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

Publishable executive summary of year 2007

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:

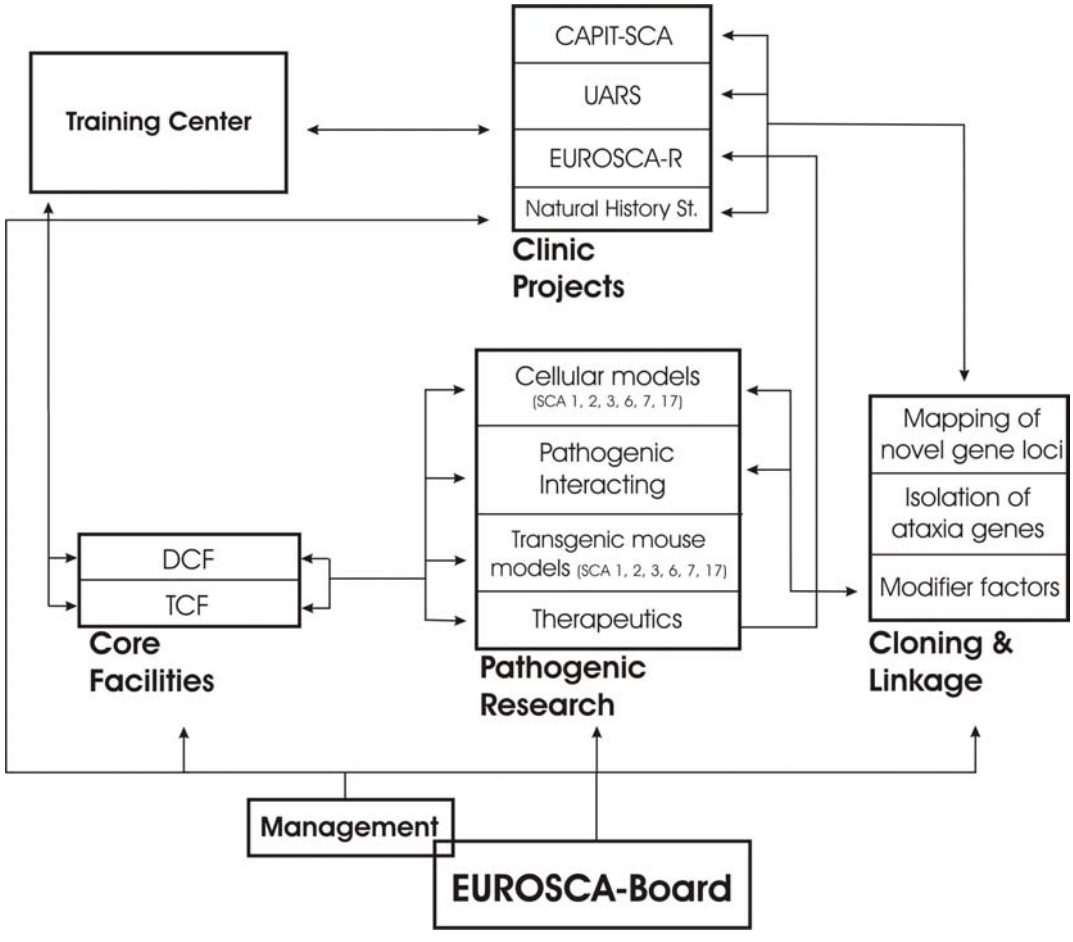
(i) The world largest SCA patient DNA registry (**EUROSCA-R**) generated by geneticists and clinicians,

(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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21	BC London	Neil Quentin McDonald	UK
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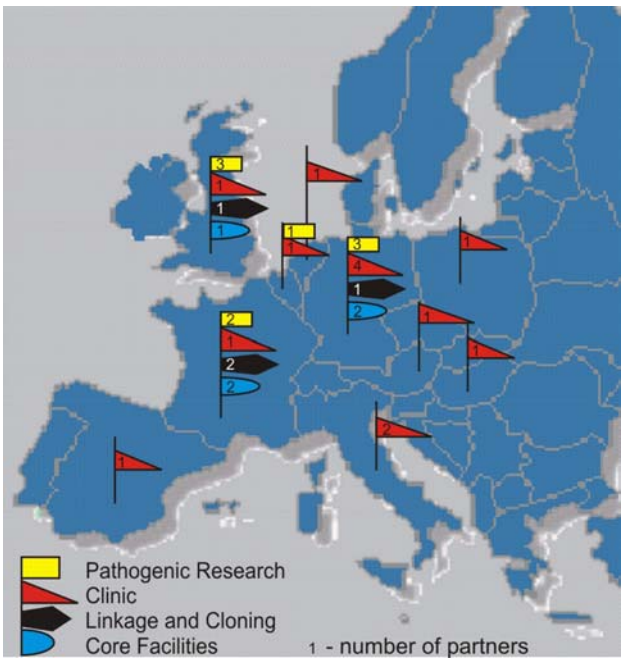

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Objectives of EUROSCA

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 2007

Objectives	Starting point in 2007
World Largest DNA registry (EUROSCA-R)	▪ Entries of 3200 SCA patients, ▪ preparation of a completely new database version that will allow data entry via internet.
Core Assessment Program for Interventional Therapies (CAPIT-SCA)	▪ SARA is a reliable and valid measure of ataxia in non-SCA ataxia patients, ▪ Completion of NHS baseline evaluation in June 2006 (523 patients, 110 MRIs and 140 electrophysiological assessments from SCA patients),
New epidemiological data	▪ Data collection almost complete
Risk prediction, modifier genes	▪ Data from 2160 patients for calculation of familiar effect, ▪ Establishment of central DNA depository, by date 1818 samples received, ▪ Genotyping of all PQ genes for all samples received AND for which informed consent is present.
Defining new gene loci, disease gene cloning	▪ SCA11 mutation identified, ▪ Study of frequency and spectrum of mutations for SCA13, SCA28 and puratrophin, ▪ 105 new DNA samples from 8 new ADCA families, ▪ Genome scan with 257 DNA samples from 20 families, ▪ Further analysis of 8 most informative families
Disease models for SCA1, 2, 3, 6, 7, and 17	▪ Knock-out model SCA3; ▪ characterization of knock-out model SCA2 and transgenic model SCA17; ▪ generation, study of pathology and therapeutical studies for SCA3,7 and 17 flies
Defining the pathogenesis	▪ No involvement of Calcineurin in the pathogenesis of

common to polyQ type SCA	SCA3, ▪ proteomics: 2D-maps from wild-type and Sca1-null mice, ▪ phosphorylation status of ataxin3, ▪ mechanisms by which PML IV acts on ATXN7, ▪ Trehalose is a novel autophagy regulator, ▪ Occurrence in vivo and in vitro of early electrophysiological dysfunctions in Purkinje cells expressing human mutated ataxin-1 prior to any morphological or behavioural anomaly, ▪ Ataxin-2 and Trap, ▪ Construction of a PPI Map, ▪ oxidative stress and DNA damage
Evaluation of 5 potential drugs in animal models	▪ Test of drugs with anti-aggregation properties for SCA3 in drosophila, ▪ trial with rapamycin with SCA3 mouse model, ▪ trial as for therapeutic effects of β1a interferon in the treatment of SCA7 in preparation, ▪ Investigation whether channel blockers may be efficient in rescuing the reduced lifespan of elavGS; SCA7-102Q flies

Work performed and results achieved in 2007

Objectives	Work done in 2007
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

Summary of year 2007

- Excellent progress during the third year of EUROSCA,
- EUROSCA achieved the majority of the 36 months deliverables and milestones,
- EUROSCA management detected problematic issues and has implemented appropriate corrective actions:
  - Relocation of Dr. Matilla from ICH London to Barcelona
- Clinical subproject: ▪ 3650 entries into EUROSCA-R, ▪ new internet-based registry has been developed and made available to the participating investigators in November 2007, ▪ Successful ompletion of first follow-up evaluation in December 2007, ▪ early symptoms study completed
- Genetic subproject: ▪ New results on effects of SCA Allele length on the age at onset variance, ▪ Re-genotyping of all PQ genes of the EUROSCA DNA depositiory in one lab, ▪ Cohorts of 1235 affected SCA patients and 2130 patients ready for analysis of familiar effect ▪ Analysis of 8 most informative families of first genome scan: update with 42 additional samples, first theoretical Zmax above +3 ▪ Second EUROSCA genome scan: 92 DNA samples from 6 new ADCA families,
- First preclinical treatment studies completed,
- Very good progress in pathogenesis projects,
- Training activities in plan,
- Some delay in regard to clinical-genetic and few research projects.

Illustration of the work done

Core facility training course at the Drosophila core Faciliy, Paris, 30-31 May 2007

Discussion during the annual meeting in Bonn 26 January 2007

EUROSCA School Day in Nijmegen, Netherlands

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

Usage of EUROSCA website in years 2004-2007