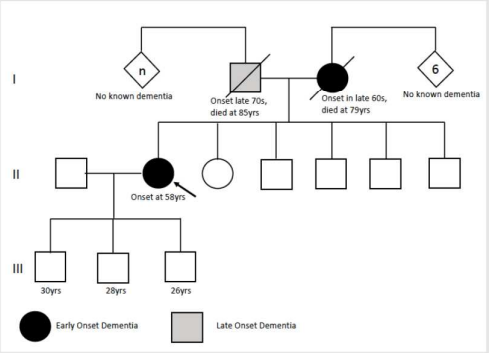
Mutations in this gene can be associated with onset of AD as early as the late 20s, with most people with pathogenic mutations developing AD before the age of 60 years [45, 46]. Although most cases are familial, *de novo PSEN1* pathogenic variants have also been found in people with sporadic EOAD, where further testing showed that neither parent had the variant, and therefore it likely occurred for the first time in the affected individual at conception [8-18, 47].

The *PSEN2* gene (OMIM 600759) [48, 49] also forms part of the gamma secretase complex. Rare mutations in this gene have been identified in <5% of FEOAD [50], although the frequency is more common in people with Volga German ancestry [51]. The age of AD onset with *PSEN2* mutations is highly variable with a range of 40 to 75 years described [52].

Despite a strong Mendelian family history, ~20-40% of FEOAD still remains unexplained [30]. This may be due to hitherto undiscovered monogenic causes, polygenic causes or due to clinical diagnostic uncertainty about AD in some cases.

B. Genetic Risk Factors and Polygenic AD (Fig 2)

Case example 2:
A 58 y.o. lady of Sicilian background was referred with a 2 year history of cognitive decline, with a family history of mother having dementia in her late 60s and father in his late 70s (type unknown). She quit schooling at year 11, had a past history of depression, had history of previous heavy smoking but no other co-morbidities. Neuropsychology assessment was indicative of possible frontal variant AD or behavioural variant FTD. Other than hypercholesterolaemia, no abnormalities were detected in standard blood and CSF analysis. CSF amyloid 1-42 and tau (total and phosphorylated) analysis indicated a neurodegenerative process, but was not strongly suggestive of AD. MRI brain showed global atrophy and brain SPECT imaging showed frontal and some right temporal hypoperfusion.



Genetics Consultation: Due to the young age of onset and the family history, an underlying genetic cause was suspected and genetic testing for a panel of dementia genes was offered after pre-test counselling.

Genetic Results:

- No pathogenic mutations in *APP*, *PSEN1* or *PSEN2*
- No pathogenic mutations in any other relevant dementia genes, including c9orf72 expansion testing
- ***APOE* ε4/ε4**

Pertinent counselling issues: *APOE* ε4/ε4 may have contributed to her dementia and is a risk factor, but not considered causative. Research based polygenic risk score indicated a very high risk of AD. Predictive testing cannot be offered to others in the family due to high variability in phenotype.

Fig 2: Polygenic Alzheimer disease

As opposed to the monogenic causes described above, which were discovered through genetic linkage studies in large families with Mendelian inheritance, the association of the risk factor *APOE* ε4 genotype with AD was found through large case control studies and has been consistently replicated in genome wide association studies (GWAS) [53-55]. The gene *APOE* (OMIM 107741) encodes apolipoprotein E, which is involved in transport of cholesterol and other hydrophobic molecules, including Aβ. Three major isoforms of *APOE* (termed ε2, ε3, ε4), determined by two single nucleotide polymorphisms (SNPs) in the gene have been known to influence the risk of AD. The *APOE* ε3 isoform is considered the wild-type, being most common in the general population. The *APOE* ε4 genotype increases the risk and the *APOE* ε2 genotype protects against AD [56, 57].

Although the biological relationship between the *APOE* ε4 genotype and AD remains elusive, the association holds in both late onset AD and EOAD cases. It is to be noted that these

families do not generally display a Mendelian pattern of inheritance and even in cases where a family history of AD is seen, there is tremendous variability in ages of onset as well as severity of the disease [58-60].

The presence of *APOE* ε4 in the heterozygous form confers a 2-3-fold increase in the odds of developing AD and in the homozygous form this confers up to a 15-fold increase in the odds compared with carriers of the most common *APOE* ε3 allele, which is considered to be the population baseline [53]. Moreover, the presence of *APOE* ε4 was found to lower the age of onset of AD, with the mean age of onset being 84.3 years in non-carriers as opposed to 68.4 years in those who were *APOE* ε4/ε4 [56]. The *APOE* ε2 allele was found to be protective, with lower frequencies in AD patients compared to the general population [56].

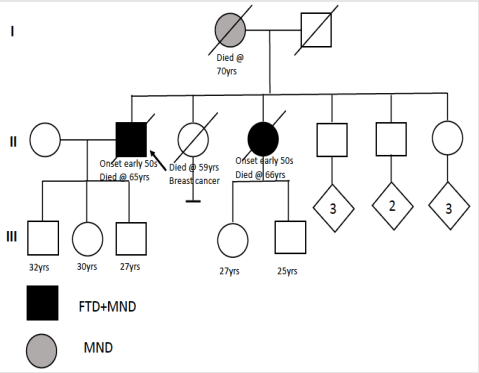
Despite the high risk, it has been recognised that there is considerable phenotypic diversity among *APOE* ε4 homozygotes, ranging from EOAD to a lifetime of no symptoms [61-64]. The reasons for this phenotypic diversity remain largely unexplained, although other modifying genetic variants influencing the risk as well as environmental/lifestyle related factors could be playing a part. Due to this variability in risk, *APOE* ε4 genotype, even in the homozygous state has not demonstrated reliable clinical utility in risk prediction for AD and therefore, whilst the *APOE* ε4/ε4 genotype is considered a risk factor for AD, asymptomatic family members are not generally offered clinical testing for this genotype for risk prediction [65, 66].

Through GWAS studies, polygenic risk scores (PRS) where multiple genetic variants including the *APOE* genotypes (ε2, ε3 or ε4) and other variants of smaller effect size, in combination are used to assess risk of AD have been formulated. Large longitudinal studies

of PRS in AD have shown promise in their ability to predict the age of onset and risk of developing dementia [67-69]. However, unless these PRSs show consistent results in rigorous, clinically oriented validation studies in well-defined populations, they cannot be currently used for clinical risk prediction.

Fronto-temporal Dementia (Fig 3)

Case example 3:
A referral was received from the Brain Bank after pathological examination of a 65 year old person's brain was suggestive of FTLD. Collateral history from family suggested that the deceased male had onset of cognitive symptoms likely in his early 50s, but was also a heavy alcoholic. He became homeless at the age of 57yrs and lost contact with his family. Other than sporadic presentations to hospitals, no medical investigations were sought. An MRI brain at the age of 59yrs indicated minor generalised atrophy, hippocampal atrophy and dilatation of lateral ventricles. Brain histopathology showed scattered TDP-43 neuritic tangles and intraneuronal tau in frontal cortex with a neuro-pathological diagnosis of FTD-TDP (type 3).



Genetics Consultation: The children in their late 20s/30s sought genetic counselling to find out their own risk. Due to the FTD+MND phenotype in the family and the brain pathology results, *C9orf72* testing was offered on DNA extracted from the brain tissue in the deceased.

Genetic Results:

- *C9orf72* testing revealed heterozygous pathogenic (>145 GGGGCC repeats)

Pertinent counselling issues: One son had a positive test result after successfully using pre-test counselling to confront mortality fears and adjusted well to the result. The daughter tested negative but experienced survivor guilt and disrupted relationships with her gene positive siblings. Another son was gene positive but regretted knowing because he felt he had no means to change his life plans such as travelling more and experienced ongoing worry for his children.

Fig 3: Fronto-temporal dementia

Frontotemporal dementia (FTD) involves behavioural, personality and language dysfunction in the setting of degeneration of the frontal and/or temporal lobes [70]. Frontotemporal lobar degeneration (FTLD) is the neuropathological feature associated with this type of dementia [71].

FTD was reported to be the second most common dementia in <65 year olds with 3.5 cases detected per 100,000 person years (compared with incidence of AD in the same group being 4.2 per 100,000 person years) in a 2008 study of EOD [26]. The median age of onset reported

is between 57 and 59 years (range 33-80 years) [71-73]. Three main clinical subtypes have been described which include behavioural variant FTD (bvFTD) and two forms of primary progressive aphasia (PPA) which include semantic variant PPA and non-fluent PPA [74]. bvFTD is the most common subtype [71, 75].

Motor neuron disease (MND) and FTD are more recently recognised to be a spectrum disorder with up to 50% of patients with MND showing defects in frontal lobe testing and around 15% fulfilling criteria for diagnosis of FTD [76]. Conversely, ~40% of FTD patients have motor dysfunction and around 15% fit the diagnostic criteria for MND [77].

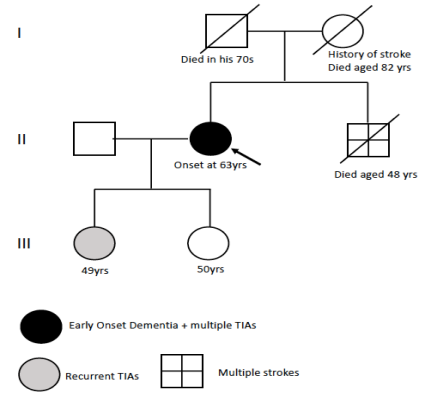
FTD is highly heritable with around 40% of people with FTD having at least one other member in the family with FTD and ~10% showing a clear autosomal dominant history [7]. Three genes strongly associated with autosomal dominant FTD: *MAPT*, *GRN* and *C9orf72* account for >80% of familial FTD [78]. Mutations in multiple other less common genes have also been found in patients with FTD phenotypes. These genes include *CHMP2B* [79], *FUS* [80], *VCP* [81] , *SQSTM1* [82], *OPTN* [83], *UBQLN2* [84], *TBK1* [85].

Mutations in the *MAPT* gene cause neurofibrillary tangles within cerebral neuronal cells, comprised of intracellular accumulation of hyperphosphorylated tau (p-tau) protein [86, 87]. When tau is hyperphosphorylated, it is unable to interact with microtubules and contributes to neurodegeneration [88]. The most common phenotypes associated with mutations in *GRN* are bvFTD or non-fluent PPA, with the reported age of onset varying widely from 35 to 87 years even within the same family [89-91]. *GRN* encodes for progranulin, the function of which in neurodegeneration is not well known, although it may be associated with neuroinflammatory mechanisms [92].

Abnormal hexanucleotide repeat expansions (GGGGCC) in the first intron of the *C9orf72* gene account for the majority of familial FTD/motor neuron disease (MND) spectrum [93, 94]. The function of the protein that this gene codes for is not clearly known. Up to 30 repeats can be present in individuals without the disease, but larger expansions, sometimes up to 4000 repeats, are found in individuals with FTD. However, the exact expansion size at which disease occurs is not yet clearly defined [95]. The most common presenting feature in patients with pathogenic *C9orf72* expansions is bvFTD with or without MND, although semantic variant PPA has also been described [96, 97]. GWAS studies have not been as successful compared to AD in delineating polygenic or high-risk SNPs for FTD [98, 99].

Vascular Dementia

Case example 4:
A 70 y.o. lady referred by neurologist due to unspecified cognitive decline with onset at age 63 years on the background of recurrent transient ischaemic attacks (TIAs). Trigger for genetics review was that her daughter aged 49 years had sought consultation for frequent migranous headaches and had hospital admissions for recurrent TIAs. MRI brain in both mother and daughter showed severe white matter signal abnormalities uncharacteristic for their age and raised a question of CADASIL. Further history revealed the proband's brother had died at 48 years after recurrent strokes.



Genetics Consultation: As the clinical suspicion for CADASIL was high on the background of a suggestive family history, genetic testing for all monogenic causes of vascular dementia was organised after pre-test counselling.

Genetic Test Results: NM_000435.2 (***NOTCH3***): c. 619C>T p.Arg207Cys (in both mother and affected daughter)

Pertinent counselling issues: Confirmation of clinical diagnosis by way of genetic testing was sought by the family as well as the medical specialists looking after these patients and in this case genetic testing was able to provide diagnostic clarity. The genetic diagnosis enabled communication to other at-risk family members about the option of predictive testing and prenatal or IVF-based genetic testing.

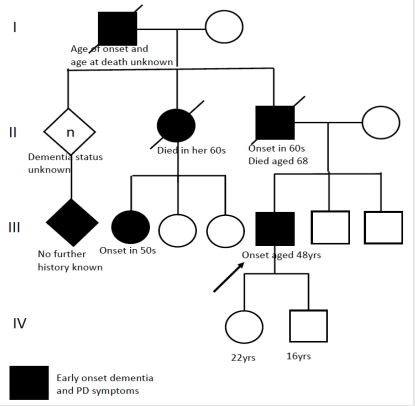
Fig 4: Monogenic vascular dementia

The various diagnostic criteria for vascular dementia (VaD) are heterogeneous and do not identify matching groups of patients with dementia. In addition, there are no specific pathological criteria for diagnosis, at least in the absence of frank infarction (as distinct from diffuse white matter hyperintensities on MRI). It can be difficult to differentiate VaD from AD, and indeed their co-occurrence seems to be common, at least in late onset dementia.

Other than the uncommon but well-recognised monogenic forms, the genetics underlying VaD is poorly understood. The monogenic forms are caused by pathogenic variants in *NOTCH3* (causing cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (OMIM 125310) (Fig 4)), *GLA* (causing Fabry disease with X-linked inheritance), (OMIM 301500)), *TREX1* (causing retinal vasculopathy with cerebral leukodystrophy, autosomal dominant (OMIM 192315)), *COL4A1* (causing brain small vessel disease with or without ocular anomalies, autosomal dominant (OMIM 607595)) and *HTRA1* (causing cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) (OMIM 600142) and CADASIL type 2 (OMIM 616779)). The commonly seen sporadic type of VaD is likely to be polygenic in addition to being influenced by the genetics of hypertension, dyslipidaemia and type 2 diabetes mellitus, as well as environmental factors such as smoking.

Dementia with Lewy Bodies and Parkinson Disease Dementia

Case example 5:
A 50 y.o. man referred by neurologist with a history of fluctuating memory impairment for 18 months and right upper limb tremor, progressive slowness and episodes of freezing of gait for 12-18 months with a suspicion of DLB. Wife also reported symptoms of REM sleep disturbance. Family history as indicated in pedigree below. On examination he had right upper limb resting tremor, moderate hypomimia and hypophonia, mild to moderate bradykinesia and rigidity, marked reduction in step length and arm swing with some degree of stooping of posture. Brain MRI was normal. SPECT and PET scans showed diffuse parietal and temporal dysfunction with a suspicion of AD like picture.



Genetics Consultation: Due to the early onset Parkinsonian symptoms along with dementia and an autosomal dominant family history, NGS based genetic testing for monogenic causes for PD/DLB was offered after pre-test counselling.

Genetic Test Results: No pathogenic variants corresponding to the phenotype were found in initial testing. Chromosomal microarray revealed a partial genomic duplication of ~1 megabase involving the *SNCA* gene.

Pertinent counselling issues: As *SNCA* gene duplications are known to be associated with DLB, chromosomal microarray or multiplex ligation-dependent probe amplification (MLPA) should be done if DLB suspected. Segregation testing in other affected family members is underway.

Fig 5: Dementia with Lewy Bodies

The question of whether dementia with Lewy bodies (DLB) and Parkinson disease dementia (PDD) are distinct entities or belong to different ends of the spectrum of the same pathology remains unanswered and still debated [100, 101]. Longitudinal observational studies suggest that most people with Parkinson disease (PD) go on to develop dementia in later stages of their disease [102, 103]. Clinical diagnosis of probable DLB involves the central feature of progressive cognitive decline, with the presence of any two of the three core features of fluctuating cognitive state, Parkinsonism (occurring <1 year before cognitive decline) and visual hallucinations [104]. PDD is diagnosed when parkinsonian motor features occur >1 year before the onset of cognitive changes [105]. Although clinically, and even pathologically, differentiating DLB/PDD from AD is difficult, this differentiation remains important, especially as up to 50% of patients with DLB can manifest severe neuroleptic sensitivity and hence these medications should be avoided unless absolutely necessary [106].

Although most PD and DLB are sporadic, and most likely due to polygenic causes, some monogenic forms of PD/DLB with early onset of cognitive decline are recognised. There is now increasing evidence that some variants in the gene *GBA* (OMIM 606463), which causes Gaucher disease, a lysosomal storage disorder when biallelic mutations are found, acts as a risk factor for PD with dementia [107, 108]. In particular, two variants in *GBA* c.1226A>G p.Asn409Ser (rs76763715) and c.1448T>C p.Leu483Pro (rs421016) were found to be highly associated with cognitive impairment in PD patients [109]. Increase in the amount of alpha synuclein in the brain - the major protein constituent of Lewy bodies, due to certain mutations in the *SNCA* gene (OMIM 163890), especially gene duplications (Fig 5), is associated with autosomal dominant DLB/PDD [110]. *SNCB* (OMIM 602569) which may be involved in alpha synuclein regulation, is also a possible associated gene [111]. Biallellic pathogenic mutations in *ATP13A2* (OMIM 610513) are known to cause very early onset PD and dementia in an autosomal recessive pattern [112]. Other monogenic causes of PD such as *LRRK2, DJ1, PINK1, PRKN, VPS13C, VPS35* do not have dementia as a prominent feature, but cognitive can occur at later stages.

Other genetic dementias:

A search in the Human Phenotype Ontology database for genes associated with the term dementia results in a list of 168 genes [113]. Most of these genes, however, are not causative of pure dementia syndromes. Dementia, in these cases co-occurs with other neurodegenerative disorders which may present variably. These disorders generally have other presenting symptoms such as a movement disorder or ataxia or other neurological features. Examples of such conditions include Huntington disease, some forms of spinocerebellar ataxias or complicated forms of hereditary spastic paraparesis. Rapid deterioration can indicate rare conditions such as genetic Creutzfeldt-Jakob disease or its

variant forms [114]. Niemann-Pick disease type C, which is a lipid storage disorder caused by biallelic pathogenic mutations in the gene *NPC1* (and rarely *NPC2*) is very rare, but should be considered in patients with childhood to early adulthood onset of ataxia, dementia and vertical supranuclear gaze palsy [115]. Mitochondrial disorders, lysosomal storage disorders and leukodystrophies can also cause genetically determined dementias.

Genetic testing techniques – advantages and limitations

NGS is a newer genetic technology in which millions of DNA fragments across many different genes can be sequenced in parallel. This has significantly reduced the time it takes to obtain a genetic diagnosis in a patient, compared with single-gene testing and could also reduce the overall cost associated with multiple diagnostic tests. In addition, the ability to simultaneously examine multiple genes has meant that many disorders of variable expressivity, that may not be high on a list of differential diagnoses based on a patient's clinical investigation, can be examined at the same time as high priority genes [28].

Three types of NGS techniques are currently available for clinical use. The first is targeted-panel gene sequencing, where only pre-specified genes are sequenced for a particular disorder. Targeted panels generally have a higher depth of reads compared to other techniques meaning that chance of errors due to inadequate read depth are generally low. Whole exome sequencing (WES) is able to read sequences from all coding regions (exons) in a genome. Whole genome sequencing (WGS) has the advantage of being able to identify genetic variants in both coding and non-coding regions of the genome such as promoter and enhancer regions, in addition to traditional Mendelian risk genes; however the link between these non-coding parts of the DNA and genetic disorders is not always known.

Large duplications, deletions or other structural variations (SV) cannot always be detected by traditional NGS techniques which rely on short read technology (i.e. sequence <1000 bp in each read). If such SVs are suspected in a gene of interest, a separate test designed to detect these changes, such as gene specific multiplex ligation-dependent probe amplification (MLPA) or chromosomal microarray or karyotyping (depending on whether there are enough markers covering the gene of interest), will be required. This is especially relevant for conditions such as DLB where *SNCA* duplications are associated with disease. Also, if short tandem repeats (STR), such as the CAG trinucleotide repeats in the *HTT* gene seen in Huntington disease, or the GGGGCC hexanucleotide repeats in *C9orf72* seen in FTD is suspected, either a specifically designed polymerase chain reaction-based test or Southern blot test will be required. Newer bioinformatic techniques are exploring SV and STR analysis in WES and WGS data, although many of these techniques are not ready for clinical application yet [116].

Genetic Counselling in Dementia

Although there have been several technological advances in genetic testing in recent times, the utility of these techniques for an individual patient and their family needs to be carefully considered before such complex tests are undertaken. Firstly, availability of such sophisticated tests does not always guarantee the identification of a precise genetic cause for dementia in a family, even when the family history is strong. There may still be genes that are yet to be discovered or the genetic test used may be insufficient to pick up all types of mutations. Previous publications using NGS techniques show ~12-13% mutation detection rate in dementia patients with a young age of onset with or without a family history, especially in the *PSEN1* gene [5, 8]. Analysis of WGS data from a clinical cohort of patients with dementia onset ≤65 years, (authors' unpublished data) also showed a 14% chance of

finding a causative mutation in those with dementia onset under the age of 65 and a further 20% chance of finding a genetic risk factor for their dementia, with most patients having no cause identified. Therefore, the majority of patients, despite a young age of onset and a family history, could remain without answers despite genetic testing.

Moreover, not all genetic variants are disease causing. Reports of previous publications alone are insufficient to categorise a variant as being pathogenic in the clinical setting. The American College of Medical Genetics and Genomics (ACMG) set stringent criteria to classify a variant as being pathogenic (i.e. disease causing) [117]. Many factors such as population frequency of a variant, *in silico* predictions, functional studies, and consistency with previously reported phenotypic information, are considered before determining if a genetic variant is clinically relevant for dementia in a patient [117-119]. When a genetic variant does not fit these criteria, it may be classified as a variant of uncertain significance (VUS).

Despite recent attempts at standardising the results through laboratories, interpretation in one laboratory may not match the interpretation in another and careful consideration of the experience of a laboratory and criteria used for reporting the results is important, along with multi-disciplinary team review ideally involving medical geneticists, neurologists, bioinformaticians, and genetic counsellors. Frequently, one or more VUS are found, and cannot be used for diagnostic purposes or to offer predictive type of testing to other family members until there is further clarity about the variant, which often takes several years. Certain genetic risk factors, such as the *APOE* ε4 risk allele also pose several challenges as the penetrance of dementia with these risk factors is variable. The variability in AD phenotype despite the high risk has meant that testing for the *APOE* ε4 genotype has been

discouraged by the ACMG, especially in the predictive context in asymptomatic individuals [120]. VUS or genetic risk factors may leave patients and families with the troubling knowledge that a genetic finding has been made but its implications in terms of risk to family members is unknown. For these reasons, genetic counselling prior to testing can be beneficial in communicating the complex information in a way that facilitates decision-making for the affected person and/or family member(s).

It should also be noted that, even in cases where no family history is reported, an underlying genetic mutation may be uncovered. Occurrence of dementia may appear "sporadic" where there is an autosomal recessive genetic cause with no affected siblings (eg *NPC1* mutations); an X-linked condition (eg *UBQLN2* mutations) with mildly affected or no other traceable affected members in the family; some mitochondrial genetic disorders (eg. mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes i.e. MELAS); anticipation as seen in STR disorders (eg. *C9orf72* expansions); *de novo* events where the mutation occurs for the first time in the affected family member (eg. *PSEN1*); as well as an incomplete family history with premature death or lack of accurate diagnosis. Clinical assessment regarding the type of dementia in combination with a thorough three generational family history would assist in most cases in determining utility of genetic testing.

The pre- and post-test counselling is important in facilitating adaptation to the result, and avoiding family conflicts which can frequently arise. Relatives may have opposing coping strategies such as avoidance and information-seeking [121]. Genetic counselling is especially relevant in the setting of dementia, where families have often experienced a lengthy diagnostic odyssey alongside the stressors of caring for a relative, changes in roles and

relationships, experiences of distressing behaviour change sometimes with violence, and family tensions [122].

Where there is a strong family history, the affected person and their own children may be struggling with specific fears brought into sharper focus by their lived experience in seeing other relatives deteriorate and die from the same condition [123]. Psychological impacts of being at potential risk of hereditary dementia can include conscious or subconscious barriers to long term relationship or family planning, and/or thoughts about having a "way out" via suicide or euthanasia [124]. Genetic counselling can help individual relatives, couples, siblings, parents and children, work through some of these emotions and thoughts ahead of receiving results to improve coping and support.

Furthermore, there may be complexities in obtaining consent for testing when a person has dementia, particularly if the person has partial capacity to decide about their own test but the benefit is mainly for the relatives, a formal proxy decision-maker may not have been arranged, or if two relatives with differing views on genetic testing have a joint informal or formal role in decision-making. Medical genetics clinics specialise in such genetic counselling issues and genetic counsellors are trained in navigating the psychological, ethical and family problems associated with genetic testing in this setting, and are well placed to refer clients if needing further support from neuropsychiatrists, social workers, psychologists or neuropsychologists, and community support organisations.

Conclusion and Future Directions:

Performing multi-gene testing in dementia may enable more precise diagnosis for a proportion of patients and simplify the diagnostic odyssey that many of these patients and

their families undergo. A precise genetic diagnosis may inform prognosis, and enable the option of predictive genetic testing for the known familial dementia gene in asymptomatic family members, and is likely to be cost-effective compared with the status quo. Currently, if an asymptomatic person has inherited the causative gene variant, there is no easy way to accurately predict the age of onset or symptom type or progression. Polygenic risk scores and better understanding of the environmental/lifestyle factors that influence dementia, may aid in the future development of better risk prediction models. Finding the genetic pathways influenced by genetic factors will take longer but may open up new approaches in therapeutic trials of dementia.

There will be significant clinical implications of genetic testing in dementia when treatments become available for various types of dementias. In recent years, this has been well exemplified by advances in the development of 'gene silencing' anti-sense oligonucleotide drugs. Anti-sense oligonucleotides, which can alter the expression of mutated proteins, have been used in early phase clinical trials in Huntington disease, and shown to reduce the expression of mutant huntingtin by between 40 and 60% [125]. Anti-sense oligonucleotides are being further investigated in other nucleotide repeat disorders such as *C9orf72* FTD/MND and spinocerebellar ataxias [126]. Single-dose gene therapy trials for patients with *GBA1* related PD and Gaucher disease have now reached phase 1 / 2 trial stages. Pre-clinical gene therapy trials are also underway for *GRN* mutation related FTD and α-synucleopathies including DLB and PD [127]. One of the limitations of these gene therapy trials is the need for intrathecal administration of the trial drugs.

A phase 3 trial of a recombinant human anti-human sortilin monoclonal antibody targeting the sortilin-progranulin axis is exploring this antibody in patients with *GRN* mutations [128].

In AD, studies such as Dominantly Inherited Alzheimer Network (DIAN) are exploring biomarkers of AD in asymptomatic relatives of gene positive individuals [129]. An arm of the DIAN study DIAN-TU is currently investigating the monoclonal antibodies Gantenerumab and Solanezumab in individuals with monogenic AD. Other therapies being studied for AD include agents targeting the metabolism of amyloid precursor protein (e.g. BACE1 or gamma-secretase inhibition, other antibodies directed against Aβ), increasing neuroprotection (e.g BDNF, GDNF), or inflammation modulators (e.g IL4) [130, 131]. Despite a large number of AD trials disease modification remains elusive [131].

More widespread genetic testing for dementia is likely to improve our overall understanding of the genetic aetiologies underlying the disease, which may subsequently inform the design of improved therapies or preventive strategies. Dedicated multidisciplinary dementia clinics with clinical geneticists, genetic counsellors, neurologists, neuropsychiatrists, aged care specialists and social workers specialised in this area are essential in helping these vulnerable patients and families navigate the vastly complex diagnostic and research paths compounded by their own progressive cognitive decline and the possibility of seeing other family members face the same. Many genetics clinics also offer outreach services to rural and regional areas. Embedding a geneticist and a genetic counsellor in regional/rural memory clinics could add more diagnostic value and decrease the time to diagnosis in these patients who may be disadvantaged due to distance from tertiary referral centres.

Data Availability Statement

Data included in this study (barring patient details) is available upon reasonable request from the corresponding author.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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