SEVENTH FRAMEWORK PROGRAMME Health

Theme: HEALTH.2012.2.1.1-1-B

Clinical utility of -omics for better diagnosis of rare diseases

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NeurOmics

Integrated European –omics research project for diagnosis and therapy in rare neuromuscular and neurodegenerative diseases

Instrument: **Collaborative Project**

Periodic report

Period covered: from 01.10.2012 to 30.09.2013 Date of preparation: 29.11.2013

Start date of project: 01.10.2013 Duration: 60 months

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Project coordinator organisation name: Eberhard Karls-Universitaet Tuebingen

NeurOmics: Integrated European –omics research project for diagnosis and therapy in rare neuromuscular and neurodegenerative diseases

PUBLISHABLE EXECUTIVE SUMMARY FOR PERIODIC REPORT

1. Summary description of project context and main objectives

Neurodegenerative (ND) and neuromuscular (NM) diseases is one of the most frequent classes of rare diseases, affecting life and mobility of 500,000 patients in Europe and millions of their caregivers, family members and employers. This NeurOmics project brings together the leading research groups in Europe, five highly innovative SMEs and relevant oversea experts using the most sophisticated Omics technologies to revolutionize diagnostics and to develop pathomechanism-based treatment for ten major ND and NM diseases. Specifically we aim to:

(i) use next generation WES to increase the number of known gene loci for the most heterogeneous disease groups from about 50% to 80%,

(ii) increase patient cohorts by large scale genotyping by enriched gene variant panels and NGS of so far unclassified patients and subsequent phenotyping,

(iii) develop biomarkers for clinical application with a strong emphasis on presymptomatic utility and cohort stratification,

(iv) combine -omics approaches to better understand pathophysiology and identify therapeutic targets,

(v) identify disease modifiers in disease subgroups cohorts with extreme age of onset

(vi) develop targeted therapies (to groups or personalized) using antisense oligos and histone deacetylase inhibitors, translating the consortiums expertise in clinical development from ongoing trials toward other disease groups, notably the PolyQ diseases and other NMD.

To warrant that advances affect a large fraction of patients we limited the selection to a number of major categories, some of which are in a promising stage of etiological and therapeutic research while some others are in great need of further classification. The efforts will be connected through a NeurOmics platform for impact, communication and innovation that will provide tools and procedures for ensuring trial-readiness, WP performance, sustainability, interaction with the chosen Support IRDiRC and RD-Connect project and involvement of stakeholders in the NDD/NMD field.

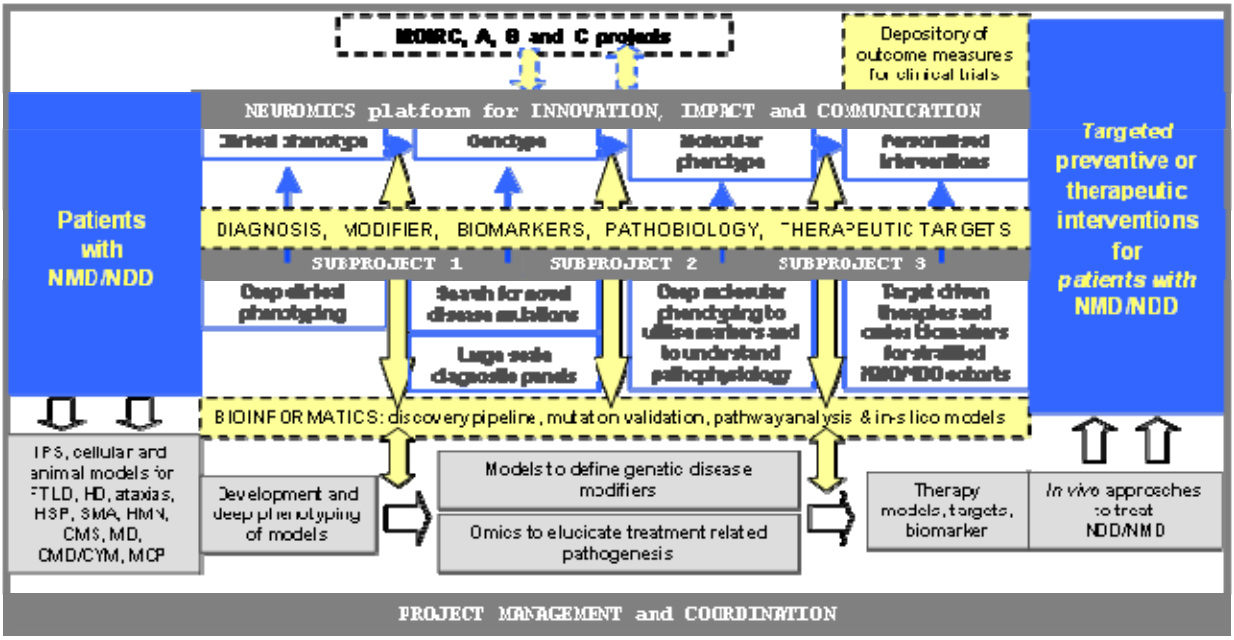


Figure 1: Concept of clinical-genetic and basic-applied research of NeurOmics

2. Description of the work performed since the beginning of the project and the main results achieved so far

Broken down to aims, the work performed and results achieved can be summarised as follows:

Ad aim i: deCODE has set up a pipeline for whole exome sequencing (WES) using Illumina´s Nextera technology. 288 samples have been sequenced. 15 new genes and 25 potential pathogenic variants have been identified. An NGS workshop on deCODE's "Clinical Sequence Miner" for NGS data analysis has been held. Informed consent forms have been developed which include data sharing and WES. Separate consent forms and information leaflets have been set up for adults, adolescents and children.

Ad aim ii: Clinical data sheets for the conditions studied have been created using the Human Phenotype Ontology to build a phenotypic database at PhenoTips. More than 1100 patients have been recruited and phenotypically characterised. The Care and Trial Site Registry has been expanded to include not only NMDs but also NDDs. Targeted NGS panels have been designed for SCA and HSP, NMD and SMA/LMND. A "supercapture" panel has been developed to meet the needs of the smaller Australian population. >10 samples have been processed per panel and passed to the bioinformatics pipeline. For the development of an automated 3DM mutation prediction system new alignment generation algorithms have been generated to achieve a more high-throughput approach. First 3DM information systems have been created.

Ad aim iii: SOPs have been developed for HD, SCA, FTLD and HSP patient sampling for biomarker studies. Samples are currently being collected to identify novel and to validate and optimise known biomarkers. Profiling methods for metabolites and lipids in plasma and CSF based on UPLC-HRMS have been developed. This database now includes >2000 unique lipid signals from 6 families and 22 different classes.

Ad aim iv: hiPSCs have been generated for the SPG5 subtype of HSP, from selected distal HMN patients and discordant SMA siblings overexpressing PLS3. The underlying mechanism causing responsiveness to VPA in SMA patients has been solved and the differential response in GABA-ergic neurons derived from hiPSC of these patients has been confirmed. In a novel conditional transgenic animal overexpressing the protective modifier for

SMA, the underlying protective mechanism has been identified. 45 disease pathway maps have been developed and curated for polyQ diseases using expression data. These pathway maps have identified a list of potential genes involved in modulation of mutant polyQ protein aggregation and toxicity. Proteins that are shared binding partners of Htt and ataxins have been identified which suggests common mechanisms and points of intervention for different polyQ disorders.

Ad aim v: 48 Huntington's disease samples from the Track-HD study with atypical disease progression have been sequenced by WES. >80 families have been identified in the autosomal dominant subtype of HSP (SPG4) with discrepant age of onset within the family of >20 years. Once all WGS, WES and targeted NGS mutational data are available via the EGA, they will be analysed for potential disease modifying effects.

Ad aim vi: We have developed an efficient method to selectively inhibit the function of type I TGFβ receptors based on AON-mediated exon skipping. This was efficiently tested *in vitro* and in *mdx* mice. AON exon skipping for dysferlin has been established *in vitro* in wild type cells and in cells from patients with compound heterozygous mutations in exons 8 and 9. It has been demonstrated that exon-skipping can bypass disease-causing mutations in exon 32. This is being tested in animal models. For HD, we have shown reduced caspase cleavage of the huntingtin protein after AON treatment. SCA3 exon skipping in *in vitro* experiments is ongoing to show reduced calpain cleavage of the ataxin-3 protein.

3. Description of the expected final results and their potential impacts and use

NeurOmics will have significant impact for a large group of patients with rare diseases - 120-150 patients/100,000, (500,000-600,000 patients in Europe). The project will integrate and extend existing networks and tools within the NDD/NMD field to ensure maximum impact and benefit from these and avoid duplication of efforts.

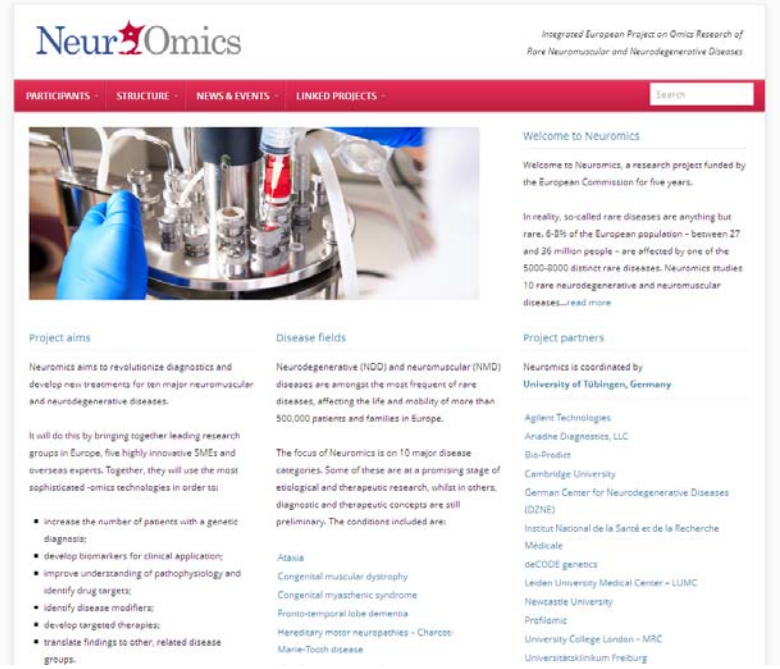
This will be done in close **interaction with the RD-Connect** project to address the major challenges identified through the IRDiRC initiative in the field of rare neurological diseases. Specifically, WP13 will extend the care and trial site registry (CTSR) developed for the neuromuscular field in order to incorporate neurodegenerative centres and ensure that the information gathered includes that needed for –omics research, supporting future clinical trials in these areas. The extended CTSR will also enable members to search for undiagnosed patients in other centres across the world fitting a particular phenotype profile. With RD-Connect, we will ensure that high quality; well annotated biospecimens are collected through harmonized biobanks and registries. Through its bioinformatics work, NeurOmics will provide a comprehensive knowledgebase for pathway informed target and biomarker search to increase our understanding of pathogenic commonalities for rare and common NDDs/NMDs. Stakeholders including patient organizations, regulatory authorities and industry will be integrated into the study to support joint studies and widen the project's reach. All **major outcomes** of NeurOmics will have an impact directly linked to clinical utility:

- **Diagnostic kits** for up to 80 % of NMD/NDD will result in the availability of targeted genetic testing for familial NMD/NDD mutations This will help physicians provide the most appropriate treatment, allow affected families to make informed family planning decisions, form better-stratified patient cohorts for interventional trials, shorten the time to diagnosis and avoid unnecessary or invasive test procedures.
- Discovery and validation of **biomarkers** will increase implementation and appropriateness of new treatments by better stratifying patient cohorts. Monitoring of treatments will be improved. Better insight into pathogenic commonalities for NMD/NDD/RD will be achieved.
- Proof of concept of **new therapeutic approaches** for NDDs/NMDs wil result in the availability of therapeutic interventions for up to 10 diseases eventually improving the quality of life of thousands of patients with NDDs/NMDs. This will enable physicians

to provide therapies for currently incurable diseases whilst patients will benefit from participating in clinical trials and from the resulting new therapies.

- NeurOmics will **improve health and quality of life** of NMD/NDD patients and decrease disease related costs through improved and early diagnoses, characterization of stratified patient cohorts, improved understanding of disease complications through deep phenotyping and development of new treatment strategies.
- NeurOmics' **communication tools** and procedures across all stakeholder groups will help to ensure trial-readiness, efficient and effective testing of new hypotheses and the rapid implementation of new recommendations by disseminating the latest findings, promoting data-sharing, extending existing tools and networks and developing appropriate SOPs (see Neuromics website at www.rd-neuromics.eu). This will reduce time-to-trials significantly, reach most appropriate patients to form specific cohorts and ensure standards of care throughout the entire care and trial sites network through tailored training programs.

NeurOmics web site **NeurOmics logo**



www.rd-neuromics.eu

4. Participants involved in NeurOmics

No	Participant	Country	PIs
1 (coordi-nator)	Eberhard Karls Universitaet Tuebingen (EKUT)	Germany	Olaf Riess, Ludger Schöls, Holm Graessner
2	Academisch Ziekenhuis Leiden – Leids Universitair Medisch Centrum (LUMC)	The Netherlands	Gert-Jan van Ommen, Annemieke Aartsma-Rus
3	Klinikum der Universitaet zu Koeln (UK Cologne)	Germany	Brunhilde Wirth
4	University of Newcastle upon Tyne (UNEW)	UK	Volker Straub, Hanns Lochmueller, Kate Bushby
5	Deutsches Zentrum fuer Neurodegenrative Erkrankungen EV (DZNE)	Germany	Thomas Klockgether
6A	University College London, Institute of Child Health (UCL-ICH)	UK	Mike Hanna, Henry Houlden
6B	University College London, MRC Centre for Neuromuscular Diseases (UCL-IoN)	UK	Francesco Muntoni
6C	University College London, Institute of Neurology (UCL-IoN)	UK	Sarah Tabrizi
7	Universite d'Aix Marseille (AMUMS)	France	Nicolas Levy
8	Institut National de la Sante et de la Recherche Medicale (INSERM)	France	Alexis Brice, Alexandra Durr
9	VIB (VIB)	Belgium	Vincent Timmerman
10	Universita Degli Studi di Milano (UMIL)	Italy	Elena Cattaneo
11	Universita Degli Studi di Ferrara (UNIFE)	Italy	Alessandra Ferlini
12	The Chancellor, Masters and Scholars of the University of Cambridge (UNICAM)	UK	David Rubinsztein
13	Islensk Erfdagreining EHF (deCODE)	Iceland	Hreinn Stefansson
14	Ariadne Diagnostics LLC (Ariadne)	USA	Elena Schwartz
15	Profilomic SA (Profilomic)	France	Bruno Corman
16	Agilent Technologies Sweden AB (Agilent)	Sweden	Frederik Roos
17	Bio-Prodict BV (Bio-prodict)	The Netherlands	Henk-Jan Joosten
18	The University of Western Australia (UWA)	Australia	Nigel Laing
19	Universitaetsklinikum Freiburg (UKL-FR)	Germany	Janbernd Kirschner

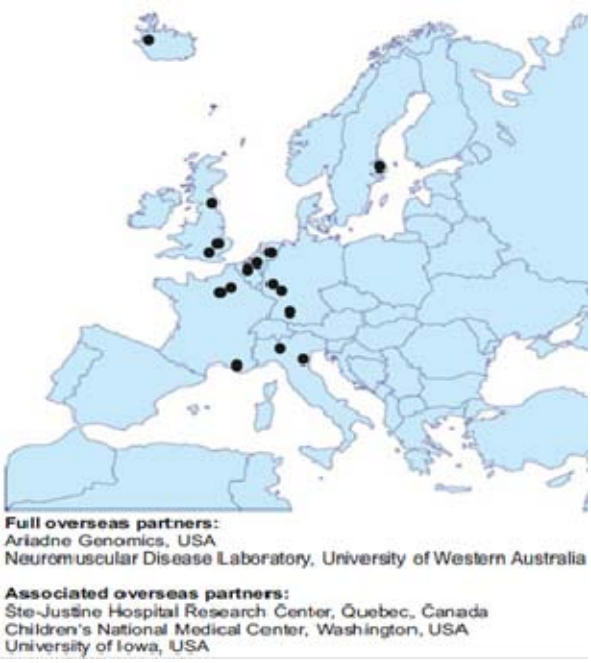


Figure 2: Involved European countries in NeurOmics

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