European Integrated Project on Spinocerebellar Ataxias (EUROSCA): Pathogenesis, genetics, animal models and therapy

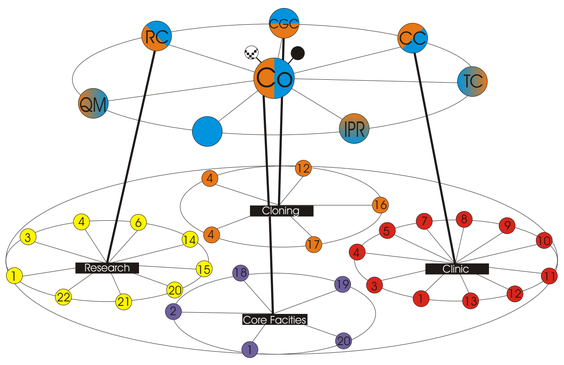
Holm Graessner, Michael Bonin, Peter Bauer, Olaf Riess,
Department of Medical Genetics, University of Tübingen

Integrated Project

Abstract

Twenty two European groups from 9 countries with an excellent reputation of clinical, clinical-genetic and basic research on spinocerebellar ataxias (SCA) will jointly form an Integrated project to develop a treatment for patients suffering from this rare, late manifesting, and autosomal dominant inherited group of neurodegenerative diseases. To reach this goal, an international standard on the clinical evaluation in form of a Core Assessment Program for Interventional Therapies of SCA (CAPIT-SCA) will be developed based on clinical rating scales, structural imaging, and electrophysiology. The generation of the world largest collection of information on SCA, the European SCA Registry (EUROSCA-R), will ensure standardized data acquisition. This powerful tool will facilitate continuous recruitment of SCA patients throughout Europe for linkage analysis, identification of novel ataxia genes and natural history studies. The potential to include all larger European SCA families into linkage analysis will lead to the identification of new SCA loci and to the cloning of novel ataxia genes, respectively. Genotype-phenotype correlations will follow. Subsequently, for the first time such a combined effort will offer a systematic large scale search for genetic modifier factors in SCA allowing a better comprehension of factors accounting for wide clinical variability with application for prognosis and to identify new potential targets (modifier genes). EUROSCA will also implement strong research projects to generate and characterize cellular and transgenic models, which will allow a more defined study of the pathogenesis and will serve as a tool for first therapeutic studies. 9 European research groups will be supported by five core facilities such as transgenic Drosophila work, Expression-Chip-Technology, Proteomics, yeast two hybrid technology, and monoclonal antibodies. Training programs will complement research efforts and clinical work.

Funding: 9,45 Million Euro **Duration: 01.01.2004 - 31.12.2008**



Coordinator, Riess, Ger; Coordinator Pathogenic Research, Matilla, UK; Coordinator Linkage and Cloning, Brice, F; Coordinator Clinic, Klockgether, Ger; Pandolfo, B; Coordinator Training Di Donato, I; Coordinator IPR, van der Warrenburg, NI; Coord. Quality Man., Rubinsztein, UK; Partner Pathogenic Research: Auburger, Brice, Mandel, Pastore, McDonald, Riess, Rubinsztein, Servadio, Klockgether; Partner Cloning: Brice, Wood, Zühlke, Sablonniere; Partner Clinic: Berciano, Riess, Di Donato, Wood, Klockgether, Melegh, Pandolfo, Schöls, Zaremba, van der Warrenburg; Partner Core Facilities: Riess, Matilla, Tricoire, Mandel, Wanker; Administrative Officer; Scientific Manager, Graessner, Ger;

Status

22.11.2003 Kick off meeting
01.01.2004 Start of project
18.03.2004 Signature of contract

Training (first 18 months)

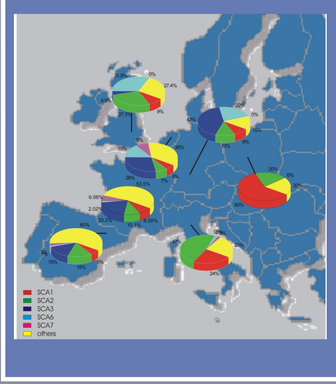
Three Clinical-genetic workshops
Five core facility trainings
Clinical and research fellowships

Spinocerebellar Ataxias

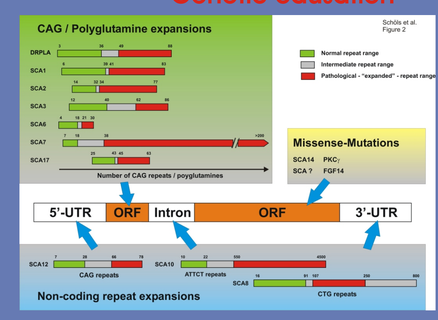
"Orphan Disease"

Frequency 1 : 10.000
Highly heterogenous
NO cure, patients die after years of suffering
Autosomal dominantly inherited,

Frequency of genetically defined SCA subtypes in Europe



Genetic causation



Common symptoms

Cerebellar Ataxia
disturbance of the coordination of movements

Bulbar signs
e. g. swallowing problems

Pyramidal signs
e. g. Spasticity

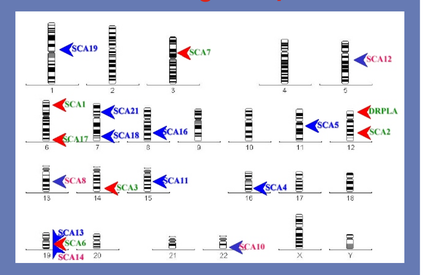
Extrapyramidal signs
e. g. Parkinsonism

Peripheral neuropathy
burning and teasing sensat.
muscle wasting

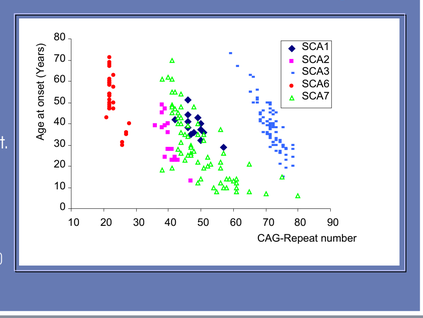
Ophthalmoplegia
paralysis of the eye muscle

Affected brain regions Cerebellum & brain stem (mainly)

Genetic heterogeneity



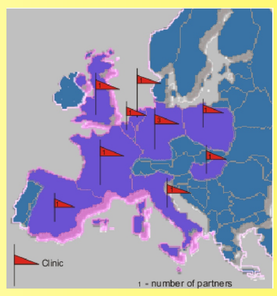
Correlation between age at onset and CAG repeat length



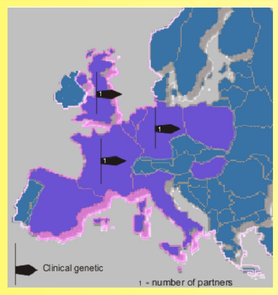
Clinical projects

Description / Month	0	6	12	18	24	30	36	42	48	54	60
Development of Clinical Standards											
Validation of Clinical Standards											
Recruitment of patients	Participants 1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13										
EUROSCA-R	Sum	96			360			504		648	792
11 clinical centres (patients per 6 month)		96	192	72	72	72	72	72	72	72	72
Natural history study	Sum				240						
11 clinical centres (patients per 6 month)				120	120						
Management and Coordination											
Meeting clinical groups	T	T	T	T	T	T	T	T	T	T	T
EUROSCA clinical-genetic workshops			T	T	T						
Milestones and Deliverables											
Development of EUROSCA-R		Dr	R								
Development of UARS		Dr	R								
MRI protocol		Dr	R								
Electrophysiology protocol		Dr	R								
MRI pilot measurements			R								
Electrophysiological results			R								
Complete recruitment natural history study				R							
Interim analysis of natural history study						R					
Design of an intervention study (drug trial)							Dr	R			
Start of intervention study											R
792 patients recruited for EUROSCA-R											R
Natural history study completed											R

Active work within the task | Dr Drafting of reports, publications | Patient recruitment
Research activies | P Reports, publications | T Training activities



11 groups from 9 different countries
Coordinating
Prof. Dr. Th. Klockgether (Neurology Bonn, Germany)
Objectives
EUROSCA-Registry
Unified Ataxia Rating Scale
Natural history study
Intervention studies (drug trials)



4 groups from 3 different countries
Coordinating
Prof. Dr. A. Brice (INSERM Paris, France)
Objectives
Identification of new ADCA genes
Identification of new ADCA loci
Modifier genes
Intervention studies (drug trials)

Clinico-genetic projects

Description / Month	0	6	12	18	24	30	36	42	48	54	60
New ADCA genes and loci											
Mapping of new ADCA genes	Family selction				Mapping (SCAn)						
Refinement and cloning (SCA ID)	SCA4 SCA11, SCA13, SCA21						SCAn				
Modifier genes for SCA											
Recruitment of patient groups	SCA3, SCA7 SCA1, SCA2										
Whole genome mapping					SCA3, SCA7		SCA1, SCA2				
Candidate genes, polymorphisms						SCA3, SCA7				SCA1, SCA2	
Management and Coordination											
EUROSCA clinical-genetic workshops			T	T	T	T					
Milestones and Deliverables											
Mapping of new ADCA genes						P					
Protocols for molecular routine testing				P	P						P
Patient groups completed			P		P						
Candidate genes									P		P

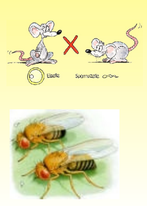
Dr Drafting of reports, publications | Research activies
P Reports, publications | T Training activities

Co-operation with SCA research groups worldwide
e.g. CAG (USA)

Vision:
Find a cure for Spinocerebellar Ataxias

Co-operation with Lay organisations
e.g. Euro-Ataxia

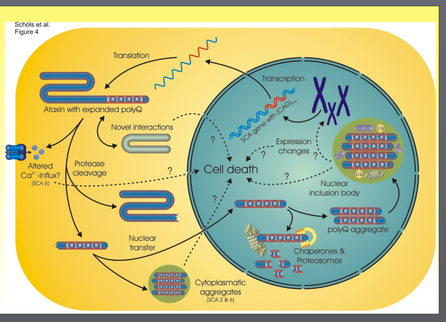
Research projects



Description / Month	0	6	12	18	24	30	36	42	48	54	60
Animal models of SCA											
Conventional mouse model	SCA17 knock-in generated				SCA17 characterization						
Double transgenic models		cJun (JunAla) with R7E				SCA17 with SCA3			Hsp 70 with SCA		
Inducible transgenic mouse models	SCA1 & SCA3										
Expression profile (CF)		SCA3	cJun + R7E	SCA7		SCA 17	SCA 17+3	SCA2 k.o.		Hsp +SCA	
Biochemical and behaviour studies (CF)			cJun + R7E		Inducible SCA1+3		Transgene SCA17+3			Hsp70+SCA	
Immunhistochemistry based on expression data		SCA3 + SCA7 mice compared to human brain						SCA2 mice compared to human brain			
Knock-out mice	SCA2 knock-out model				Characterization of SCA2 k.o.						
Drosophila models (CF)	SCA7			SCA3			SCA17				
Biochemical and behaviour studies (CF)		SCA7			SCA3			SCA17			
Modifier-screen in drosophila (CF)				SCA7			SCA3			SCA17	
Therapeutic targets in Drosophila							SCA7/SCA3		SCA2	SCA7/SCA3	

9 groups from 4 different countries
Coordinating
Dr. A. Matilla (ICH London, UK)
Objectives
Pathogenesis of ataxias
Animal models of ataxias
Therapeutic targets in ataxias

Description / Month	0	6	12	18	24	30	36	42	48	54	60
Pathogenesis of ataxias											
Identification of interacting proteins	Throughout the project for SCA2, SCA3, SCA7 and novel SCA proteins and interactors										
Prevention of cell death in cell culture	Throughout the project for SCA2, SCA3, SCA7 and novel SCA proteins and interactors										
Expression profiling cell culture		SCA3	SCA7	SCA2	SCA1						
Inducible cell lines for SCA2, 3, 7	Generation -> Pathology -> Expression profile -> Histology -> Structural models -> Functional domains										
Therapeutic targets in cell culture	Two drugs tested			Two drugs tested			Two drugs tested				
Functional assays protein degradation	Throughout the project for SCA2, SCA3, SCA7 and novel SCA proteins and interactors										
Autophagy and protein clearance	Inducible yeast model		RNAi experiments		Yeast k.o.	Characterize of yeast k.o.		Mammalian orthologues		Characterize "autophagy" genes	
Role of heat shock proteins	Constructs, cell culture and transgenic models			Neurotoxic stress and JNK pathway			Signal transduction				
Structural analysis	Production insect cells, Calimetry, Cystalization		NMR								

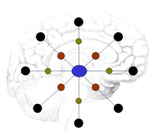


Core facilities

Transcriptome CF Tübingen
Dr. Michael Bonin

Proteome CF London
Dr. Antoni Matilla

Protein-protein interaction CF Berlin
Dr. Erich Wanker

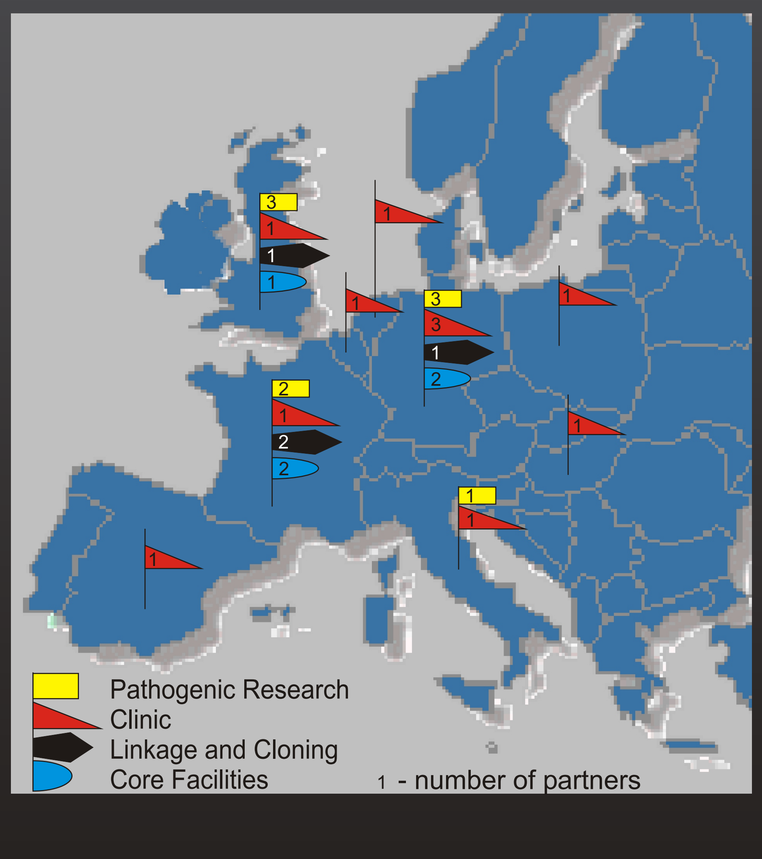


Drosophila CF Paris
Dr. Hervé Tricoire

Antibody CF Strassbourg
Dr. Yvon Trottier

Consortium

The consortium consists of 22 partners from different European countries. The consortium is well balanced bringing together all the needed resources and expertise to form a critical mass in the research field concerned. It includes partners with complementory roles: Clinical experts (Bonn, Tübingen; Bochum, Paris, London, Milan, Bruxelles, Nijmegen, Warsaw, Pécs, Santander), cloning and linkage groups (Paris, Lübeck, Lille, London), and excellent rersearchers in pathogenesis (Tübingen, Bonn, Frankfurt, Paris, Illkirch, London, Cambridge, Birkbeck, MRC) which will be supported by high quality core facilities (Tübingen, MDC, CNRS, Illkirch, London).



Germany
- Eberhard-Karls-Universität Tübingen
- University Clinic Bonn
- Ruhr-University Bochum
- Klinikum der Johann Wolfgang von Goethe Universität
- University of Lübeck
- Max Delbrück Centrum for Molecular Medicine

France
- Institut National de la Santé et de la Recherche Médicale (INSERM) Paris
- INSERM Lille
- Centre National de la Recherche Scientifique
- Centre European for Research in Biology and Medicine Illkirch

Great Britain
- Institute of child health, University College London
- Institute of Neurology, University College London
- The Chancellor, Masters and Scholars of the University of Cambridge
- Birkbeck College, University of London
- Medical Research Council

Italy
- Istituto Nazionale Neurologico Carlo Besta Milan
- Universita dell' Insubria

Belgium
- Université Libre de Bruxelles

Netherland
- University Medical Center Nijmegen

Poland
- Institute of Psychiatry and Neurology Warsaw