Universiteit Antwerpen
Faculteit Geneeskunde en
Gezondheidswetenschappen

Exploring hereditary ataxia and spasticity in the era of whole exome sequencing

Proefschrift voorgelegd tot het behalen van de graad
van doctor in de Medische Wetenschappen
aan de Universiteit Antwerpen door

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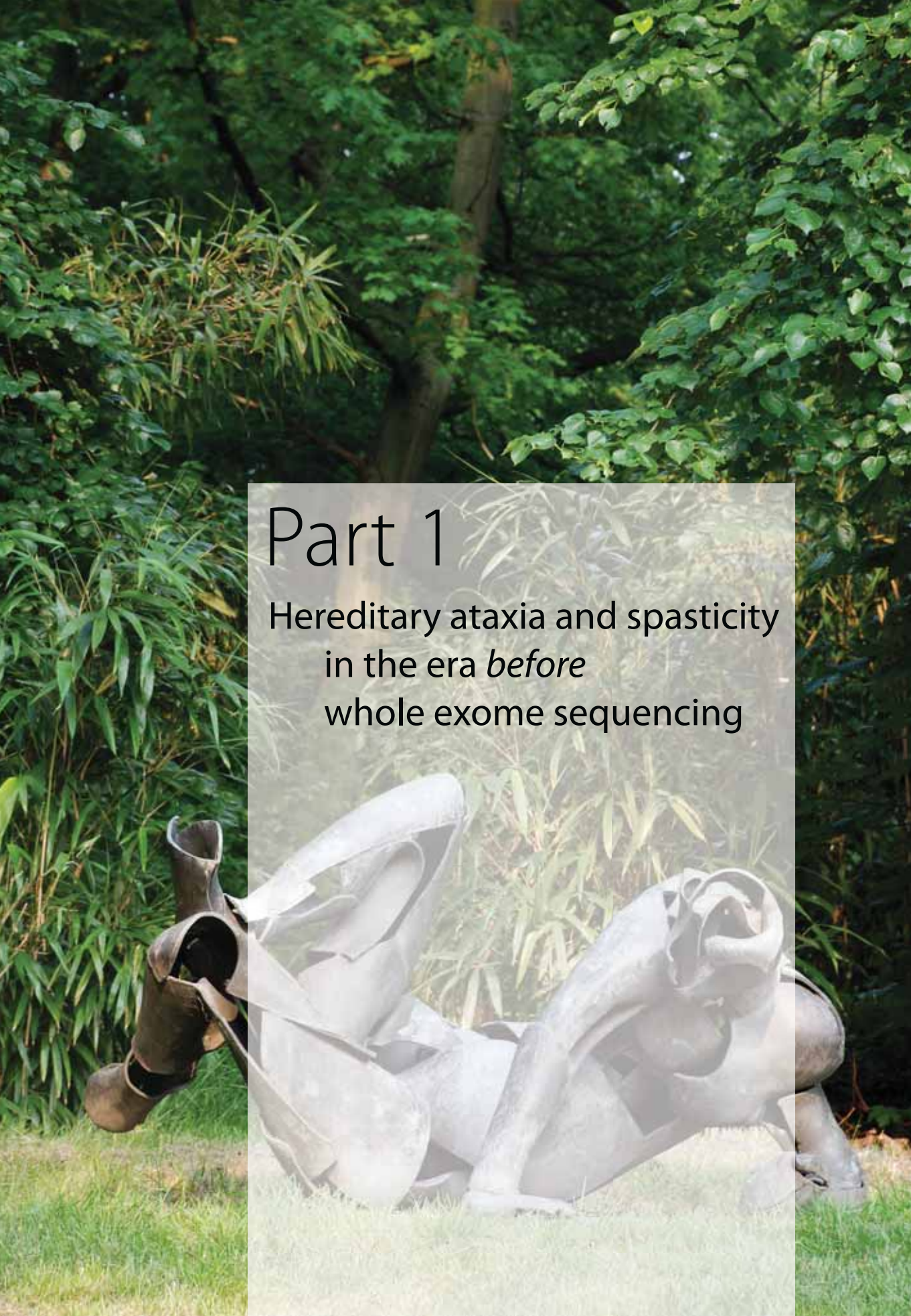

Part 1

Hereditary ataxia and spasticity in the era *before* whole exome sequencing

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Chapter 1
Partial deletion of *AFG3L2* causing spinocerebellar ataxia type 28

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A partial deletion of *AFG3L2* causing spinocerebellar ataxia type 28.
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Chapter 1: Contents

Introduction

Spinocerebellar Ataxias (SCAs) are a clinically and genetically heterogeneous group of neurodegenerative cerebellar disorders [1,2]. Autosomal dominant SCA type 28 (SCA28) represents one of 11 autosomal dominant SCA subtypes not caused by repeat expansions [3-9]. SCA28 is characterized by a juvenile-onset, slowly progressive cerebellar ataxia with ophthalmoparesis and ptosis as prominent features. Heterozygous mutations in *AFG3L2* cause SCA28 [6]. A total of 17 families have been published to date [3-9]. *AFG3L2* encodes a subunit of the *m*-AAA protease, a component of the ATP-dependent metalloprotease, located on the inner mitochondrial membrane. *AFG3L2* is highly homologous to *paraplegin*, the causal gene of autosomal recessive hereditary spastic paraparesis type 7 (SPG7)[10]. A homozygous *AFG3L2* missense mutation has been reported in a single autosomal recessive spastic ataxia 5 family (SPAX5)[11]. We expanded the genetic spectrum of SCA28 through the identification of an identical partial deletion of exons 14 to 16 of AFG3L2 in 2 autosomal dominant SCA families. Furthermore, we provide a detailed brain autopsy and MRIs, confirming superior vermis atrophy in this disease. With additional functional work we identify haploinsufficiency as the underlying disease mechanism in our families.

Patients and methods

Patients

Genealogical studies showed a clear autosomal dominant inheritance in both Family 1 (F1) (Figure 1.1A) and Family 2 (F2) (Figure 1.1C) Both families are of Belgian origin and live in the same region in Flanders. We collected clinical information and blood samples from all affected (table) and unaffected individuals. For this study all living patients were clinically reexamined (K.S. and P.D.J.). MRI studies, muscle and brain pathology and electrophysiological studies have been performed in the University Hospital of Antwerp.

Methods

Standard protocol approvals, registrations, and patient consents. All patients or legal representatives signed informed consent before enrollment. The local institutional review board approved this study.

Table 1.1. Clinical features and investigations of Belgian individuals with *AFG3L2* partial deletion.

Family	**F1**				**F2**														
Generation	**I.**	**II.**	**II.**	**III.**	**I.**	**II.**	**II.**	**II.**	**III.**	**III.**	**III.**	**III.**	**III.**	**III.**	**III.**	**III.**	**IV.**	**IV.**	**IV.**
Patient	**1**	**2**	**3**	**1**	**2**	**1**	**3**	**6**	**1**	**2**	**4**	**5**	**7**	**9**	**11**	**13**	**1**	**3**	**5**
Onset-age/y, sex	30, f	54, m	35, m	36, m	50, f	70, m	48, f	48, f	43, m	49, m	20, f	35, m	33, f	30, f	28, f	30, m	33, f	26, f	28, f
Exam-age/y	74	55	47	49	/	88	60	60	662	68	28	54	59	58	57	52	33	26	28
X, Current age/y	X:75	X:75	X:52	49	X	89	X	X	63	69	X	54	59	58	57	52	33	26	28
Disease duration	45	21	17	13	?	19	?	?	20	20	?	19	26	28	29	22	<1	<1	<1
Gait ataxia	++	+	+	+	+	+	+	+	+	+	+	+	+	++	+	++	+	-	-
Dysarthria	++	++	+	+	/	+	+	+	+	++	+	+	+	++	++	++	-	-	-
Ophthalmoparesis	+	+	+	+	/	-	+	+	-	+	+	+	-	+	-	++	-	-	-
Hypometric saccades	+	+	+	+	/	+	+	+	+	+	+	+	+	+	+	++	-	+	+
Ptosis	++	++	++	+	+	-	+	++	++	++	+	-	-	++	-	++	-	-	-
Nystagmus	++	+	+	+	/	+	+	+	+	+	+	-	-	++	+	++	-	+	-
Increased reflexes in LL	+	-	-	+	/	-	+	++	-	+	++	+	-	-	-	++	-	-	-
Babinski Sign	-	-	-	-	/	-	+	-	-	+	+	-	-	-	-	-	-	-	-
Spasticity	-	-	-	-	/	-	-	+	-	+	+	-	-	-	-	-	-	-	-
Dementia	-	-	-	-	/	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Epilepsy	-	-	-	+	/	-	-	-	-	-	+	-	-	-	-	-	-	-	-
Family		F1-									F2-								
Generation	I.	II.	II.	III.	I.	II.	II.	II.	III.	III.	III.	III.	III.	III.	III.	III.	IV.	IV.	IV.
Patient	1	2	3	1	2	1	3	6	1	2	4	5	7	9	11	13	1	3	5
Muscle weakness	-	LL	LL	-	/	-	-	-	-	+	+	-	-	-	-	-	-	-	-
Muscle atrophy	-	pLL	pLL	-	/	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Wheelchair	no	yes	yes	no	no	no	no	no	yes	no	yes	no	no	no	no	yes	no	no	no
Initial MRI	va	va	/	ca	/	/	/	va	ca	ca	ca	ca	ca	ca	va	coa	/	/	/
(age/Y)	?	55		46				68	47	53	22	35	34	36	36	44			
MRI DTI + VBM	/	/	/	va	/	/	/	/	/	/	/	va	va	va	va	va	/	/	/
(age/Y)				48								53	58	57	55	51			
Muscle Biopsy	/	/	n	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/
EMG	/	n	n	/	/	/	n	/	n	n	N	n	n	n	/	n	/	/	/
Brain Autopsy	coa	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/

Abbreviations: F= Family; y= years; Exam= examination; X= died; f= female; m= male; += present and moderate; ++= present and severe; - = absent; /= not done; LL= lower limbs; pLL= proximal lower limbs; ca= cerebellar atrophy; va= vermis atrophy; n= normal; coa= cerebello-olivary atrophy; DTI=Diffusion Tensor Imaging; VBM= Voxel Based Morphometry ; ?= unknown.

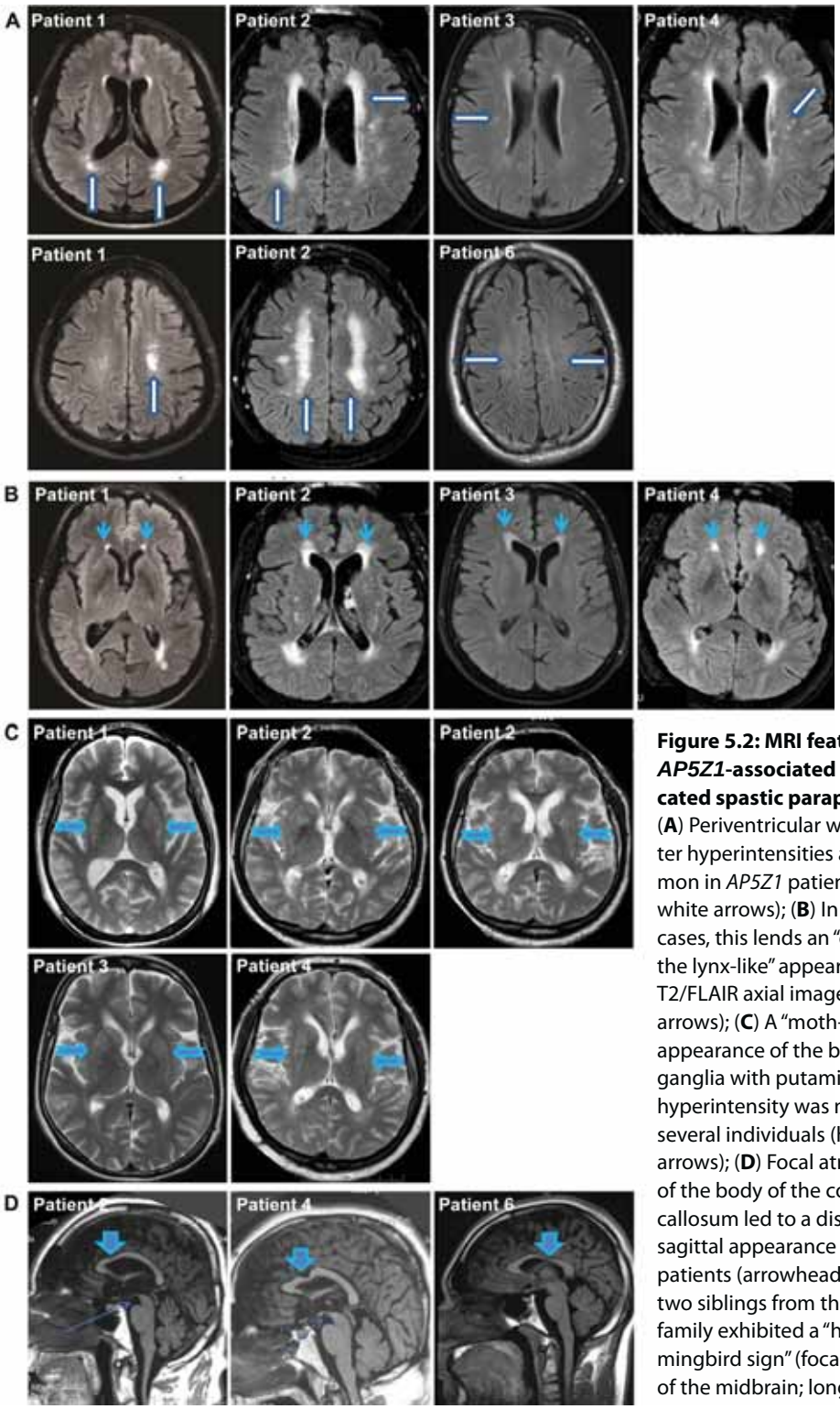

Figure 5.2: MRI features of *AP5Z1*-associated complicated spastic paraplegia. (**A**) Periventricular white matter hyperintensities are common in *AP5Z1* patients (Blue-white arrows); (**B**) In some cases, this lends an "ears of the lynx-like" appearance to T2/FLAIR axial images (blue arrows); (**C**) A "moth-eaten" appearance of the basal ganglia with putaminal rim hyperintensity was noted in several individuals (hatched arrows); (**D**) Focal atrophy of the body of the corpus callosum led to a distinctive sagittal appearance in several patients (arrowheads), while two siblings from the Belgian family exhibited a "hummingbird sign" (focal atrophy of the midbrain; long arrows).