The Role of Aristaless Related Homeobox *(ARX)* Gene Mutations in Intellectual Disability

A thesis submitted for the degree of **Doctor of Philosophy**
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Tod Fullston
B.Sc. (Hons)
Student No 1067053

Neurogenetics Laboratory
Discipline of Paediatrics
School of Paediatrics and Reproductive Health
Women's and Children's Hospital campus

Primary supervisor: Professor Jozef Gécz
Co-supervisor: Professor John Mulley

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ABSTRACT

Intellectual disability (ID) affects ~1-3% of the population, profoundly impacting the lives of affected individuals and their families. An approximate 30% excess of males with ID implicates X-chromosome genes. The most common inherited form of ID is fragile-X syndrome, affecting ~1/5,000 live male births. Another X-linked gene, the aristaless related homeobox *(ARX)* gene, is also frequently mutated causing X-linked ID (XLID).

At least 50 pathogenic mutations spanning the *ARX* open reading frame (ORF) have been reported in 110 families. These mutations cause at least 10 clinically distinct pathologies, all of which include ID. These clinical entities range in severity from X-linked lissencephaly with ambiguous genitalia (XLAG) to mild ID with no other consistent clinical features.

Of the known *ARX* mutations 60% occur in the section of the ORF that encodes for the first two tracts of uninterrupted alanine, *ie* polyalanine (pA) tracts. This is likely due to the extraordinarily high GC content of these regions of the gene (>97%). Two recurrent mutations (c.304ins$(GCG)_7$ – pA1 and c.429_452dup – pA2) arise from expansion of their respective pA tracts. The c.429_452dup mutation alone accounts for ~40% of all reported *ARX* mutations.

To assess the frequency of *ARX* mutations among the intellectually disabled, genomic DNA from 613 individuals were screened for the most frequent *ARX* mutations. Of these, 500/613 samples were screened for mutations in the entire *ARX* ORF by either SSCP, dHPLC or direct Sanger sequencing. A subset of 94/500 patients were also screened for sequence variations in ultraconserved (uc) elements flanking the *ARX* gene, which likely act as *ARX* enhancers. Subsequently, using transient transfection studies we assessed the subcellular localisation of selected mutations and wildtype ARX proteins.

Six different *ARX* mutations were detected in eight individuals (8/613; 1.3%) and potentially pathogenic sequence variations were found in uc elements in three more individuals. A total of five duplication mutations were discovered in pA2, two larger than the recurrent c.429_452dup, confirming exon 2 of *ARX* as a mutation 'hot spot'. Increased aggregation was observed as a function of pA1 and pA2 length, aligning with the patient's phenotypic severity.

Three missense mutations were detected. A familial c.81G>C mutation caused a premature termination codon in exon 1, leading to Ohtahara syndrome (OS) and West syndrome (WS) in two male cousins. Although the c.81G>C mutation should truncate the ARX protein, re-initiation of translation at a down-stream methionine codon (c.121_123) likely occurs, 'rescuing' these patients from the otherwise severe XLAG phenotype.

Two point mutations (c.1074G>T/p.R358S; c.1136G>T/ p.R379L) that alter key residues within the homeodomain were found in two individuals with brain/genital malformations and led to increased ARX protein mislocalisation. These mutations impair vital properties of ARX's transcription factor function by perturbing its localisation into the nucleus (p.R379L) or DNA binding (p.R358S).

This study confirms that *ARX* mutations contribute significantly to XLID and that the majority of mutations occur within exon 2, specifically within the region of pA2. Moreover, there is a correlation between the subcellular localization of the mutant protein and the clinical severity in the patients.

STATEMENT AND DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to **Tod Fullston** and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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'*Constant dripping hollows out a stone*.' Lucretius.

'*Long is the way, and hard, that out of hell leads up to light.*' John Milton.

TABLE OF ABBREVIATIONS

Abbreviation	Full description
A, C, G, T	adenosine, cytosine, guanine, thymine – nucleotides
aa	amino acid
ACC/AG	absence of the corpus callosum with abnormal genitalia
ADI-R	autism diagnostic interview – revised
AG	abnormal genitalia
AGRE	autism genetic research exchange
ANOVA	analysis of variance
ARID	autosomal recessive intellectual disability
aut	autism
BERA	brainstem evoked response audiometry
BLAST	basic local alignnment tool
BLAT	BLAST-like alignment tool
bp	base pairs
c.	coding sequence
CA	cytoplasmic positive with or without aggregates in either the nucleus or cytoplasm
cDNA	complimentary DNA
CGH	comparative genome hybridisation
CNS	central nervous system
CNV	copy number variation – deletion or duplication (> 1 kb)
CSF	cerebrospinal fluid
CT	computerised tomography (scan)
DAPI	4',6-diamidino-2-phenylindole
del	deletion
dHPLC	denaturing high pressure liquid chromatography
DMSO	dimethyl sulphoxide
DNA	deoxyribonucleic acid
dNTP	deoxynucleoside triphosphate
dup	duplication
EEG	electroencephalogram
EFMR	epilepsy and mental retardation limited to females
EIEE	early infantile epileptic encephalopathy
EMG	electromyogram
epi	epilepsy
exp	expansion
FosTeS	fork stalling and template switching
FXS	fragile-X syndrome
FXTAS	fragile-X associated tremor/ataxia syndrome
GABA	gamma-aminobutyric acid
HEK293T	human embryonic kidney; cell line 293T
hex	hexachlorofluorescein
HYD/AG	hydranencephaly with abnormal genitalia
ID	intellectual disability
ID/TS/Dys	intellectual disability with tonic seizures with dystonia
IEDE	infantile epileptic-dyskinetic encephalopathy
iGOLD	international genetics of learning disability
indels	insertions and deletions and (<1 kb)
ins	insertion
IQ	intelligence quotient
ISSX	infantile spasms syndrome, X linked
kb	kilo base pair

(*Cont. next page*)

Abbreviation	Full description	*Cont.*
LCL	lymphoblastoid cell line	
LGS	Lennox-Gastaut syndrome	
LOD	logarithm of the odds	
Mb	mega base pair	
MGB	minor groove binder	
milliQ	ddH_2O water from a Millipore milliQ system	
MIM	Mendelian inheritance in man – online reference	
miRNA	micro ribonucleic acid	
mis	missense	
MRI	magnetic resonance imaging	
mRNA	messenger ribonucleic acid	
MRS	magnetic resonance spectroscopy	
NGS	next generation sequencing	
NI	nuclear inclusions only	
NLS	nuclear localisation sequence	
NMD	nonsense mediated decay	
non	nonsense	
nsXLID	non syndromic X-linked intellectual disability	
OCF	occipital-frontal circumference	
ORF	open reading frame	
OS	Ohtahara syndrome	
p.	protein residue	
pA	polyalanine tract	
PAGE	polyacrylamide gel electrophoresis	
PBS	phosphate buffered saline	
PCR	polymerase chain reaction	
PRTS	Partington syndrome	
PS	Proud syndrome	
PTC	premature termination codon	
qPCR	quantitative real-time polymerase chain reaction	
RNA	ribose nucleic acid	
RNA	ribonucleic acid	
RT-PCR	reverse transcription polymerase chain reaction	
SDS	sodium dodecyl sulfate	
sil	silent	
SNP	single nucleotide polymorphism	
SSCP	single stranded conformational polymorphism	
STS	sequence-tagged site	
sXLID	syndromic X-linked intellectual disability	
Taq	Thermus aquaticus	
TBS	tris-buffered saline	
uc	ultraconserved elements	
UCSC	University of California, Southern California	
UTR	untranslated region	
UV	ultraviolet	
WS	West syndrome	
wt	wildtype	
XLAG	X-linked lissencephaly and ambiguous genitalia	
XLID	X-linked intellectual disability	
XMESID	X-linked myoclonic epilepsy with spasticity and intellectual disability	