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INFORMATION SHEET

What causes Dementia?

There is still much to learn about what causes dementia.

There are many different types of dementia and the cause varies with type. The information below provides details of some of the major research areas.

Research into the genetics of dementia

Genes carry patterns for the many proteins that form our bodies. Proteins are the essential building blocks of life - forming cells, organs, and enzymes which help the body to function. Once they are made, proteins can be folded into different structures and shapes to fulfil their many functions. Genes are found in every cell in the body in packages of twisted DNA called chromosomes. Half of these chromosomes are inherited from each parent - providing the basis for genetic inheritance. Genes explain why family resemblances occur and why some diseases can run in families.

There is still much we don't know about the role of genes in Alzheimer's disease and other dementias, but researchers continue to study this area. In most cases, dementia occurs sporadically, is not directly caused by a single gene and has no clear pattern of family inheritance. However, in a minority of cases, Alzheimer's disease and some other types of dementia can be directly caused by an inherited gene mutation. The table below summarises some of the genes that have been found to cause or be involved in dementia. Each type is discussed in more detail under the relevant section below.

DISORDER	GENE	PROTEIN
Alzheimer's disease	PSEN1	presenilin-1
	PSEN2	presenilin-2
	APP	amyloid precursor protein
	ApoE	apolipoprotein E
Frontotemporal dementia	MAPT	tau
	PGRN	progranulin
	VCP	valosin-containing protein
CADASIL inherited form of vascular dementia	CHMP2B	chromatin-modifying protein 2B
	Notch3	notch 3
Huntington's disease	IT15	huntingtin

Research into the cause of Alzheimer's disease

THE ROLE OF PLAQUES AND TANGLES IN ALZHEIMER'S DISEASE

The biological causes of Alzheimer's disease are not fully understood and research continues to examine factors involved in the development of Alzheimer's disease.

The two most common hallmarks of Alzheimer's disease in the brain are beta-amyloid plaques and neurofibrillary tangles. The role of plaques and tangles in Alzheimer's disease is not fully understood. Both are present in the brains of older people who do not have Alzheimer's disease, although they are more widespread and predominant in the brains of people with Alzheimer's disease. Research is ongoing to determine more about the role of both plaques and tangles in the development of Alzheimer's disease.

In Alzheimer's disease, sticky beta-amyloid fragments clump together and form the basis of plaques. Recent research suggests that smaller clumps of beta-amyloid known as oligomers may actually be more toxic than the plaques. Researchers continue to study many aspects of beta-amyloid to establish its role in Alzheimer's disease, including the mechanisms of plaque formation, and how plaques might be removed from the brain.

The second common sign of Alzheimer's disease is neurofibrillary tangles. Tau is a protein which normally helps to maintain the structure of brain cells by strengthening the internal scaffolding of the cell (known as microtubules). In the brain cells of people with Alzheimer's disease, tau proteins don't function properly and instead form protein tangles inside the cell. This leads to a breakdown in the brain cell's ability to communicate with other brain cells and eventually to cell death.

Research has revealed that the tau protein also forms tangles in several other neurodegenerative conditions including frontotemporal dementia, indicating that tau may have a wider role in neurodegeneration. Ongoing research is examining the role of tau tangles in the initial development in Alzheimer's disease and the relationship between tau tangles and beta-amyloid plaques.

THE GENETICS OF ALZHEIMER'S DISEASE

Perhaps 40-50% of what causes Alzheimer's disease is thought to be attributable to our genes. That means that at least half of the cause is not genetic, but unknown. Gene mutations that directly cause Alzheimer's disease (discussed further below) are very rare and account for only around 5% of cases. One strong risk factor gene (discussed further below) has been identified that may account for 25-40% of cases. Genome wide association studies (GWAS) are now being undertaken to identify other risk factor genes, which may account for another 5% of the cause.

That still leaves at least half of all cases where the cause is unknown and means a great deal more research is needed to understand why some people develop Alzheimer's disease and others do not. Gene – gene interactions, gene – lifestyle interactions and gene – environment interactions that may contribute to the cause of Alzheimer's disease will be the next frontier of genetic research.

Comprehensive information about the research into the genetics of Alzheimer's disease is available at the AlzGene website.

GENES THAT CAUSE ALZHEIMER'S DISEASE

Familial Alzheimer's disease has a clear pattern of family inheritance and is very rare - accounting for perhaps 5% of all cases. Symptoms usually begin in the 30s, 40s, or 50s. There are currently three genes that have been linked to familial Alzheimer's disease, but it is possible that more genes will be identified.

The three genes linked to familial Alzheimer's disease are Presenilin 1 (PSEN1), Presenilin 2 (PSEN2), and the Amyloid Precursor Protein (APP) gene. These genes act to influence protein processing in the brain and the mutations that cause Alzheimer's disease cause abnormal proteins to be formed.

A mutation in the APP gene causes an abnormal type of APP protein to be formed, which is more likely to produce the beta-amyloid plaques that accumulate in the brain in Alzheimer's disease.

The exact function of the presenilin genes PSEN1 and PSEN2 are not known. Some studies have indicated that they might code for specialised enzymes which cut APP into different protein fragments including beta-amyloid protein. Damage to the enzymes (through the gene mutation) could change the way APP is cut and increase the production of beta-amyloid.

When one of these mutated genes is inherited from a parent, the person will almost always develop Alzheimer's disease. This inheritance pattern is referred to as "autosomal dominant" inheritance. Children have a 50/50 chance of inheriting the mutated gene and developing familial Alzheimer's disease if one of their parents carries the gene.

The discovery of these genes was critical because it showed that genetics are involved in Alzheimer's disease and helped identify important aspects in the disease process. Research into familial Alzheimer's disease continues in the hope of learning more about how the disease develops and how it can be treated.

GENETIC RISK FACTORS FOR ALZHEIMER'S DISEASE

In most cases, Alzheimer's disease is not directly caused by a single gene mutation, and in fact there is no clear cause. However, researchers have identified at least one gene that increases the risk of developing Alzheimer's disease.

Everyone has two copies of the apolipoprotein E (ApoE) gene, which codes for a protein involved in cholesterol transport. There are three common variants of the ApoE gene - e2, e3 and e4.

- APOE e2 is relatively rare and may provide some protection against Alzheimer's disease. If Alzheimer's does occur in a person with this variant, it develops later in life than it would in someone with the APOE e4 gene.
- APOE e3 is the most common variant. It is believed to play a neutral role in Alzheimer's disease—neither decreasing nor increasing risk.
- APOE e4 is present in about 25-30% of the population and occurs in about 40% of all people who develop late-onset Alzheimer's disease. Research has confirmed that APOE e4 is associated with an increased risk of developing the disease, but why is not yet understood. People who inherit 1 or 2 copies of APOE e4 tend to develop Alzheimer's disease earlier than those who don't carry this gene variant.

APOE e4 is called a risk factor gene. It is important to note that having the ApoE e4 gene variant does not mean you will definitely develop Alzheimer's disease. Many people who have the ApoE e4 gene do not develop Alzheimer's disease and many people who do have Alzheimer's disease do not have the ApoE e4 gene. Many studies are underway to find more genes which may influence the development of Alzheimer's disease. Other genes are being identified that appear to increase the risk of developing Alzheimer's disease, but these have a very small effect on risk compared to APOE e4.

THE ROLE OF INFLAMMATION IN ALZHEIMER'S DISEASE

Inflammation is part of the immune system response to fight off damage from disease or injury. However, people with Alzheimer's disease have high levels of brain inflammation and there is some evidence that this could contribute to the disease. Some evidence suggests that beta-amyloid plaques attract immune cells, leading to a build up of inflammatory factors at the site of plaques, but it is not known whether this is beneficial or harmful.

Several studies have found that earlier use of anti-inflammatory drugs might lower the risk of developing Alzheimer's disease. However, trials of non-steroidal anti-inflammatory drugs (NSAIDs) to treat people with Alzheimer's disease have not been successful and NSAIDs are associated with some serious side effects. Research continues to explore the involvement of inflammation in Alzheimer's disease.

RESEARCH INTO THE CAUSE OF VASCULAR DEMENTIA

Vascular dementia is the second most commonly diagnosed type of dementia, and may account for 15 - 20% of all cases. Vascular dementia is caused by chronic reduced blood flow to the brain, usually as a result of a stroke or series of strokes. It can often coexist with Alzheimer's disease.

Stroke, small vessel disease, or a mixture of the two can cause vascular dementia. Most commonly there is a blockage of small blood vessels somewhere in the network of arteries that feeds the brain. Blockages may be caused by plaque build up on the inside of the artery wall, or by blood clots which have broken loose. Clots can form as a result of abnormal heart rhythms, or other heart abnormalities. Also, a weak patch on an artery wall can balloon outward and form an aneurysm, which can burst and deprive brain cells of oxygen.

It is estimated that about 50% of cases of vascular dementia result from high blood pressure, which can lead to a major stroke or a series of strokes and a build up of brain damage over time. Less common causes of vascular dementia are associated with autoimmune inflammatory diseases of the arteries such as lupus and temporal arteritis, which are treatable with drugs that suppress the immune system.

There are a number of different types of vascular dementia, the two most common being Multi-infarct dementia and Binswanger's disease. Multi-infarct dementia is caused by a number of strokes, often accumulating progressively over a period of time. Binswanger's disease (also known as subcortical vascular dementia) is associated with damage to the brain's white matter, or nerve fibres. It is caused by high blood pressure, thickening of the arteries and inadequate blood flow.

An inherited form of vascular dementia known as CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is caused by a mutation on the Notch3 gene. This is a very rare form of dementia and only affects families carrying the Notch3 gene mutation.

Many people with dementia are found to have vascular related brain damage in addition to the plaques and tangles that characterise Alzheimer's disease. Recent findings concerning the overlap between risk factors for cardiovascular disease and Alzheimer's disease, such as high blood pressure, diabetes and high cholesterol, have indicated that there may be a strong connection between the development of Alzheimer's disease and vascular conditions. It may be that having Alzheimer's disease and vascular events increases the risk of dementia more than either one alone, and that there are interactions between the two. These findings may have important implications for preventative strategies, suggesting that reducing vascular risk factors could reduce risk for both Alzheimer's disease and vascular dementia, in addition to heart disease. Research is ongoing to further examine the vascular contribution to dementia.

Research into the cause of Frontotemporal dementia

Frontotemporal dementia is the name given to a group of dementias when there is degeneration in one or both of the frontal or temporal lobes of the brain. The behavioural variant of frontotemporal dementia involves the frontal lobes and includes Pick's disease. The language variant involves the temporal lobes and includes Progressive non-fluent aphasia and Semantic dementia.

The genetics of frontotemporal dementia are not fully understood and are the subject of ongoing research. About 30% of people with frontotemporal dementia have a family history of the disease. Only about 15% have a known genetic mutation that causes the disease. Mutations have been identified in the MAPT and PGN genes on chromosome 17, which code for the tau and progranulin proteins respectively. Other genes such as VCP and CHMP2B have been found to be affected in several rare cases of the disorder.

These gene mutations are inherited in an autosomal dominant pattern. This means that each child of someone with the mutation has a 50% chance of inheriting it. Those with the mutation are destined to develop the dementia. Together, the MAPT and PGN gene mutations account for about half of the cases of familial frontotemporal dementia. This means that there are other responsible genes yet to be discovered.

The majority of cases of frontotemporal dementia are sporadic, with no strong family history, and their cause is unknown. A number of different underlying cellular brain changes can be associated with frontotemporal dementia. Research is continuing to attempt to discover how these changes arise and lear more about their relationship with the clinical syndromes of frontotemporal dementia.

For more information about research into frontotemporal dementia, visit the website of Frontier research group on frontotemporal dementia at Brain Mind Centre at *https://www.sydney.edu.au/brain-mind/our-clinics/frontotemporal-dementia-clinic.html*

Research into the cause of Dementia with Lewy bodies

Dementia with Lewy bodies is characterised by the presence of abnormal spherical structures, called Lewy bodies, which develop inside nerve cells in the brain. Lewy bodies are accumulations of a protein called alpha-synuclein. It is thought that these contribute to the degeneration and death of nerve cells.

Dementia with Lewy bodies sometimes co-occurs with Alzheimer's disease and/or vascular dementia. It may also be hard to distinguish dementia with Lewy bodies from Parkinson's disease, which is also associated with Lewy bodies, and some people who have Parkinson's disease develop a similar dementia.

At present there is no known cause of dementia with Lewy bodies and no risk factors have been identified. In very rare cases, the disease appears to be inherited, but a genetic cause has not yet been found. In short, we do not know why Lewy bodies form in the brain and research continues in the attempt to find an answer. Much of this research is focussed on searching for the genetic roots of dementia with Lewy bodies, exploring the mechanisms of alpha-synuclein accumulation, and discovering how Lewy bodies cause the particular symptoms of dementia with Lewy bodies.

Research into other causes of dementia

Dementia is also associated with other conditions such as AIDS, Creutzfeld-Jakob disease, chronic alcohol abuse, Down Syndrome, Huntington's disease and Parkinson's disease.

- A genetic component has been found for a very rare subtype of Creutzfeld-Jakob disease.
- Individuals with Down Syndrome have an extra copy of chromosome 21, which contains the gene for the Amyloid Precursor Protein, increasing their likelihood of developing Alzheimer's disease.
- Huntington's disease is caused by a mutation in the gene that codes for the huntingtin protein. Everyone who inherits the mutated version of this gene will eventually develop the disease. Dementia occurs in the majority of cases.

This information has ben sourced from Dementia Australia: *https://www.dementia.org.au/about-dementia/dementia-research/causes-of-dementia*

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