Towards a mechanism-based taxonomy of Alzheimer's and Parkinson's disease

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Facts & Figures

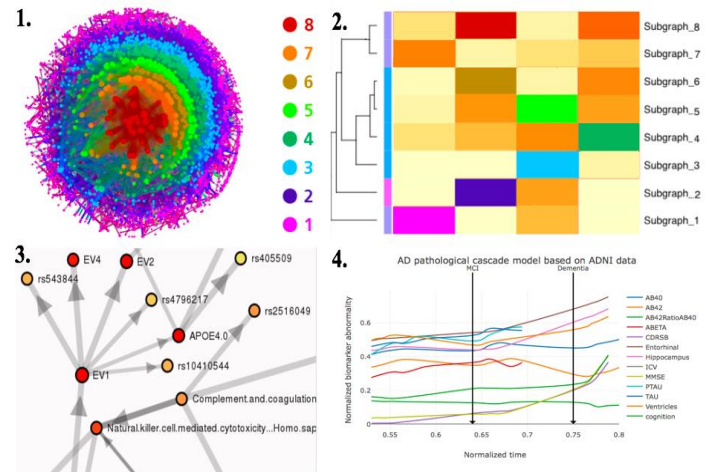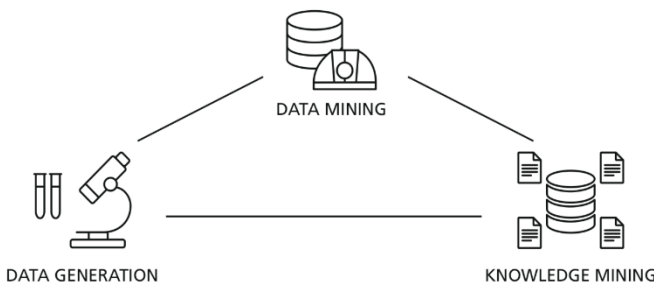|	
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End date:	31/12/2018
Contributions	
IMI funding:	7 993 234 €
EFPIA in kind:	8 021 460 €
Other:	1 797 522 €
Total Cost:	17 812 216 €
Project website:	www.aetionomy.eu

Challenge

The diagnoses of Alzheimer's disease (AD) and Parkinson's disease (PD) are currently based on heterogeneous phenotypes related to progressive memory loss and motor symptoms, respectively. While the endeavors in recent decades have lead to a better mechanistic understanding of the underlying pathologies, attempts at targeting these phenotypes in order to prevent disease progression have failed. This is likely due to the multifactorial nature of the two disorders and the relatively long time course between the first molecular dysregulation processes and the initial clinical symptoms. If we are to make progress in prevention of these idiopathic disorders, the exact role of dysregulated molecular and biological pathways that lead to transition from a 'normal physiology state' to a 'disease state' must be identified, though it is a non-trivial undertaking.

Approach & methodology

The goal of AETIONOMY is to organize the mechanistic knowledge in the field of AD and PD and generate a mechanism-based taxonomy that could drive the stratification of patient subgroups. The academic and pharmaceutical project partners collaborated to collect, curate, harmonize, and warehouse public and proprietary data in a framework that is both human- and computer-readable and formed the foundation of all data- retrieval and reannotation. Once all of the available data brought together into a dedicated knowledge base, it was used to organize the knowledge around AD and PD that culminated in an inventory of candidate mechanisms. A combined knowledge- and data-driven approach used the mechanistic hypotheses and the clinical data to identify new molecularly defined patient subgroups in AD and PD.

Results

1) AD and PD inventory of candidate mechanisms based on the disease-specific knowledge [1].

2) Patient stratification based on their genomic variation profile on a mechanistic level.

3) With the help of a Bayesian network, the entire course of a multivariate clinical trial has been described [2].

4) The hypothetical longitudinal standard model for AD.

Value of IMI collaboration

The IMI AD-platform [3] facilitated the cooperation of AETIONOMY with the two other main IMI projects in the area of neurodegenerative diseases: EPAD and EMIF-AD. In particular, AETIONOMY benefited from the longitudinal aspect addressed in EPAD, enabling longitudinal mechanistic interpretation. EMIF-AD partner University of Oxford (Prof. Simon Lovestone) provided access to one of the key longitudinal studies in AD, the AddNeuroMed cohort. Finally, the ambitions and challenges of the project imposed the need of teaming up with partners with complementary expertise and resources; in particular pharmaceutical partners (i.e., UCB, Sanofi, Novartis, Boehringer Ingelheim, Pharmacoidea) that provided domain expertise and clinical data.

Impact & take home message

AETIONOMY has:
- generated the first draft of a mechanism-based taxonomy for AD and PD.
- organised and curated the majority of public data and knowledge in the field of neurodegenerative diseases.
- become the first FAIR data project in neurology (FAIR: findable, accessible, interoperable and reusable).
- generated the world's largest inventory of computable mechanism underlying neurodegeneration disease.
- developed new methods for patient stratification and mechanistic interpretation of longitudinal data.

References

1) Domingo-Fernández D et.al. (2017). Multimodal Mechanistic Signatures for Neurodegenerative Diseases (NeuroMMSig): a web server for mechanism enrichment. *Bioinformatics*. 33.22:3679-3681

2) Khanna S. et.al. (2018). Using Multi-Scale Genetic, Neuroimaging and Clinical Data for Predicting Alzheimer's Disease and Reconstruction of Relevant Biological Mechanisms. *Sci Rep*. 8.1:11173

3) Vaudano E et.al. (2015). Boosting translational research on Alzheimer's disease in Europe: The Innovative Medicine Initiative AD research platform.". *Alzheimers Dement*. 11.9:1121-1122