CHAPTER 1

INTRODUCTION

1.1 Background

Normal range of CGG repeat length in the fragile X mental retardation 1 (*FMR1*) gene is from 6 to 54. CGG repeats greater than 200 results in methylation and an absence of transcription leading fragile X syndrome. CGG repeat length of 55 to 200 in the *FMR1* gene is called premutation, which is associated with a spectrum of conditions including fragile X-associated primary ovarian insufficiency (FXPOI), anxiety, depression, and various medical and neurological problems, such as migraine, fibromyalgia, neuropathy, sleep apnea, hypertension, hypothyroidism, and fragile X-associated tremor/ataxia syndrome (FXTAS).[1] In addition, some young carriers can experience developmental delays, autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD).[2,3] Among these conditions, FXTAS is a debilitating neurodegenerative disease in carriers of the premutation.[1] Initially, motor deficits and cognitive impairment as well as psychiatric symptoms in FXTAS were previously thought to occur only in older individuals (above age 50 years) who have CGG repeats within the premutation range (55 to 200) in the fragile X mental retardation 1 (*FMR1*) gene.[4-7] However, FXTAS features have recently been reported in patients with grey zone/intermediate alleles (45 to 54 CGG repeats),[8,9] as well as

individuals with an unmethylated full mutation (CGG repeats > 200)[10] and full mutation/premutation mosaicism.[11]

Intranuclear inclusions are a pathologic marker of the FXTAS brain, thought to be built up by proteins sequestered by the expanded *FMR1* mRNA.[12-14] Also, the expanded CGG repeats trigger repeat-associated non-AUG-initiated (RAN) translation of a cryptic polyglycine-containing protein, FMRpolyG.[15]

Cell viability was reduced in cultured human neural cells transfected with mRNA containing expanded CGG repeat,[16] and murine hippocampal neurons expressing *FMR1* premutation have been shown to die early in culture.[17]

Brain atrophy has been shown to be a strong predictor for cognitive decline, dementia, and functional disabilities in the normal elderly population.[18-20] Furthermore, brain atrophy has been used as a biomarker of disease progression in other neurodegenerative disorders such as multiple sclerosis,[21,22] Alzheimer's disease,[23] Huntington's disease,[24] and Parkinson's disease,[25] with the tendency of higher rates of atrophy as compared to the normal elderly population.[26]

The radiologic features of FXTAS include white matter hyperintensities (WMH) on T2-weighted magnetic resonance imaging (MRI) in the middle cerebellar peduncles (MCP) and cerebral white matter, as well as moderate-to-severe generalized atrophy.[5] Studies in the normal elderly population have shown that increased subcortical WMH volume is associated with increased rate of ventricular cerebrospinal fluid volume (VCSFV) change.[27] In FXTAS, increased ventricular volume correlated with advanced FXTAS stage.[28] The hypothesis of this study is that

the neuronal dysregulation leading to neuronal loss[1] in FXTAS may cause brain volume changes manifested as decreased whole brain volume (WBV) and increased VCSFV, and may be used as a measure of disease progression in FXTAS.

The present research will provide essential information about the rate of brain changes with FXTAS progression with FXTAS progression that could in the future allow assessment of person-specific pathologic changes for the purposes of evaluating disease progression and guiding treatment.

1.2 Research questions

1. Is there any effect of annualized WBV and VCSFV change on the occurrence of high FXTAS stage (stage 4-5)?
2. Are there any differences of mean brain volumes between FXTAS subjects and healthy controls?
3. What is the rate of annualized brain volume changes in FXTAS?

1.3 Study objectives

1.3.1 General Objective

This thesis is to assess brain volume changes in FXTAS and its relationship with clinical stage.

1.3.2 Specific objectives

1. To determine the effect of annualized WBV and VCSFV change on the occurrence of high FXTAS stage (stage 4-5).
2. To compare mean brain volume measurements in the FXTAS subjects to healthy controls.
3. To assess mean annualized brain volume changes in FXTAS.
4. To examine the relationship between *FMR1* CGG repeats and mRNA, and annualized WBV and VCSFV change.

1.4 Research benefits

This result will provide better insight in order to detect and evaluate FXTAS, leading to a more comprehensive diagnosis, prognosis and better treatments in FXTAS.

1.5 Originality

There is only one previous cross-sectional study regarding volumetric brain changes in FXTAS. The study did not assess brain volume changes in FXTAS longitudinally. However, it assessed gender difference in brain volumes and measured cerebellar volume, which were not performed in this study.

Table 1. List of previous study

Publication	Methods	Results
Adams JS, Adams PE, Nguyen D, Brunberg JA, Tassone F, Zhang W, *et al*. Volumetric brain changes in females with fragile X-associated tremor/ataxia syndrome (FXTAS). Neurology. 2007; 69(9):851-9	Volumetric MRI studies, clinical staging, cognitive testing, and molecular analysis were conducted in 15 female premutation carriers affected by FXTAS (age 59.5 +/- 10.3 years), 20 unaffected female carriers (43.3 +/- 11.2 years), 11 genetically normal female controls (51.0 +/- 10.3 years), 36 affected male carriers (65.0 +/- 5.6 years), 25 unaffected male carriers (53.5 +/- 12.5 years), and 39 male controls (58.0 +/- 15.0 years).	Reduced brain volumes associated with the presence of FXTAS in females compared with female controls. A significant associations between reduced cerebellar volume and both increased severity of FXTAS symptoms and increased length of the CGG repeat expansion in male premutation carriers, but not in females.

CHAPTER 2

LITERATURE REVIEW

2.1 Prevalence of FXTAS

The *FMR1* premutation occurs in approximately 1/148-209 females and 1/290-468 males in the USA.[29-31] Although the prevalence of FXTAS in the general population is unknown, FXTAS occurs in approximately 45% of male premutation carriers and 8–16% of female premutation carriers over the age of 50[4,32] In a study of males recruited through known Fragile X families in California, the prevalence was approximately 17% at age 50-59, 38% at age 60-69, 47% at age 70-79 and 75% at age ≥ 80.[33] FXTAS occurred in 8.3% women with premutation in a study at UC Davis MIND Institute.[34] FXTAS has rarely been reported in Asian population. Only 2 male cases have been reported in Japan[35,36] and 3 male cases of FXTAS have been reported in Indonesia.[37]

2.2 Clinical phenotype of FXTAS

2.2.1 Spectrum of FXTAS symptoms

Besides core symptoms of intentional tremor and cerebellar ataxia,[4-6, 33, 38-42] there is an increased frequency of neurological, psychological, endocrine, and immune-related characteristics in patients with FXTAS[1] as seen in panel.