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

Publishable executive summary of year 2008

EUROSCA aims to understand and integrate the clinical natural history and biology of autosomal dominant spinocerebellar ataxias (SCAs) in order to set a foundation for the discovery and testing of rational therapeutics for this heterogeneous group of diseases. EUROSCA consists of five equal and integrated sub-structures:

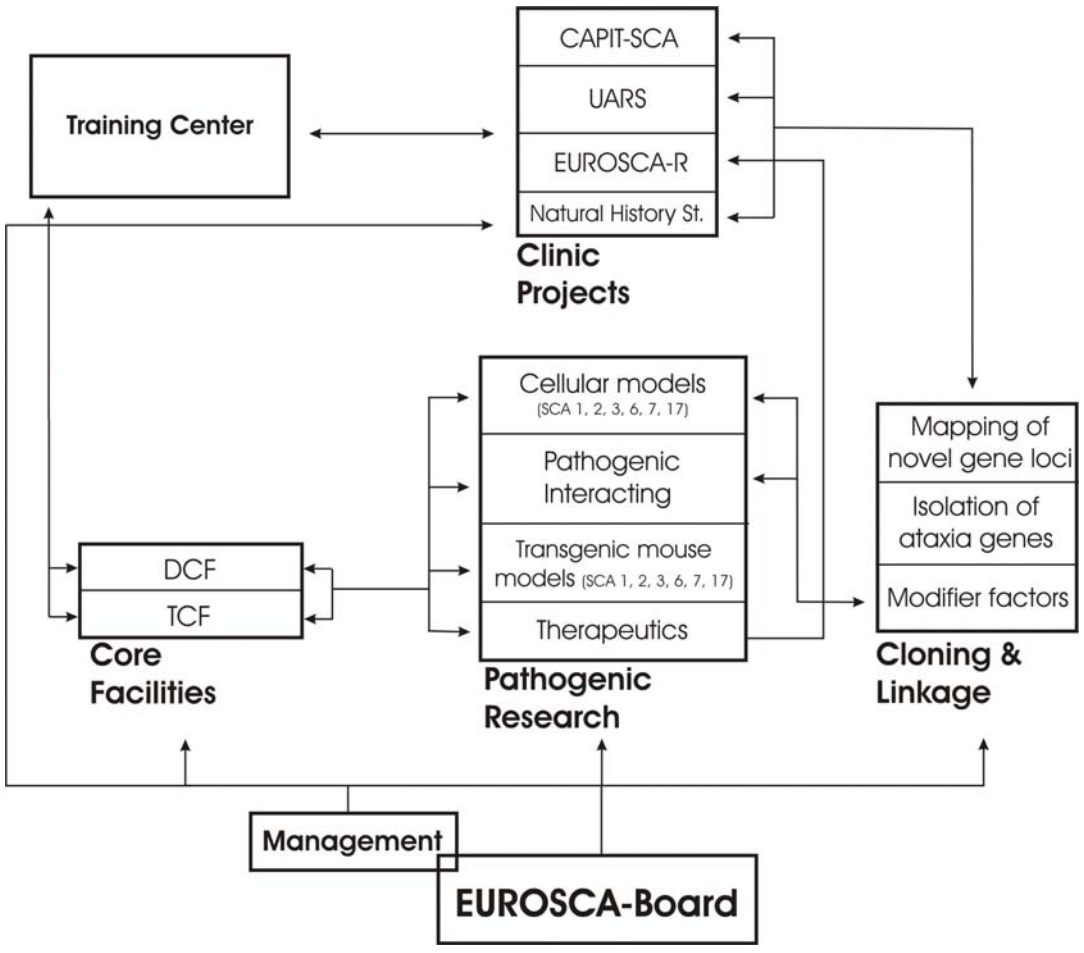
(i) The world largest SCA patient DNA registry (**EUROSCA-R**) generated by geneticists and clinicians,

(ii) A combined effort primarily of neurologists to establish the first **Unified Ataxia Rating Scale** (**UARS**) leading to a Core Assessment Program for Interventional Therapies (**CAPIT-SCA**),

(iii) Tight clinical-genetic collaborations to identify **novel SCA families, novel SCA genes** and **modifier factors,**

(iv) Eight basic research projects focusing on the **pathogenesis** of the most common SCA sub-forms and on **cellular, fly and mouse models.** A major objective of these studies is to develop **therapeutic targets**, and

(v) Two **core facilities** to generate, analyse and use Drosophila models, and to analyse the transcriptome.



Participants involved in EUROSCA

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3	Neurology Bonn	Thomas Klockgether	GER
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8	Nijmegen	Bart van de Warrenburg	NL
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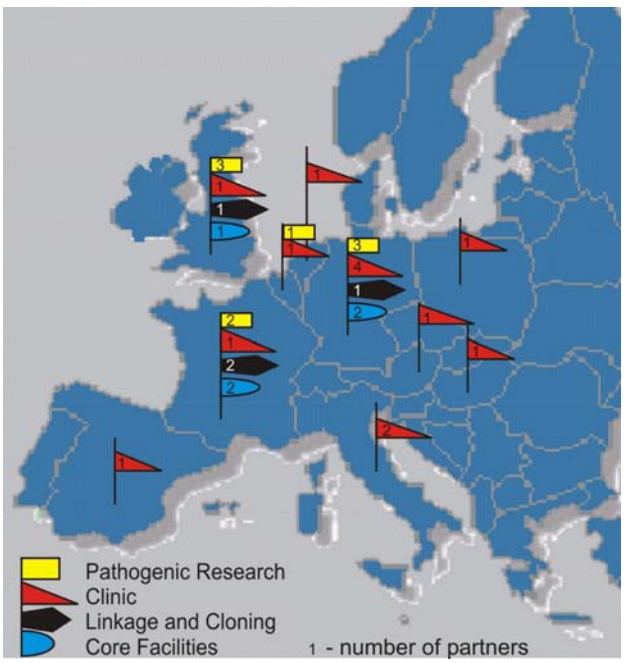
19	MDC Berlin	Erich E. Wanker	GER
20	IGBMC Illkirch	Yvon Trottier	F
21	BC London	Neil Quentin McDonald	UK
22	NIMR London	Annalisa Pastore	UK
23	HUM Göttingen	Jörg B. Schulz	GER
24	IGTP Badalona	Antoni Matilla	ES



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Objectives of EUROSCA

Objectives	Users of the Results
World Largest DNA registry (EUROSCA-R)	Geneticists
Core Assessment Program for Interventional Therapies (CAPIT-SCA)	Clinicians and patients
New epidemiological data	Health authorities
Risk prediction, modifier genes	Clinicians & health authorities
Defining new gene loci, disease gene cloning	Basic scientists, patients and persons at risk
Disease models for SCA1, 2, 3, 6, 7, and 17	Basic scientists, geneticists, clinicians
Defining the pathogenesis common to polyQ type SCA	Geneticists, patients in the long run
Evaluation of 5 potential drugs in animal models	Patients and physicians

Starting point EUROSCA at begin of 2008

Objectives	Starting point in 2008
World Largest DNA registry (EUROSCA-R)	▪ 3650 entries, ▪ new internet-based registry has been developed and made available to the participating investigators in November 2007, ▪ registry allows data capture for clinical studies and trials
Core Assessment Program for Interventional Therapies (CAPIT-SCA)	▪ Completion of first follow-up evaluation of the Natural History Study in December 2007, of the 526 patients enrolled in that study, 445 have been seen for the first one-year follow-up, comparison between the rater-based clinical scale SARA with a compound measure of timed tests (SCAFI) in 412 patients from the baseline visit completed, ▪ determination of a subset of 18 transcripts, which can correctly predict the disease state, ▪ early symptoms study completed
New epidemiological data	▪ Data collection almost complete
Risk prediction, modifier genes	▪ New results on effects of SCA Allele length on the age at onset variance new result: interaction between both alleles has a stronger influence on the age at onset in the SCA1, SCA2 and SCA6 subtypes than the long-pathological allele alone, ▪ Re-genotyping of all PQ genes in one lab: 1488 SCA1, 2, 3, 6 and 7 patients (69% of total entries): original genotype and CAG repeat length in both alleles confirmed in 91%, ▪ Cohorts of 1235 affected SCA patients and 2130 patients ready for analysis of familiar effect
Defining new gene loci, disease gene cloning	▪ Analysis of 8 most informative families of first genome scan: update with 42 additional samples, including 6 new affected members, first theoretical Zmax above +3 in family PAR-0193, ▪ Second EUROSCA genome scan: 92 DNA

	samples from 6 new ADCA families, ▪ further analysis of candidate regions
Disease models for SCA1, 2, 3, 6, 7, and 17	▪ Generation of transgenic mice carrying ataxin-3 with inactivated NES elements; ▪ characterization of knock-out model SCA2 and transgenic model SCA17; ▪ generation transgenic flies for SCA3 constructs with different polyQ streches (15 or 70) and different mutations at the CKII phosphorylation sites, ▪ worlwide first attempt to screen targeted RNAi induced loss of function lines for their effect in polyQ diseases (on SCA1 flies)
Defining the pathogenesis common to polyQ type SCA	▪ Analysis of known polymorphisms in the cohort of 480 SCA3 patients ▪ Analysis of nuclear import (NLS) and export signals (NES), identified within Ataxin-3 ▪ Analysis of the functional consequences of phosphorylation of AT3 on nuclear import ▪ Development of an *in vitro* model for SCA7 ▪ biological significance of SUMO modification on either cellular localization or on toxicity of mutant ataxin-7 ▪ novel two-step screening process for the discovery of safer drugs but with similar effects as rapamycin ▪ neurophysiological changes in Purkinjie cells from SCA1 mice related to Kv channel function ▪ Western blot analyses of co-immunoprecipitation experiments with Ataxin-2 and Trap / ACTN1 / ACTN2 / RENT1 / SNTB1 ▪ Identification of modulators of ataxin aggregation and toxicity ▪ Study of the mechanism of neuronal death in R7E retina ▪ The josephin domain of ataxin-3 is a ubiquitin binding motif
Evaluation of 5 potential drugs in animal models	▪ Completion of trial with rapamycin with SCA3 mouse model, ▪ Preliminary results for therapeutic effects of β1a interferon in the treatment of SCA7, ▪ Positive effects of acute and chronic 3,4 DAP administration on motor behavior and cerebellar morphology in SCA1 mice, ▪ Proof-of-principle for combination treatment approach in vivo using rapamycin and lithium by showing greater protection against neurodegeneration compared to either pathway alone

Work performed and results achieved in 2008

Objectives	**Work done in 2008**
World Largest DNA registry (EUROSCA-R)	▪ In January 2008, the eCRF of the natural history study in the registry was extended to include also the SCAFI assessments. ▪ To date, the registry contains more than 3700 entries from 19 European centers, among them 3068 patients.
Core Assessment Program for Interventional Therapies (CAPIT-SCA)	▪ Of the 526 patients enrolled in that study, 446 have been seen for the first one-year follow-up and 340 for the second follow-up, the third follow-up is currently performed. ▪ For baseline, first and second follow-up, data monitoring has been completed except second follow-up data from one center (see below). ▪ Baseline data with modelling of ataxia progression and evaluation of functional measures have been published ▪ The substudy on early symptoms (L.Schöls, Tübingen) has been published, while the results of the falls substudy (B.

	van de Warrenburg, Nijmegen) was submitted. A more detailed evaluation of depressive symptoms, including data from baseline and first follow-up, is currently performed and will be prepared for publication until month 66. ▪ MRI and electrophysiology follow-up studies completed
New epidemiological data	▪ Data collection almost complete
Risk prediction, modifier genes	▪ Results of the effect of modifiers of the age at onset evidenced in SCA1, 2, 3, 6 and 7 ADCA subtypes available
Defining new gene loci, disease gene cloning	▪ Inclusion of a total of 34 large ADCA families until now and 29 of those families could be processed in genome scans ▪ One new candidate region almost validated
Disease models for SCA1, 2, 3, 6, 7, and 17	▪ SCA1, 2, 3, 7, 17 mouse and fly models used in investigation of pathogenesis and treatment approaches
Defining the pathogenesis common to polyQ type SCA	▪ SCA3: polymorphism in the promoter region of HHR23A ▪ Influence of transporter proteins on aggregate formation ▪ Role of phosphorylation of AT3 on nuclear localisation ▪ Post-translational modification of ATXN7 ▪ New autophagy inducers ▪ Identification of Rab5 as a novel autophagy regulator ▪ Role of A-type K+ currents in the early Purkinje cell ▪ Identification of 10 ataxin-1 Q79 modifiers and 7 ataxin-3 Q73 modifiers ▪ Cell division in retinal degeneration of adult mammalian retina. ▪ Demonstration for the first time that polyQ toxicity induces important neuronal remodelling. ▪ Structural study of aggregation pathway of ataxin-3
Evaluation of 5 potential drugs in animal models	▪ Preliminary results for β1a-INF treated SCA7 Knock-in mouse, ▪ Transplantation of neural precursor cells (NPCs) into the cerebellar white matter of SCA1 mice, ▪ Test of the effect of pimelic benzodiamide histone deacetylase inhibitor 106 on B05 SCA1 mice, ▪ Protection of SCA7 expressing flies with an anti aggregation drug

Summary of year 2008

- Excellent progress during the fifth year of EUROSCA,
- EUROSCA achieved the majority of the 60 months deliverables and milestones,
- EUROSCA management detected problematic issues and has implemented appropriate corrective actions:
  - Delay in entering data of the second follow-up visit of the NHS into the EUROSCA registry at IoN London

Clinical subproject: ▪ 3700 entries into EUROSCA-R, ▪ Of the 526 patients enrolled in that study, 446 have been seen for the first one-year follow-up and 340 for the second follow-up, the third follow-up is currently performed. ▪ Substudy on early symptoms published, results of the falls substudy submitted. ▪ MRI and electrophysiology follow-up studies completed

- Genetic subproject: ▪ Results of the effect of modifiers of the age at onset evidenced in SCA1, 2, 3, 6 and 7 ADCA subtypes available, one new candidate region almost validated
- Further treatment approaches studied,
- Very good progress in pathogenesis projects,
- Training activities in plan,
- Some delay in regard to a very few research projects and in regard to treatment study due to breeding difficulties.

Illustration of the work done

EUROSCA final meeting in Palma 5-6 December 2008

EUROSCA website

www.eurosca.org

EUROSCA logo

	Hits	Pageviews	Sessions	KBytes sent
2004				
Total	95589	16219	6750	1308525
Average per month	7965	1351	562	109043
2005				
	126862	24117	11111	2274240
Average per month	10571	2009	925	189520
2006				
	101441	19864	13436	2438214
Average per month	8453	1655	1119	203185
2007				
	111112	23172	15994	3217739
Average per month	9259	1931	1332	268145
2008				
	108578	22279	12303	3131886
Average per month	9048	1856	1025	260991

Usage of EUROSCA website in years 2004-2007