Chapter 5

Summary
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In the first part of this thesis, we focus on the clinical aspects of inherited dementia. Chapter 2.1 provides an overview of genetic causes of dementia. We explained that although dementia is in most cases a complex disease with multiple factors contributing, dementia is Mendelian inherited in a small percentage of the cases. We described that mutations in the \textit{presenilin 1} (\textit{PSEN1}) gene are the most common genetic cause of early onset Alzheimer’s disease (AD), whereas \textit{amyloid precursor protein} (\textit{APP}) and \textit{presenilin 2} (\textit{PSEN2}) mutations are less frequent. Frontotemporal dementia (FTD) may be caused by mutations in the \textit{microtubule-associated protein tau} (\textit{MAPT}) or \textit{(pro)granulin} (\textit{GRN}) gene, or by a hexanucleotide repeat expansion in the \textit{chromosome 9 open reading frame 72} (\textit{C9orf72}) gene. All these genes show autosomal dominant inheritance with a high penetrance. We describe genotype-phenotype correlations and conclude that phenotypes overlap. Furthermore, we provide algorithms for genetic testing in patients with early onset Alzheimer’s disease or frontotemporal dementia, with the most important recommendation to consider offering genetic testing to all patients with bvFTD, both familial and sporadic.

In chapter 2.2, we describe our study on the effect of predictive testing of individuals at risk of Huntington’s disease (HD) or familial FTD. Since most follow-up studies on predictive testing for neurodegenerative diseases focussed on psychological outcome, we aimed to investigate whether the life of mutation carriers of adult-onset neurodegenerative diseases differs negatively from non-carriers and untested at risk individuals. We invited individuals aged \(\geq 35\) years, tested while asymptomatic for HD, FTD or AD more than 2 years before the start of the study or at 50\% risk for one of these diseases, to complete a questionnaire of 70 items and an additional questionnaire of 47 items sent within a year afterwards. Of the selected individuals, 115 (39.6\%) were willing to participate. Of these, 17 carriers, 30 non-carriers and 27 untested persons fulfilled the criteria and completed both questionnaires. We found no significant differences between carriers and non-carriers or untested individuals at risk in employment, financial situation and lifestyle or anxiety and depression. Carriers were more often single and childless, though these differences were not significant. Although the outcome of this study is likely to be influenced by a response bias, these findings suggest that in most individuals, an unfavourable outcome of predictive testing on adult onset neurodegenerative diseases does not have a large negative effect on social and personal life.
In chapter 3, we investigated the frequency of causative mutations in patients with dementia and the associated phenotype. In chapter 3.1, we describe the clinical and neuropathological characteristics of hexanucleotide repeat expansions in the C9orf72 gene in a large cohort of Dutch patients with FTD. We determined the repeat length in a cohort of 353 patients with sporadic or familial FTD with or without amyotrophic lateral sclerosis (ALS), and 522 neurologically normal controls. We identified hexanucleotide repeat expansions in 37 (28.7%) of the individuals with familial FTD and 5 (2.2%) of the sporadic FTD patients. In the repeat expansion carriers, the mean age at onset of the FTD was 56.9 ± 8.3 years (range 39-76), and the mean disease duration 7.6 ± 4.6 years (range 1-22). Most patients with the C9orf72 repeat expansion had behavioural variant FTD (bvFTD) (n = 34), and 7 patients had concomitant amyotrophic lateral sclerosis (ALS). Neuroimaging was characterized by predominant temporal atrophy in 13 of 32 patients. Pathological examination showed frontotemporal lobar degeneration with neuronal transactive response DNA binding protein (TDP)-positive inclusions of variable type, size and morphology in all 10 investigated brains.

In chapter 3.2, we investigated the frequency of causative mutations in the common dementia genes in a cohort of patients with early onset dementia. Furthermore, we investigated whether mutations in the recently identified gene PRKAR1B were present in this cohort. We performed mutation analysis of the genes PSEN1, APP, MAPT, GRN, C9orf72 and PRKAR1B on DNA of 229 patients with the clinical diagnosis AD and 74 patients with the clinical diagnosis FTD below the age of 70 years. We found PSEN1 and APP mutations in respectively 3.5% and 0.4% of AD patients, and none in FTD patients. C9orf72 repeat expansions were present in 0.4% of AD and in 9.9% of FTD patients, whereas MAPT and GRN mutations were both present in 0.4% in AD patients and in 1.4% resp. 2.7% in FTD patients. We did not find any pathogenic mutations in the PRKAR1B gene. We concluded that in Dutch patients with early onset dementia, PSEN1 mutations are the most common genetic cause, though rare, in AD and C9orf72 repeat expansions the most common mutation in FTD patients. PRKAR1B mutations are probably rare in Dutch patients with a clinical diagnosis of early onset AD or FTD.

Chapter 4 describes the genetic defects and the associated phenotype of two families with assumed autosomal dominant dementia. In chapter 4.1, we present three siblings with cognitive complaints, reduced amyloid-beta-42 in CSF and multiple cerebral lobar microbleeds, and a positive family history for autosomal dominant early onset dementia. With whole exome sequencing, we identified in all three siblings a novel frame shift variant generating a premature stop codon in the CCM2 gene, one of the genes
associated with familial cerebral cavernous malformations. We did not find this variant in a cohort of 363 patients with early onset dementia, with or without multiple lobar microbleeds, or in control databases including the Dutch genetic biobank GoNL. Furthermore, two siblings were homozygous for APOE-ε4 and one heterozygous. Two of the patients had cerebral cavernous malformations, confirming the diagnosis familial cerebral cavernous malformations. The observed microbleeds could be due to the APOE-ε4, but could also be in fact bleeds from very small cavernous malformations. The cognitive complaints, reduced amyloid-beta-42 in CSF and microbleeds suggest preclinical AD, but the stability of the cognitive complaints does not. We hypothesized that both the CCM2 variant and the APOE status may have contributed to the phenotype.

In chapter 4.2, we describe a family with clinically heterogeneous AD and an assumed autosomal dominant family history, in which all four genotyped affected family members were homozygous for the APOE-ε4 allele. Affected family members presented with a mean age of symptom onset of between 61 and 74 years, with variable presence of microbleeds on cerebral imaging and electroencephalographic abnormalities. We performed exome sequencing on three affected and one unaffected family and identified a rare pathogenic variant in the VPS10 domain of the AD-related SORL1 gene. Segregation analysis showed that his variant was present in all four affected and one unaffected family member. Furthermore, three affected family members and one unaffected family member carried a rare pathogenic variant in the TSHZ3 gene. Both SORL1 and TSHZ3 are involved in the amyloid pathway, and SORL1 variants are associated with an increased risk of AD. We hypothesized a combined effect of Apoe4, the SORL1 variant of possibly also the TSHZ3 variant on AD development. Furthermore, we speculated that the convergence of multiple genetic factors over several generations might also clarify the autosomal dominant-like inheritance pattern of AD in other families.