Wolfram syndrome research

Timothy Barrett
University of Birmingham, UK
Birmingham Children's Hospital, UK
t.g.barrett@bham.ac.uk
Jan 2012

Summary of presentation

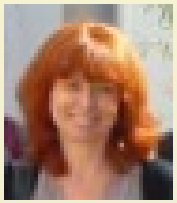
- Introduction: who we are, who's who in Europe
- Round-up of international research groups
- UK research
  - Cell models of disease
  - Candidate drug treatments
  - Markers of effectiveness
  - The European patient registry EURO-WABB
- Future plans

Some Wolfram researchers in Europe

Barrett
group
Birmingham

Tranebjaerg
Copenhagen

Tillman,
Koks group
Tartu



Paquis
group Nice

Mlynarski
Warsaw

Linnears
group
Montpellier

Nunes group
Barcelona

Rohayem
Dresden

Research in Spain, Denmark

- Nunes group
  - Clinical data on large cohort
  - Genotype phenotype correlations
  - Mitochondrial involvement in Wolfram syndrome
- Tranebjaerg
  - 8 Families
  - WFS1 variants cause optic atrophy and hearing impairment without diabetes
  - Check heterozygous carriers for eye, hearing problems

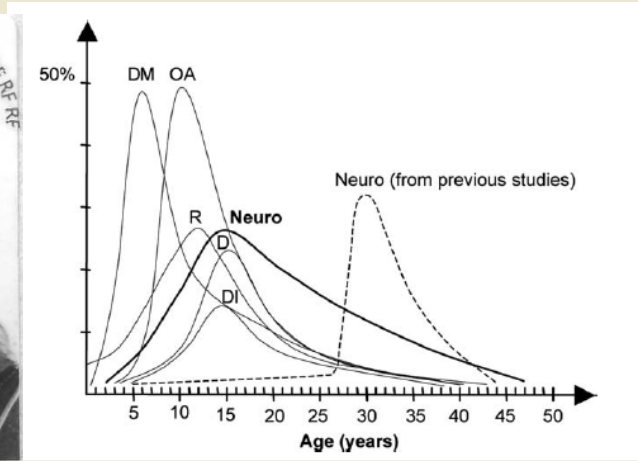
IDIBELL
Institut d'Investigació Biomèdica de Bellvitge

(Rendtorff N et al, Am J Med Genet 2011;155A:1298-313)

Research in France

- Paquis-Flucklinger V
  - Cohort of 59 patients
  - Neurological features present much earlier (aged 15 yrs in 30%) than previously reported
  - Can pick up on MRI

- Lenaers, Hamel group
  - Montpellier
  - WFS1 KO mouse
  - Characterising ophthalmic defect
  - Long term research programme into eye defect in Wolfram
  - Aiming for gene therapy of optic atrophy

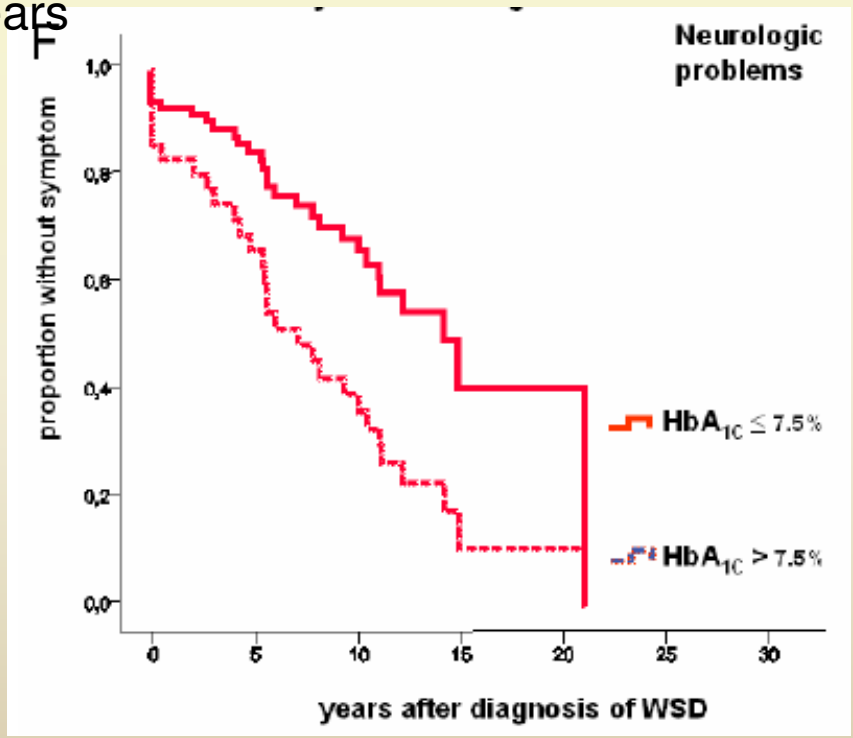


(Chaussenot A et al. Ann Neurol 2011;69:501-8)

Research in Germany, Estonia

Julia Rohayem, Dresden

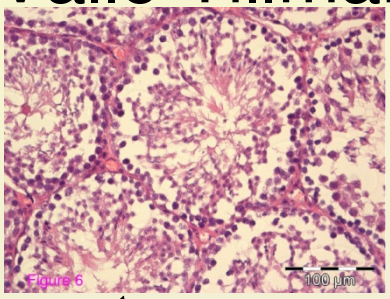
-Follow-up of 50 WS patients over 10 years

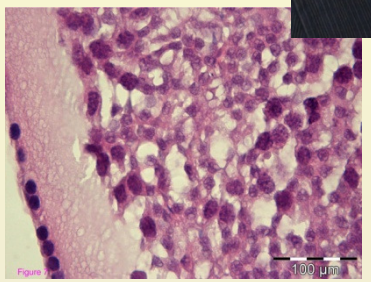


(Rohayem J Diabetes Care 2011;34:1503-10)

Sulev Koks,

Vallo Tillman, Tartu





Wild type (seminiferous tubules) WFS1 $^{-/-}$

WFS1 whole knockout mouse

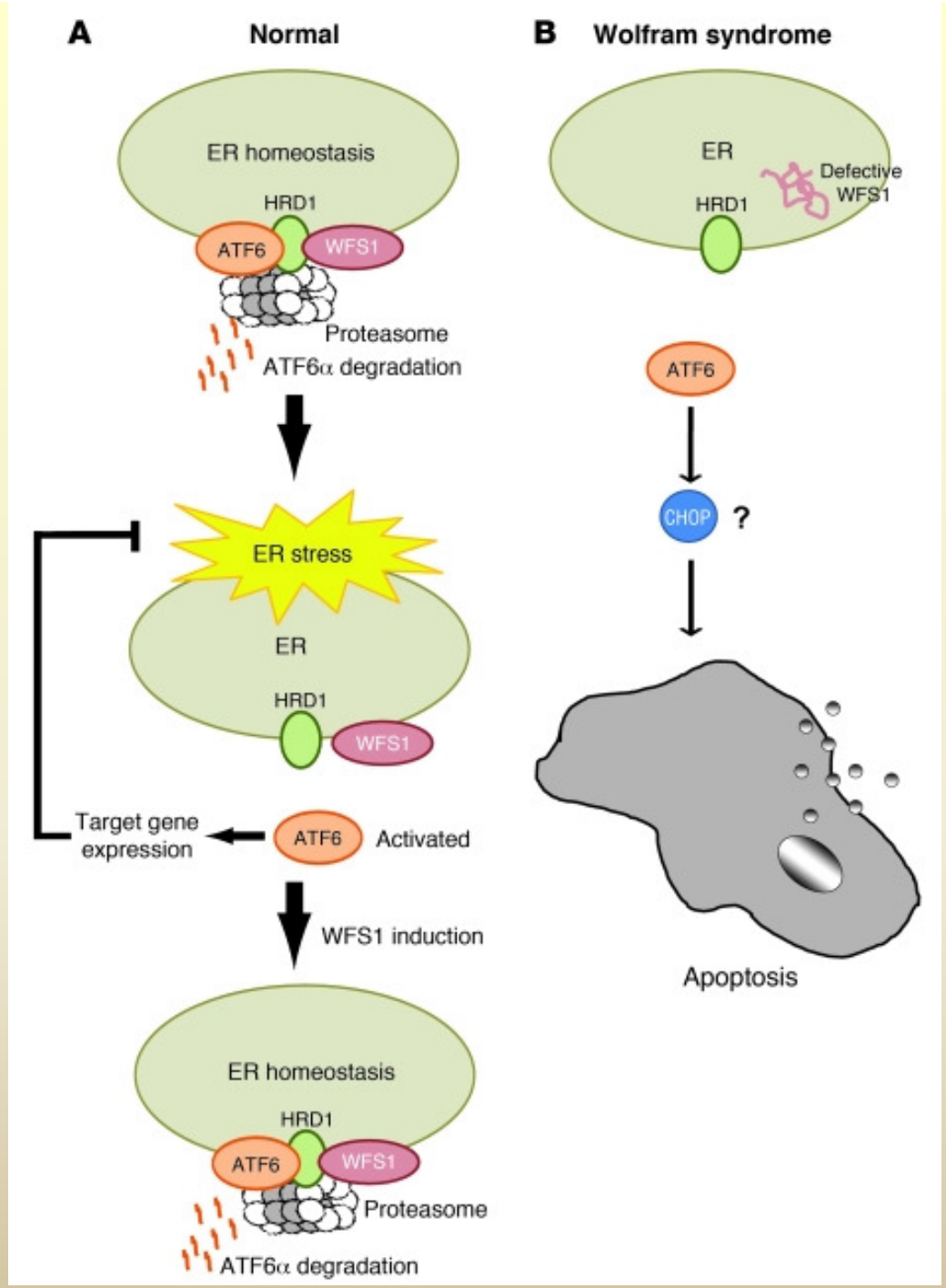
Males reduced fertility vs females
Males earlier diabetes vs females

(Norrmets K et al Reprod Biol Endocrinol 2009;7:82)

Fumi Urano, USA

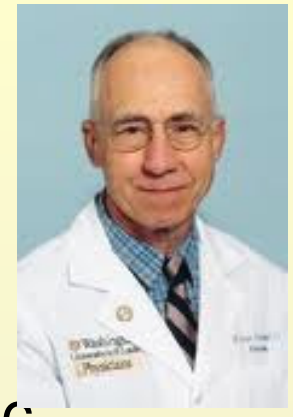
Wolfram protein acts as a negative regulator of ER stress

Drug screening program of 1000 FDA approved drugs, to treat ER stress



Fonseca et al 2010

Prof Alan Permutt: Wolfram Syndrome Research Clinic

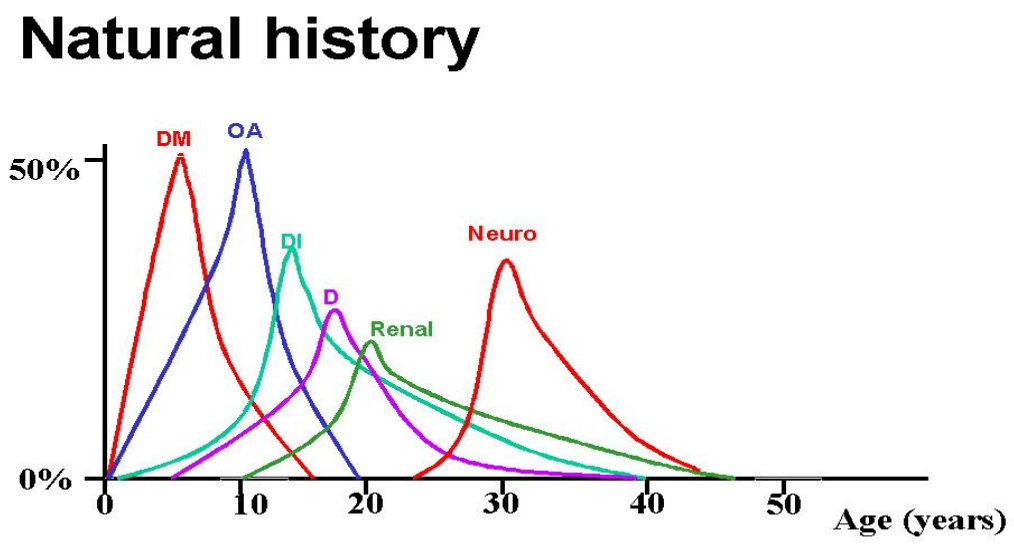


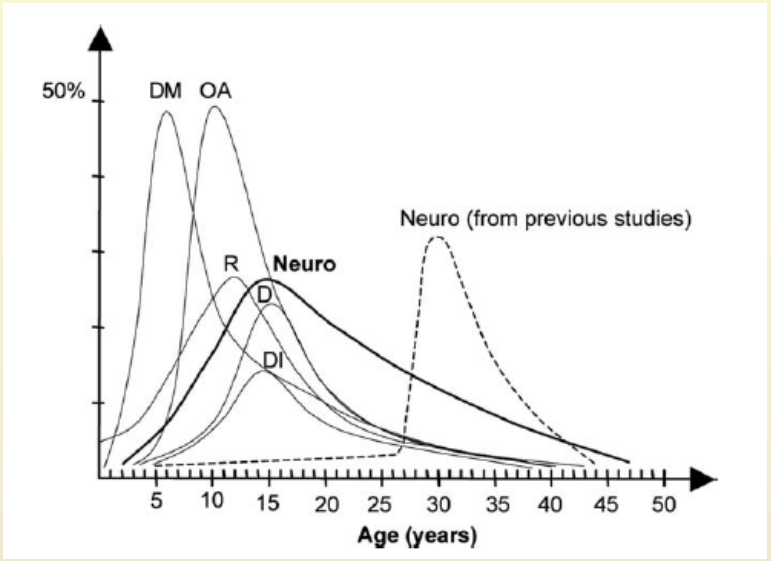
- Aim to identify markers of progression ready for therapeutic studies
- Funded by American Diabetes Association and parents' charity
- Visual acuity, refraction, ocular nystagmus, colour vision testing, pupillary light reflexes, slit lamp biomicroscopy, dilated fundus exam, visual field testing, retinal tomography
- Specific tests for gait, coordination, grip strength
- MRI scans for accurate measurement of brain volumes

Researchers in Birmingham

- Laboratory based
  - Dr Zatyka
  - Dr Astuti
  - Ms Seley Gharanei (PhD student)
- Genetics and function
  - Gene mutations
  - Animal models
  - Cell lines
- Hospital based
  - Ms Amy Farmer
  - Sr Susan Gleeson
    - Clinical studies in type 1
  - Clinical Research Facility nurses
    - ~8 studies
  - Ms Zoe Gray
    - Cohort study of type 2
- Research with children

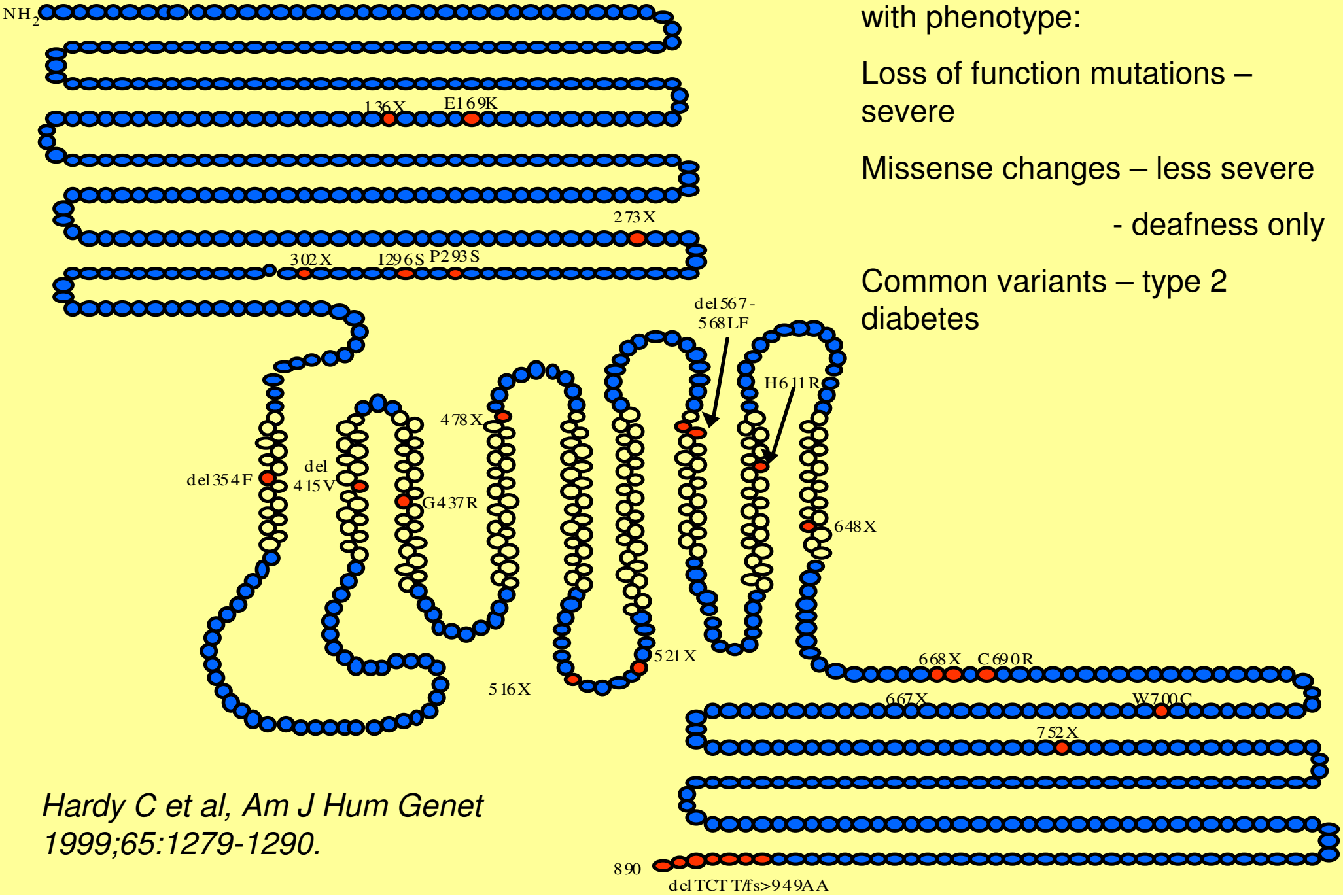
Wolfram syndrome: 45 families





(Chaussenot A et al. Ann Neurol 2011;69:501-8)

(Barrett T et al, Lancet 1995;346:1458-63)



Mutations in WFS1 gene correlate with phenotype:

Loss of function mutations – severe

Missense changes – less severe

- deafness only

Common variants – type 2 diabetes

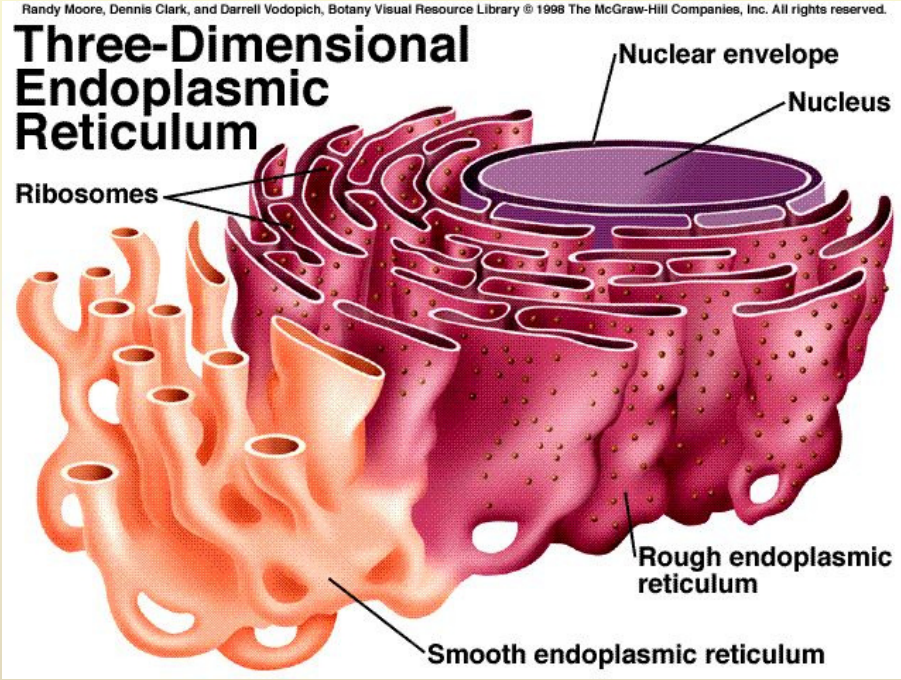
Hardy C et al, Am J Hum Genet 1999;65:1279-1290.

Clinical pattern: Wolfram syndrome

- 1 in 500,000 children
- Diabetes mellitus, deafness, blindness, diabetes insipidus, neurodegeneration
- Autosomal recessive
- Gene WFS1, makes Wolframin protein
  - What does Wolframin do?

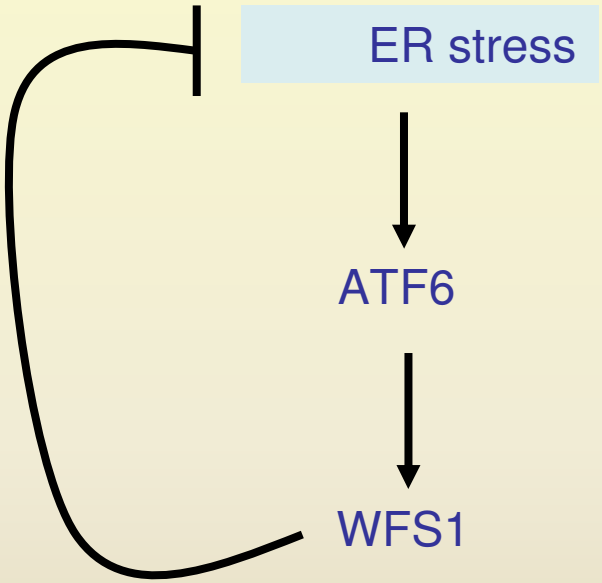
The Endoplasmic Reticulum

- Secretory pathway
- Post tranlational modifications
- Folding/assembly of oligomeric proteins
- Cellular Ca store
- Lipid synthesis



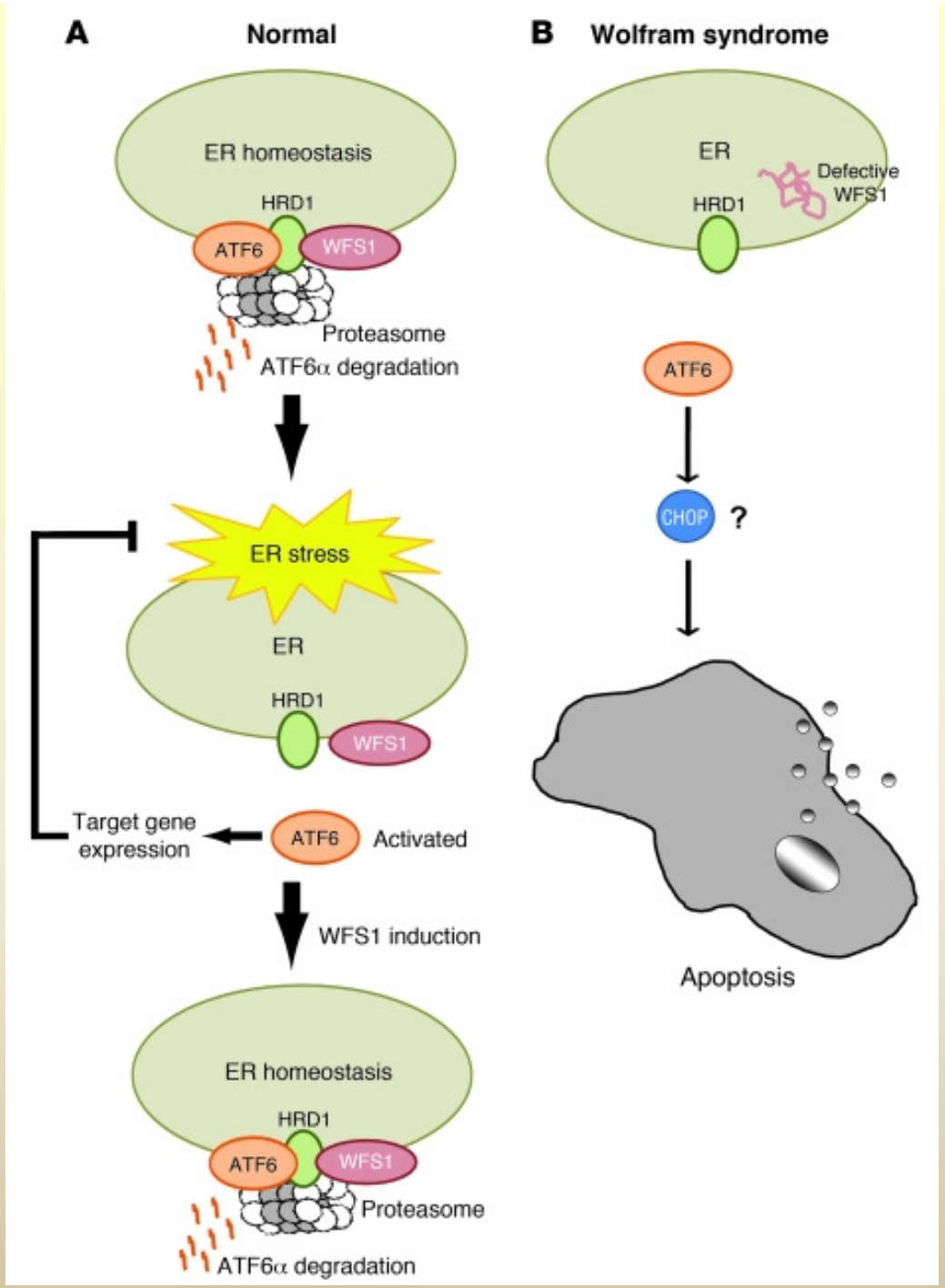
Wolframin protects cells from stress

- The gene: WFS1
- The protein: Wolframin
- The function in health:
  - to protect beta cells from stress
- The problem in disease:
  - No protection against stress, cells die



(Fonseca S et al, JBC 2005;280:39609-15)

Wolfram protein acts as a negative regulator of ER stress



Fonseca et al 2010

Our working hypothesis:

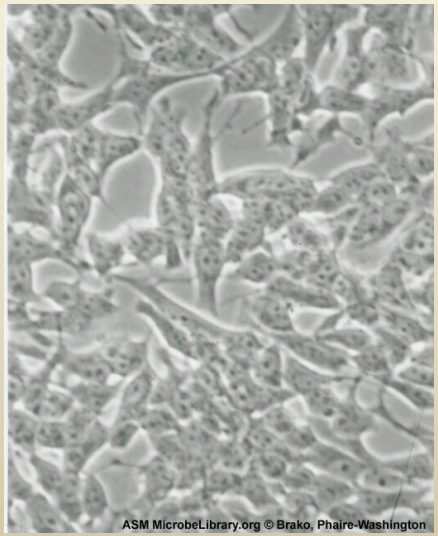
- In Wolfram syndrome, lack of the Wolfram protein leads to unregulated endoplasmic reticulum stress. This places a stress burden on the cells so that eventually they die

The research questions:

1. Can we make a lab model of the disease?
   - Human brain cell model (neuroblastoma)
2. Can we treat the stress in the model?
   - Candidate drugs VPA, TUDCA
3. Can we a non-invasive measure of effectiveness?
   - Magnetic Resonance Spectroscopy
4. Can we gather enough people for a clinical trial?
   - European rare diabetes registry EURO-WABB

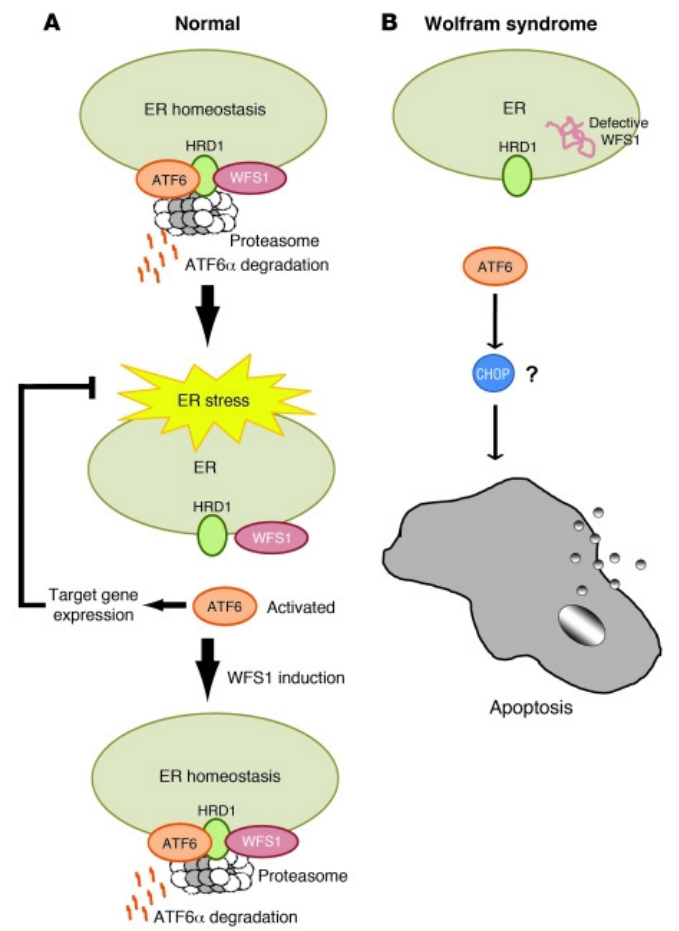
Birmingham research

- PhD project
- Human neuroblastoma cells 70% WFS1 depleted
- Characterisation as cell models for Wolfram syndrome



Human brain cell lines with depleted Wolfram protein show increased ER stress markers

Our cell model also shows increased cell death

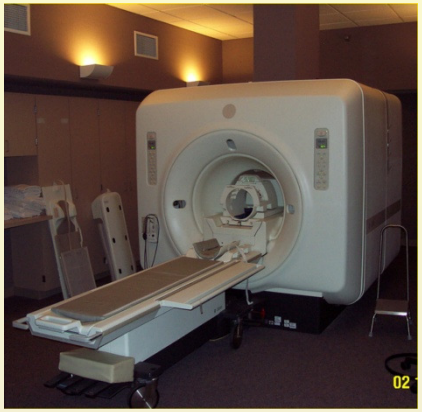


When we transfect cells with master regulator of ER stress, we can abolish the ER stress response and stop cell death

Can we find a drug that boosts the body's levels of Wolfram protein?

Can we find a drug that reduces ER stress levels?

Can we find a non-invasive biomarker to make it easier to measure the effects of treatment?



Magnetic resonance spectroscopy

EURO-WABB: A European registry for Wolfram, Alstrom, Bardet Biedl syndromes: www.euro-wabb.org

- Origin
  - French Wolfram Association wanted researchers to work together
  - Collaborative grant application to European Union
  - More likely to get funded for 3 rare diseases than for one
- The need
  - Delayed recognition, diagnosis, access to specialist care, genetic testing
  - Difficult to research, clinical trials of new treatments without a cohort.
  - No reliable patient information, training for doctors, patients suffering
- Why do we need another registry?
  - Existing registries can't reach out to enough affected people
  - Local physicians need to have some ownership of a registry
  - What do families get: reliable information, free testing, researchers liaise with local physician to support local care

EURO-WABB aims and objectives

- EU registry of clinical, molecular genetic and outcome data on up to 300 affected patients for each condition
  - To establish disease characteristics, best management, and outcomes
  - To assess effectiveness of clinical management and quality of care
  - To provide a cohort of interested patients for future clinical studies
  - To understand relations between clinical and genetic findings
- High usage by:
  - Access to rapid, free genetic testing
  - Up to date accurate patient information
  - Teaching resources for health professionals

First project meeting Paris April 2011

www.euro-wabb.org Web Design for people with low or no vision, multilingual

WP 4: Patient information sheets and health professional education material

WP 5: Genetics: Dr Dewi astuti

Free online publicly accessible database of all published mutations in WFS1, WFS2, ALMS1, BBS genes

Searchable directory fully referenced

Network of 8 EU accredited diagnostic labs for molecular genetic diagnostic testing

LOVD - Leiden Open Variation Database

Wolfram syndrome 1 (wolframin) (WFS1)

Curators: LOVD administrator and Dewi Astuti

LOVD v.2.0 Build 30 [Current LOVD status]
Welcome, Dewi Astuti
Your account | Log out

Home | Variants | Submitters | Submit | Configuration | Documentation

WFS1 homepage | Switch gene

LOVD Gene homepage

General information	
Gene name	Wolfram syndrome 1 (wolframin)
Gene symbol	**WFS1**
Chromosome Location	4p16.1
Database location	XAMPP local install
Curator	LOVD administrator and Dewi Astuti
PubMed references	View all (unique) PubMed references in the WFS1 database
Date of creation	April 06, 2011
Last update	August 10, 2011
Version	**WFS1 110810**
Add sequence variant	Submit a sequence variant
First time submitters	Register here
GenBank reference	NG_011700.1
Total number of unique DNA variants reported	**190**
Total number of individuals with variant(s)	**309**
Total number of variants reported	**584**
Subscribe to updates of this gene	

Graphical displays and utilities	
Summary tables	Summary of all sequence variants in the WFS1 database, sorted by type of variant (with graphical displays and statistics)
UCSC Genome Browser	Show variants in the UCSC Genome Browser (compact view)
Ensembl Genome Browser	Show variants in the Ensembl Genome Browser
NCBI Sequence Viewer	Show distribution histogram of variants in the NCBI Sequence Viewer

Sequence variant tables	
Unique sequence variants	Listing of all unique sequence variants in the WFS1 database, without patient data
Complete sequence variant listing	Listing of all sequence variants in the WFS1 database
Variants with no known pathogenicity	Listing of all WFS1 variants reported to have no noticeable phenotypic effect (note: excluding variants of unknown effect)

Search the database	
By type of variant	View all sequence variants of a certain type
Simple search	Query the database by selecting the most important variables (exon number, type of variant, disease phenotype)
Advanced search	Query the database by selecting a combination of variables
Based on patient origin	View all variants based on your patient origin search terms
Search through hidden entries	Find the number of variant entries in the database (including hidden entries) matching your search terms

Links to other resources	
Homepage	http://www.euro-wabb.org
HGNC	12762
Entrez Gene	7466
OMIM - Gene	606201
OMIM - Disease #1	Wofram syndrome 1
OMIM - Disease #2	Deafness, autosomal dominant DFNA6/14/38
UniProtKB (SwissProt/TrEMBL)	O76024
HGMD	WFS1
GeneCards	WFS1

What you get if you are a patient

- Get to input your own data
- Data about personal experiences confidential from your own doctor
- Can view your complete data record
- Genetic test report from an EU accredited lab
- Open access to latest research findings, patient information, health professional info via www.euro-wabb.org
- Follow research progress on Facebook, Twitter, You-Tube and Blog
- Online forum via Facebook

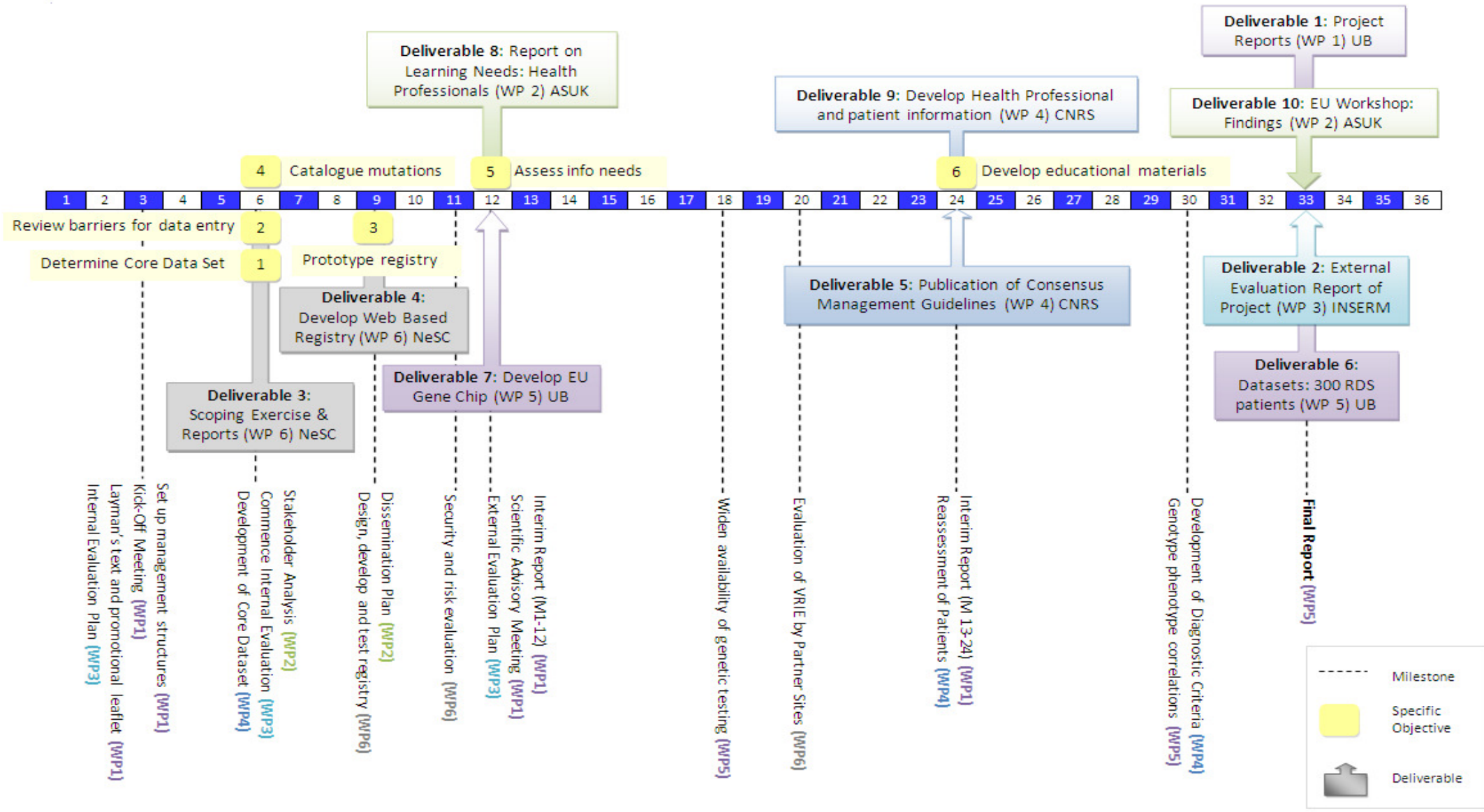
Ethics: extract from UK form

5	I agree for my child's anonymised data to be stored electronically on the EURO-WABB register that is held in the University of Glasgow, Scotland.	☐
6	I confirm that I am happy to be contacted about future research projects associated with my child's condition. I understand that information about these projects will be passed to me by my child's clinician and that other researchers won't have access to my child's personal details.	☐
7	I confirm that I am happy for my child to take part in the EURO-WABB registry *(You will be given a copy of this signed form and information sheet to take home)*	☐

The following statements are about how the EURO-WABB registry data is used. Please initial the 'Yes' or 'No' boxes, indicating whether you agree or disagree with each statement below:

8	I agree that my child's anonymised data can be included in a national disease registry for his/her condition	*Yes*	*No*
9	I agree that my child's anonymised data can be shared with other disease registries and research projects relevant to his/her condition within Europe	*Yes*	*No*
10	I agree that my child's anonymised data can be shared with international disease registries and research projects relevant to his/her condition that take place outside Europe	*Yes*	*No*

Project Timeline: start Jan 2011; Ethics 3 states July 2011, first patient recruited August 2011, Now 62 patients Jan 2012



SUMMARY: Key messages

- European Wolfram research with USA and Japan
- We need patient cohorts with stakeholder involvement
  - Need to link family support groups to influence research
- Please support EURO-WABB
- Where are we going?
  - Find an already approved drug that can treat ER stress in the brain
  - Clinical studies of drugs to halt or slow progress of disease
- To families: lots of researchers working on this, hang on in there!

Key acknowledgments

- Lesley Porter
  - Lesley.porter@bch.nhs.uk
- Kerry Leeson
  - Kerry.leeson@alstrom.org.uk
- Tracey Lynch
  - Families@wolframsyndrome.co.uk
- Amy Farmer EURO-WABB project manager
  - Amy.farmer@bch.nhs.uk
- Nolwenn Jaffre French Wolfram Association
  - Nolwenn.jaffre@voila.fr