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Systematic Analysis of GWAS Data Reveals Genomic Hotspots for Shared Mechanisms between Neurodegenerative Diseases

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Abstract

Objective: In this study, we have tried to reveal molecular mechanisms underlying "shared genetic variants" and developed a strategy to identify candidate mechanisms for shared aetiology of a pair of diseases, to uncover biological relationships between quantitative traits or related neurodegenerative diseases.

Methods: Genetic variants were collected from GWAS catalog, belonged to multiple disease association studies. Meta-analysis was performed by using Metal (a whole genome association analysis toolset), and normalized them for their different sample sizes. LD analysis was done with Haploreg DB V.4.0. Subsequently, the ENSEMBL variant database was used as a reference database. Additionally, these shared SNPs were interpreted with Regulome DB V.1.1 and finally ranked the variant lists according to predicted functional consequences attributes. Afterwards evidences were collected from gene expression studies, patents, knock-out studies and other literature.

Results: Pair-wise analysis also revealed that AD and PD have the largest number of shared disease-associated loci. Additionally, tau locus is discovered in a very novel and unique perspective of stress induced shared pathology of AD and PD, which provides suggestive evidence that the molecular mechanisms influencing aetiology and progression of selective neurodegenerative diseases are at least partly interrelated.

Conclusion: Genetic overlap between these diseases suggests that genomic locus should be considered to investigate the effects of GWAS variants rather than individual genetic variants, particularly to investigate shared pathology.

Keywords: GWAS; LD (Linkage Disequilibrium); Shared genetic loci; Genetic variants; Shared pathology; Neurodegenerative diseases

Background

Genome wide association studies have been very useful for the identification of genetic variants as disease risk markers; however, the impact of these genetic variants in disease aetiology remains largely unclear. In this study, we tried to unravel molecular mechanisms underlying "shared genetic variants" and developed a strategy to identify candidate mechanisms for shared aetiology of diseases that display similar patterns of genetic variation organized in shared genomic hotspots. We demonstrate how this approach leads to new insights that help to uncover biological relationships between quantitative traits or related neurodegenerative diseases.

Many traits or diseases have been shown to share genetic architecture [1,2]. This phenomenon, that a genetic variant affects multiple phenotypes, is often called 'pleiotropy' [3-5]. Such pleiotropic variants are particularly interesting, as the functional impact of a SNP on one or several genes may provide clues about the underlying molecular mechanism. For example, a significant overlap of shared genetic variants and pathways has been detected in immune-mediated diseases, suggesting extensive pleiotropic effects [6-8]. These shared genetics variants linked to pathways are ideally suited to identify candidate mechanisms underlying a "shared aetiology" of different diseases.

So far, various studies have been implemented across the genome, mostly on those groups of diseases, which are already well recognized or hypothesized to be interconnected [6,8-10] or by investigating influence of individual genetic variant on a wide range of diverse diseases [11-13].

Biologically, a genetic variant can influence different traits fundamentally in two different ways; firstly, it can influence two distinct phenotypes through two independent physiological mechanisms, while secondly, its effect on the second trait can be mediated through its effect on the first one.

Apparent genetic similarities in a pair of distinct diseases may be indicative for potential overlaps in the underlying disease mechanisms. Thus investigating common factors and network modules shared within a pair of distinct, but related diseases, may point at shared mechanisms. Rather than studying individual diseases separately, investigation and analysis of common dysregulated pathways or dysfunctional proteins of a pair of related diseases can be expected to reveal deeper comprehensive knowledge about pathophysiological processes.

Correspondingly, computing of shared molecular level mechanisms of related disorders can not only assist understanding of the etiology of a disease; but also such associations between shared pathways and correlation with biological processes can accelerate drug discovery efforts by suggesting promising treatment candidates for already approved drugs (known as drug repositioning) [14].

In the work presented here, we performed a systematic and comprehensive analysis of shared genomic loci likely to represent

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genomic hotspots with genes functionally involved in the aetiology of neurodegenerative diseases. We go way beyond classical meta-analysis of GWAS data by performing a 'functional context enrichment' that is tailored to embed candidate genes in these genomic hotspots in a mechanistic context. We demonstrate that this functional enrichment can lead to the identification of new candidate mechanisms for shared aetiology of Alzheimer´s Disease and Parkinsonism.

Methods

GWAS disease-associated variants are identified throughout the entire genome. In order to reveal shared genomic hotspots, that could have been comprised candidate genes for shared molecular mechanisms between two or multiple neurodegenerative and related diseases, genetic variants were collected from GWAS catalog [15] with the threshold of p-values$<1.0 \times 10^{-5}$ for five diseases; including Alzheimer's disease, Parkinson disease, Schizophrenia, Multiple sclerosis and Type 2 diabetes mellitus. These collected genetic variants were belonged to multiple disease association studies and each association study was conducted with different sample sizes. Thus according to basic principle of meta-analysis, we combined the evidence for association from individual studies, with the implementation of appropriate weights, by using a whole genome association analysis toolset Metal [16] and normalized them for their different sample sizes.

Afterwards, Linkage Disequilibrium (LD) analysis was conducted separately for each disease by using Haploreg DB V.4.0 [17]. Next, shared genetic variants were queried by pair-wise analysis for ten pairs of disease of these five diseases.

Subsequently, we made use of the ENSEMBL variant database [18-20] as a reference database to map the SNPs with their relevant chromosome, location, gene, allele and potential functional features (intergenic SNPs were mapped to the nearest gene on the chromosome). Additionally, these shared SNPs were interpreted with the characteristics of predicted functional consequences by using RegulomeDB V.1.1 [21] to get annotation from current ENCODE data (updated with recent ENCODE releases: [22,23]), Chromatin States data from the Roadmap Epigenome Consortium and updated data for DNase footprinting, PWMs, and DNA Methylation, and finally ranked the variant lists according to predicted functional consequences attributes.

Most of the GWAS identified genetic variants are located on the non-coding regions of the genome. In order to investigate, whether there are any overlapping genome stretches between the 'loci of shared GWAS and LD genetic variants' and 'loci of the well-established disease-associated genes in the literature'; in addition to the data-driven approaches described above, a comprehensive knowledge driven approach was also conducted, by searching systematically from literature with the help of a literature mining environment-SCAIView [24].

To extract shared genes for a pair of disease from literature, we were queried via SCAIView for those genes, which were studied for both diseases comprised in a pair (i.e., for AD and T2DM disease pair: {(([MeSH Disease:"Alzheimer Disease"]) and [MeSH Disease:"Diabetes Mellitus Type 2"]) and [Human Genes/Proteins]}). This literature search was conducted in a pair-wise analysis of genes for all of the ten pairs of diseases. The extracted list of "shared genes for a pair of disease from literature" (represented in the workflow as 'List: A') from SCAIView, was then used to pinpoint overlaps by comparing it with the list of "genes mapped with shared GWAS-LD genetic variants for a pair of disease" (represented in the workflow as 'List: B'); and resulting file had 'shared genes for a pair of disease' common in GWAS-LD and Literature (Figure 1).

Afterwards, we mapped list of these shared genes to biological pathways by using MsigDB [25], to identify common pathways for each pair of disease. To demonstrate the potential of the approach, we did an exploratory study on one putative shared mechanism relevant for AD and PD. The genomics locus investigated maps to chromosome 17; to a region that displays highest scores for functional consequences

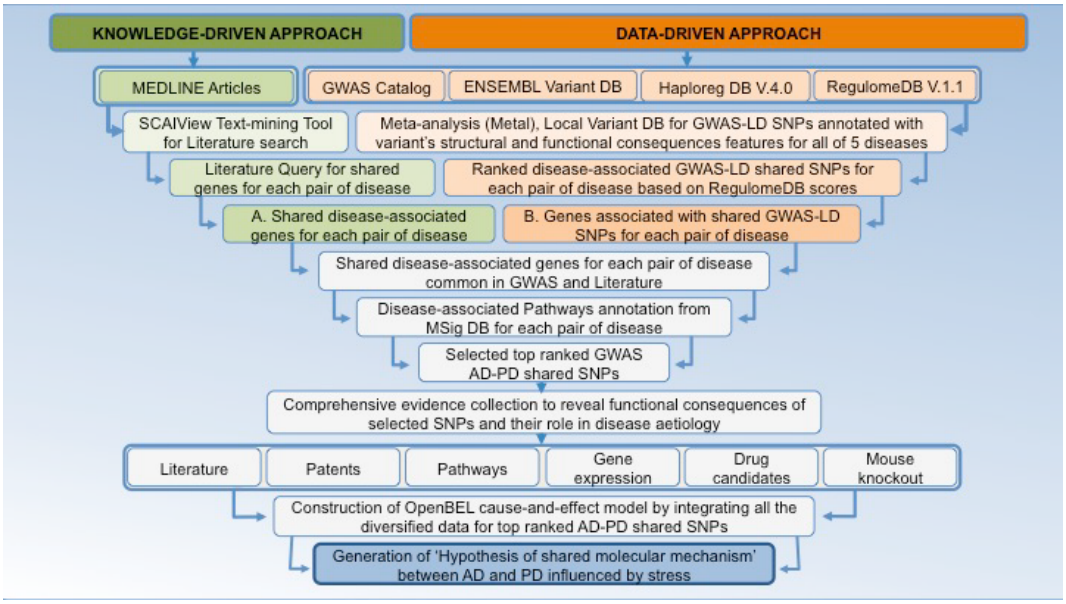

Figure 1: Flowchart for data analysis steps:

Flowchart for data analysis steps starting from GWAS Data collection to integration, mapping, annotation, filtering, Modeling and finalizing by Hypothesis generation.

in RegulomeDB and one of high ranked shared pathway between AD and PD from MsigDB result table, that is 'KEGG_LONG_TERM_DEPRESSION' (Supplementary File). The high-resolution analysis of that shared genomic locus for its potential role in the aetiology of the disease pair AD and PD includes - besides the identification of the candidate locus and the candidate genes within - the collection of evidences from gene expression studies, patents, knock-out studies and other literature, ultimately resulting in a comprehensive knowledge-driven approach towards the enrichment with supportive evidence.

Results

In an initial step, we selected five different brain diseases including Alzheimer's disease (AD), Parkinson disease (PD), Schizophrenia, Multiple sclerosis (MS) and Type 2 diabetes mellitus (T2DM).

Spatial analysis, after mapping of GWAS disease-associated intronic SNPs to the genes, they belong to; and intergenic SNPs to the most likely, nearby genes; reveals that most of the GWAS SNPs are located around specific genome loci ("genomic hotspots"). Our assumption is, that the genes existing in the vicinity of these genome loci may play a role in the dysregulation of disease-associated pathways.

Moreover, we computed pair-wise analysis for shared genetic variants to see the relevancy between each pair of diseases. However, enumerating of pair-wise shared GWAS SNPs before LD SNPs enrichment revealed that only a very limited number of individual SNPs are shared in a pair of diseases, while after LD analysis, most of the disease pairs showed a substantial count of shared variants; which also signify the genetically linkage between SNPs located on these specific genomic loci around GWAS SNPs. Thus it can be explained that these pairs of disease may share disease-associated genomic loci rather than individual genetic variants (Supplementary File).

Pair-wise analysis also revealed that AD and PD have the largest number of shared disease-associated loci. There is no doubt, that this is reflecting the bias that comes with the higher number of GWAS studies and available data around these two diseases. But it also may indicate an overlap of the genetics relevant for pathophysiology mechanisms shared between AD and PD. Other disease pairs, for instance the AD-T2DM pair, did also show a promising number of shared genetic markers and genomic loci. Successively, pairs of AD-Schizophrenia and AD-MS also presented a reasonable number of shared SNPs and genomic loci (Table 1).

The analysis of specific overlapping genome stretches between 'loci identified for shared GWAS-LD genetic variants' and 'loci of already established disease-associated genes in the literature' revealed that there was a quite significant overlap between GWAS loci and literature based disease-associated gene loci (Supplementary File), which provides suggestive evidence for an association between genetic variants and disease pathology.

Analysis of putative shared pathways was done by mapping genes in genomic hotspots to pathways using MsigDB. Shared pathways-as a functional layer on top of shared genetics - are indicative for putative pathology mechanisms shared between pairs of diseases. The analysis workflow thus identifies disease pairs that do display a high number of shared genomic hotspots, a significant number of putative shared pathways and – as a consequence - may have significantly shared molecular level mechanisms, that-when perturbed - may contribute to disease etiology.

To explore the pathophysiology of putative shared mechanisms in detail, we selected the pair of AD and PD for a mechanistic case study.

Shared SNPs and Genes Count for 10 pairs of 5 Diseases		
Disease Pair	**Shared SNP Count**	**Shared Gene Count**
AD–PD	35958	1793
AD–T2DM	2187	103
AD–Schizophrenia	867	46
AD–MS	771	62
PD–Schizophrenia	701	24
PD–T2DM	463	21
MS–Schizophrenia	421	28
T2DM–MS	250	17
PD–MS	246	19
T2DM–Schizophrenia	223	18

Table 1: List of disease pairs with GWAS associated shared genetic variants and genes count.

Amongst their shared genomic loci, we selected the well-known Tau locus, located on chromosome 17, to explore further detailed molecular mechanisms, as it showed top ranked "functional consequences" scores, based on ENCODE data, the Roadmap Epigenome Consortium data, DNase footprinting analysis, and DNA Methylation data. Apparently, selecting the tau locus seems to add nothing new and novel, as the tau locus is already well known and has been studied in detail. However, this locus has never been studied in a comprehensive way by "embedding" all the affected genes in that locus into a functional context. In our analysis, we expand the mechanistic context associated with the genes in the tau locus, by collecting and assembling all genetic, molecular and statistical evidences from the literature, from patents, from gene expression studies and from knock-out experiments in one comprehensive mechanistic model. In the following, we are presenting this locus in a very novel and unique perspective of stress induced shared pathology of AD and PD.

This genomic hotspot around tau is highlighted in many association studies for multiple statistically significant SNPs (references). The hotspot covers approximately 1 Mb of a chromosomal region characterized by linkage disequilibrium region that contains a large number of genetic variants.

Three genes are prominent in this locus: MAPT (Microtubule-Associated Protein Tau), the CRHR1 receptor-1 (Corticotropin Releasing Hormone Receptor 1) and the CRHR1-IT1 gene (CRHR1 Intronic Transcript 1). These genes are linked to several disease-associated genetic markers mapping to both, coding and non-coding regions. Moreover, disease-associated intergenic and intronic SNPs of this locus have several eQTL links with neighboring genes (Supplementary File).

In the course of our investigation of this shared genomic locus, we identified that, other than AD and PD, it also has well-established associations with Stress and Depression phenotypes. We searched for potential genetic, molecular and statistical evidences from the scientific literature and collected additional evidences from patents, gene expression studies and knock-out experiments, that all support the notion of a shared molecular mechanism linking Stress, AD and PD.

To enrich the genetics-driven identification of candidate genes with functional context and to identify potential mechanisms that bear explanatory potential for the presumed shared etiology linked to this particular locus on chromosome 17, we performed a systematic literature analysis using our literature mining environment SCAIView [26]. Contextual information relevant to the previously identified, disease-associated tau locus and being specific for the context of AD

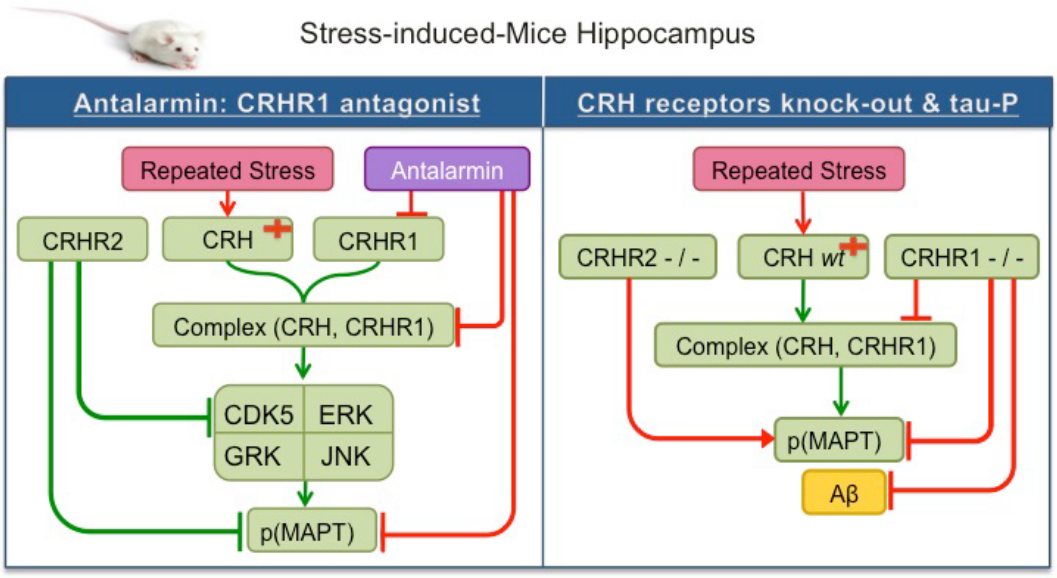

Figure 2: Experimental evidences for CRH gene and its receptors CRHR1 and CRHR2 and CRHR1 antagonist 'Antalarmin':

Experimental evidences for CRH gene and its receptors CRHR1 and CRHR2 and CRHR1 antagonist 'Antalarmin', collected from mouse model knock-out experiments to identify their role in the stress induced mice Hippocampus: Repeated stress induces the expression of the wild-type CRH gene, while inactivation of the CRHR1 gene, which is the receptor of CRH, not only inhibits the complex of CRH+CRHR1 but also causes a reduction of MAPT phosphorylation and a reduction of Amyloid beta (Aβ) peptide concentration. CRHR2, which is another receptor of CRH, inhibits MAPT phosphorylation; moreover, it has been shown to down-regulate the expression of CDK5, ERK, GRK and JNK genes. As further supportive evidence for the functional antagonism between CRHR1 and CRHR2, the CRHR1 inhibitor 'Antalarmin' blocks CRHR1 and its complex with CRH; the inhibitor also causes a reduction of MAPT phosphorylation.

and PD was systematically identified and harvested. The extracted information comprises cause-and-effect relationships representing protein-protein interactions, protein inhibitory and activating patterns, protein-complex formation, insights from disease animal model studies, patterns from knockout and gene expression studies, other genetic associations; from gene mapping (fine-mapping) and GWAS meta-analysis studies, and from drug effects; all with high specificity for either AD or PD or both. The vast amount of information extracted was subsequently encoded using the OpenBEL (Open Biological Expression Language) syntax to construct a cause-and-effect computable model [27]. Models were developed separately for human and mouse. The resulting, comprehensive BEL models represent the state of published knowledge in the context of the genes under investigation in the context of AD and PD; the models are then visualized by Cytoscape_v2.8.3 [28] and queried for disease associated molecular mechanisms to unravel mechanistic context that link molecular level perturbation with the disease etiology.

The mouse model reveals that repeated stress induces the expression of the wild-type CRH (Corticotropin Releasing Hormone) gene, while inactivation of the CRHR1 gene, which is the receptor of CRH, not only inhibits the complex of CRH+CRHR1 but also causes a reduction of MAPT phosphorylation and a reduction of Amyloid beta (Aβ) peptide concentration [29]. CRHR2, which is another receptor of CRH, inhibits MAPT phosphorylation; moreover, it has been shown to down-regulate the expression of CDK5, ERK, GRK and JNK genes [30]. As further supportive evidence for the functional antagonism between CRHR1 and CRHR2, the CRHR1 inhibitor 'Antalarmin' blocks CRHR1 and its complex with CRH; the inhibitor also causes a reduction of MAPT phosphorylation [30] (Figure 2).

The contextual BEL model specific for human pathophysiology demonstrates that a genetic variant rs1800547, located on the intron region of the MAPT gene, is positioned on the Haplotype-1 region of chromosome 17, which is associated with PD [31,32]. Its 'A' allele is associated with 'Dementia in PD patients' and its 'G' allele with 'familial FTD' [33]. This genetic variant is linked with the expression of host gene MAPT and also expression of a neighbouring gene CRHR1; thus, its 'A' allele is associated with an up-regulation of MAPT and a concomitant down-regulation of the CRHR1 gene, while the 'G' allele is associated with an up-regulation of the CRHR1 gene [33]. In addition, the 'A' allele containing SNP rs1800547 is linked to a neuro-imaging readout, the reduction of gray matter volume [33]. Likewise, the 'A' allele of another SNP named rs393152, which is located near the CRHR1 gene, is associated with the up-regulation of the MAPT gene [34]. Moreover, the rs393152-A allele has been associated with AD and PD, and seems to be linked to a reduction of gray matter volume as well as atrophy of the hippocampus and entorhinal cortex [34] (Figure 3).

BEL models are excellent tools to represent complex physiology; the representation in BEL bears great explanatory potential on how complex physiology works across scales. Our contextual BEL models representing complex physiology of genes in the Tau locus provide a mechanistic explanation, how excessive and repeated stress may modulate pathophysiology. Repeated stress induces the expression of the CRH gene in the hippocampal area [35], while under AD conditions; reduced CRH immune-reactivity is observed [36]. CRH interacts with its receptor, the CRHR1 protein; the CRHR1 gene is highly expressed in hippocampus and the complex between the hormone and its receptor (CRH+CRHR1) can be detected in that brain region [37]. In addition, the CRHR1 protein also interacts with γ-secretase, which is associated with Aβ accumulation, one of the hallmarks of AD pathophysiology [38].

The hormone receptor protein complex (CRH+CRHR1) is further

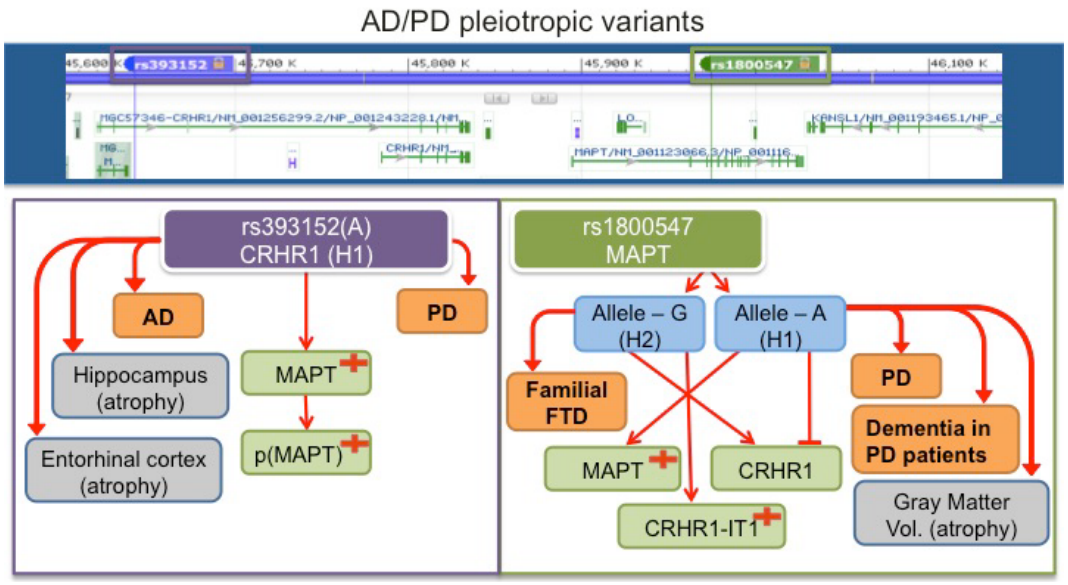

Figure 3: Experimental evidences for AD/PD pleiotropic variants, to identify the functional consequences for these variants:

A genetic variant rs1800547, located on the intron region of the MAPT gene, is positioned on the Haplotype-1 region of chromosome 17, which is associated with PD. Its 'A' allele is associated with 'Dementia in PD patients' and its 'G' allele with 'familial FTD'. This genetic variant is linked with the expression of host gene MAPT and also expression of a neighbouring gene CRHR1; thus, its 'A' allele is associated with an up-regulation of the MAPT and a down-regulation of the CRHR1 gene, while the 'G' allele is associated with an up-regulation of the CRHR1 gene. Moreover, the 'A' allele containing SNP rs1800547 is also linked to a neuro-imaging readout, the reduction of gray matter volume. Likewise, the 'A' allele of another SNP named rs393152, which is located near the CRHR1 gene, is associated with the up-regulation of the MAPT gene. Moreover, the rs393152-A allele is associated with AD and PD, and also linked with a reduction of gray matter volume as well as atrophy of the hippocampus and entorhinal cortex.

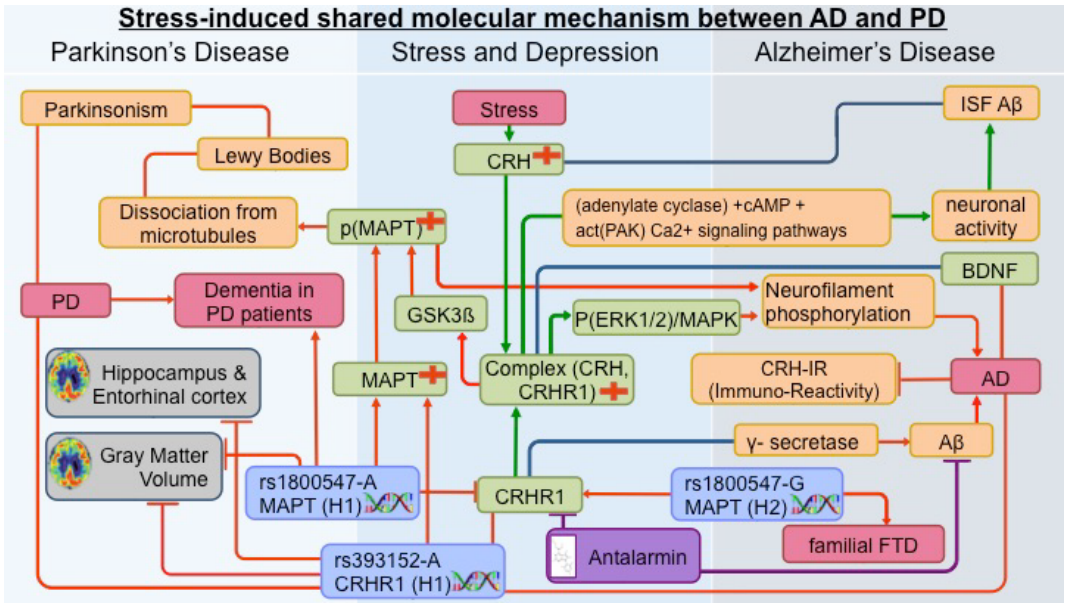

Figure 4: Stress induced comorbidity association of AD and PD by genetic variants of Tau locus genes:

Stress up regulate CRH gene expression, which interacts with its receptor, the CRHR1 protein; the CRHR1 gene is highly expressed in hippocampus and the complex between the hormone and its receptor (CRH+CRHR1) can be detected in that brain region. In addition, the CRHR1 protein also interacts with γ-secretase, which is associated with Aβ accumulation, one of the hallmarks of AD pathophysiology. The hormone receptor protein complex (CRH+CRHR1) is further linked to the up-regulation of GSK3β and the phosphorylation of essential elements of the ERK1/2/MAPK pathway. Up-regulation of GSK3β is associated with MAPT hyper-phosphorylation; in addition, phosphorylated MAPT and ERK1/2/MAPK pathway up-regulate Neurofilament phosphorylation, which has been associated with AD. The complex physiology is even increased through the interaction of the 'CRH+CRHR1' protein complex with the BDNF protein; this interaction has already been associated with AD pathology. The complex also enhances neuronal activity by interacting with adenylate cyclase, cAMP, act(PAK), Ca2 signaling pathways. The resulting enhanced neuronal activity has been shown to further accumulate interstitial fluid amyloid beta (ISF Aβ), while this accumulation of ISF Aβ is also linked with up-regulation of CRH gene expression, effectively establishing a feedback loop that can enhance negative dysregulation events. MAPT hyper-phosphorylation also increases its dissociation from microtubules, a process that has been linked to lewy-bodies and Parkinsonism, in the PD context. Finally, the CRHR1 antagonist 'Antalarmin', which is used in response of chronic stress, has been shown to reduce Aβ accumulation in brain, adding further meaningful, supportive evidence in context.

linked to the up-regulation of GSK3β and the phosphorylation of essential elements of the ERK1/2/MAPK pathway [30,39]. Up-regulation of GSK3β is associated with MAPT hyper-phosphorylation [30,40]; in addition, phosphorylated MAPT and ERK1/2/MAPK pathway up-regulate Neurofilament phosphorylation, which has been associated with AD [30,39]. The complex physiology is even increased through the interaction of the 'CRH+CRHR1' protein complex with the BDNF protein; this interaction has already been associated with AD pathology [41]. The complex also enhances neuronal activity by interacting with adenylate cyclase, cAMP, act(PAK), Ca2 signaling pathways [41]. The resulting enhanced neuronal activity has been shown to further accumulate interstitial fluid amyloid beta (ISF Aβ), while this accumulation of ISF Aβ is also linked with up-regulation of CRH gene expression [42], effectively establishing a feedback loop that can enhance negative dysregulation events. MAPT hyper-phosphorylation also increases its dissociation from microtubules, a process that has been linked to lewy-bodies and Parkinsonism, in the PD context [43].

Finally, the CRHR1 antagonist 'Antalarmin', which is used in response of chronic stress, has been shown to reduce Aβ accumulation in brain [44] (Figure 4), adding further meaningful, supportive evidence in context.

Additionally, exhaustive analysis of relevant patent literature revealed that an antagonist against the CRH receptor is effective as a prophylactic or therapeutic agent for diseases, like, anxiety, depression, AD and PD [45]. Patents also describe multiple lines of evidence that suggest the significant role of CRHR1 on neuropsychiatric disorders, and MAPT gene as a well-studied candidate gene for neuropsychiatric disorders [46]. Moreover, it is also patented that although the two receptors CRHR1 and CRHR2 share 70% sequence identity, they differ substantially in ligand binding affinity, and the CRH gene itself has a much higher affinity for CRHR1 rather than CRHR2 [47]. Another patent describes that the accumulation of hyperphosphorylated tau protein in the central nervous system, may be reduced through the administration of CRHR1 selective antagonists and/or CRHR2 selective agonists. Patent [EP2522351 A1] indeed describes methods for the prevention of the onset of Alzheimer's disease by the administration of CRHR1 selective antagonists [48] (Supplementary File).

Discussion

In the work presented here, we established an integrative approach that starts with a data-driven approach, identifies signals in GWAS data, and gains explanatory potential and allows for new insights into putative complex mechanisms through knowledge-driven context enrichment. Our approach goes way beyond classical "pathway enrichment" approaches, as it takes multimodal information into account and integrates heterogeneous information and knowledge in biologically meaningful, computable graph models. Data, a priori knowledge and inferred insights are combined in a seamless fashion. Meaningful cause-and-effect relationships are established and the signals originally identified are made interpretable in a rational modelling and mining approach.

Our workflow is tailored towards the identification of novel shared mechanisms. It starts with comparative GWAS analysis tailored to identify shared genetic variants; puts the enriched SNPs in contigs (based on linkage disequilibrium); identifies those genes belonging to the "shared" LD loci and establishes compelling evidence for shared molecular mechanisms and biological pathways associated with those genes, for a given pair of disease. The workflow was applied to a comprehensive set of related diseases and allowed us to investigate shared molecular level mechanisms between a pair of diseases, based on both, data driven and knowledge driven strategies.

We would like to emphasize that genomic loci (genomic hotspots) should be considered to investigate the effects of GWAS variants rather than individual genetic variants, particularly to investigate shared pathology. Whereas the biological impact of single SNPs is often hard to predict, the association of several SNPs in a disease-associated LD block provides evidence for a much stronger association that may affect an entire locus with several genes. As a consequence, a set of SNPs in a genomic hotspot may contribute to dysregulation events involving several genes.

Modelling the functional context of these genes in computable cause-and-effect models can be very helpful to identify possible molecular level perturbation mechanisms that contribute to disease pathology. As such, computable mechanistic models are essential to integrate diverse types of data as well as relationships between the nodes; they can help to discover unknown links to illustrate the possible mechanism of dysregulation.

At this point we would like to stress that we are not talking about pathways when we talk about mechanisms. Although pathways are abstractions of biological functional context that is shared by many cell types and often conserved across species boundaries, the pathway concept as it was established over the last 30 years is not taking into account genetic variation information and is not well-suited to take into account the specifics of cell-cell-interactions. "Chains of causation" as we find them in the BEL model graphs may as well exist in pathways, but in pathways they are confined to one type (one "mode" or "level") of information. Integrative models based on causal relationships, however, span over multiple levels and scales and establish links e.g. from SNPs to imaging features in one single, computable graph model. We would encourage the community to clearly distinguish between pathways (representing canonical information) and mechanisms (representing causes and effects associated with a disease context). Mechanistic modeling allows us to be highly specific with respect to the available knowledge in a given context, without restricting us to make use of canonical knowledge if we wish to include that type of common information.

The mechanistic hypothesis generated from our 'tau locus BEL model' establishes a rational, how stress could cause deficits in memory [49-54]. We may actually have established a functional context that puts a "sensor" for environmental and life style into a pathophysiology mechanism that could play a significant role in the etiology of Alzheimer's disease. Our model provides also mechanistic clue, how hippocampal atrophy may be linked to the pathophysiology of stress [49,51-54] The stress-related HPA axis activation (linked to the CRH-CRHR1 complex) may thus represent a pathophysiological initiation of memory loss [52]. Likewise, it is reported that the decline in CRH Immuno-Reactivity (CRH-IR) in AD is due to the reciprocal accumulation of CRH receptors in affected cortical areas [37]. The alteration in pre- and postsynaptic indicators for CRH is significantly correlated with decline in ChAT (choline acetyltransferase) activity [37].

The H1 haplotype of MAPT extends towards the 5' region and includes the contiguous gene CRHR1. Linkage Disequilibrium (LD) of this region is substantially associated with PD patients [55]. Strikingly, the oldest and most extensively case-control studies for PD demonstrated the greatest evidence for MAPT and H1 haplotype association. By genotyping H1 haplotype SNPs within the CRHR1-MAPT interval, we can hypothesize that the CRHR1 gene may be responsible for at least part of the disease association of this locus due to

the genetic variability and could become a good biomarker candidate, since it is significantly involved in both, immune and nervous systems physiology [55]. Missense and splicing genetic variants in MAPT were first uncovered in 'frontotemporal dementia with parkinsonism' associated with chromosome 17 (FTDP-17) [31].

Thus, forgoing studies have already specified associative links between stress, CRH-CRHR1, and tau pathology mediated by CRH-CRHR1 dependent activation of tau kinases induced by stress [30,41,56]. On the other side, the H1 haplotype is associated with the accumulation of hyperphosphorylated Tau in neuronal cell bodies, which has always been associated with neurodegenerative diseases [57,58].

Though AD and PD are likely to have different mechanisms underlying their etiology and may affect different brain regions, and display different clinical features, still they have a significant overlap in the progression of neurodegenerative processes. A recent study has been investigating AD and PD GWAS SNPs to identify AD-PD pleiotropic genetic variants/loci. They found, that the 'A' allele of rs393152, within the CRHR1 and CRHR1-IT1 region (MAPT locus) on chromosome 17, with a MAF (minor allele frequency) value of 23.1%, significantly increased AD and PD risk, additionally, that allele is linked to the up-regulation of MAPT expression [33]. With APOE-stratified GWAS, another study revealed that genetic variants in the chromosome 17q21.31 region are associated with AD [59].

Besides all the genetic evidences that support our mechanistic model, there is also evidence from pharmacology that adds to the plausibility of the pathophysiological context we have established. Rissman et al. described that the selective CRHR1 blocker "antalarmin" blocks stress-induced escalations in tau phosphorylation. This points at a direct function for CRF-dependent signaling in the stress response [30]. Fully in line with this observation is the finding, that CRHR1 antagonist antalarmin is able to suppress amyloid beta accumulation associated with AD pathology, in mice [60].

It is also notable that CRHR1 has a vital role in inflammation [61,62] and the CRHR1 antagonists that are used to treat depression [63,64], also control peripheral inflammation [65-67]. Similarly, those antidepressants, which are known to modulate inflammatory responses, also confer protection against cytokine-induced depressive-like behavioral and biological modifications [68-72].

In a clinical study with MCI (Mild Cognitive Impairment), AD and control groups, Arsenault-Lapierre et al. [73] couldn't find group differences in cortisol levels. This contradicts several previous studies that found different cortisol levels between normal and AD [74-78] and between normal and MCI groups [78,79]. Contrarily, it supports the literature that found no correlation between cortisol level and perceived stress in different populations [80-82]. Whereas, in this study more MCIs were diabetic, and diabetic patients have been found to secrete higher cortisol levels [83-85], likewise more AD patients were on sedatives or antidepressants. These medications may affect levels of cortisol and perceived stress measured in the patients [73]. However, these findings support our hypotheses that with the mechanism introduced here and the link between HPA axis, genetics and major determinants of AD and PD pathophysiology, we see a source for the highly stochastic nature of sporadic NDDs.

Repetitively, in a recent publication, Park HJ stated that stress response meditated by CRH-CRHR1 mechanism could also contribute to AD pathogenesis [38]. But he also described that under some circumstances, CRHR1 antagonism does not achieve required results against acute stress-induced Aβ production, rather he suggested that either direct targeting of CRH or G protein-biased CRHR1 agonist that could suppress β-arrestin recruitment to CRHR1 might be required to effectively target associated pathway for therapeutic benefit in AD [38].

Conclusion

Our work has established an integrative approach that gains explanatory potential and allows for new insights into putative complex mechanisms through both, data-driven and knowledge-driven context enrichment. Our workflow is tailored towards the identification of novel shared mechanisms and established compelling evidence for a new, shared molecular pathophysiology mechanism associated with AD and PD.

Starting with signal detection in a GWAS meta-analysis, our approach integrates heterogeneous information and knowledge in biologically meaningful and computable graph models. The computable mechanistic model we generated integrates diverse types of data as well as relationships between the nodes, resulting in an efficient 'functional context enrichment'. We demonstrate that this functional enrichment of genetic variants can lead to the identification of new candidate mechanisms explaining a putative shared aetiology of a given pair of diseases, in our case Alzheimer´s Disease and Parkinsonism.

Though AD and PD affect different brain regions and display different clinical features, still they have a significant overlap in the progression of neurodegenerative processes and our analysis provides compelling evidence for a shared mechanism linking both clinical syndromes.

We emphasize that genomic loci should be considered to investigate the effects of GWAS variants rather than individual genetic variants, particularly to investigate shared pathology, since the biological impact of individual SNPs is often hard to predict.

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Authors Contributions

EY proposed the idea; MN, EY and MHA designed data analysis process; MN analysed the data, generated the results and wrote the manuscript. MHA read, corrected and improved the manuscript. All authors read and approved the manuscript.

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