ALZHEIMER'S DISEASE

A needle for Alzheimer's in a haystack of claims data

In the era of big data, looking for insights in large datasets has become the norm — and health data are no exception. Combining systems-biology-driven, endophenotype-based analysis of drug targets with large-scale medical claims data points to sildenafil as a potential treatment opportunity for Alzheimer's disease.

Emre Guney and Alejandro Athie

Despite more than half a century of biomedical research, there is no known effective therapy for Alzheimer's disease (AD). Drugs that are currently used for AD aim at slowing cognitive decline, merely ameliorating the symptoms of the disease. The unmet clinical need for AD is reflected in the approval of aducanumab by the US Food and Drug Administration (FDA) in June of this year, amid concerns raised by an independent advisory panel on the efficacy of the drug to slow progression of the disease. Consequently, the first drug approval to come for AD in almost two decades was accompanied by controversy, casting a shadow upon the hopes of the more than 40 million people affected by AD worldwide. Can big data in biomedicine and healthcare, accumulating at an exponential rate, come to the rescue? To address this question, a study in this issue of *Nature Aging* by Fang and colleagues[1] turned to a database containing individual-level diagnosis codes, procedure codes and pharmacy claim data from 2012 to 2017 across 7.23 million patients. The authors showed that use of sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor that was originally developed for pulmonary arterial hypertension and angina, was associated with a substantially reduced incidence of AD, in particular in male individuals (Fig. 1).

Sildenafil is a drug that blocks the degradative action of PDE5 on cyclic GMP (cGMP) in smooth muscle cells and causes relaxation of the smooth muscle cells that line blood vessels. Interestingly, this is not the first time that sildenafil has been placed in the spotlight for a use that differs from its intended indication. During the clinical trials that investigated the use of sildenafil for hypertension, it became apparent that it had a rather unusual side effect — inducing penile erections in male patients. Turning the problem to an opportunity, the company behind sildenafil pursued the compound as a treatment for erectile dysfunction, making it one of the best known examples of drug repurposing. More recently, an increasing number of studies suggest the use of sildenafil and other PDE5 inhibitors for preventing the breakdown of cGMP that is associated with cognitive decline and neuroinflammation in the pathology of AD (as previously reviewed[2,3]). The findings of Fang et al.[1] from analysis of insurance claims data provide supporting evidence at the population level for the potential benefit of the drug for decreasing AD risk.

What makes this study interesting is that it starts with a systems biology approach to shortlist a priori the drugs that could target the endophenotypes that underlie AD. Initially proposed within neuropsychiatry, endophenotypes are intermediate phenotypes that correspond to biological pathways with a clear genetic connection to the disease pathology[4]. To separate AD — a broad disease phenotype that is typically categorized on the basis of observed symptoms — into more mechanistically defined biological processes that underlie the disease pathology (such as amyloid plaque formation and

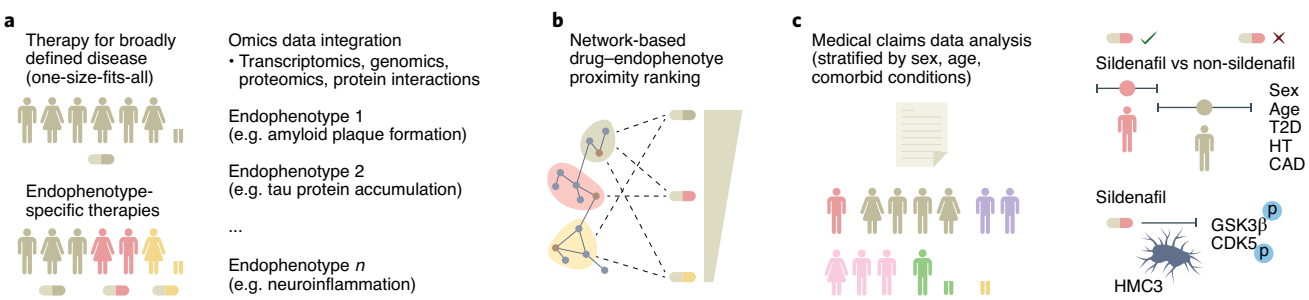

Fig. 1 | Endophenotype-based drug prioritization and population-based validation for drug repurposing in Alzheimer's disease. a, Current diseases are broadly defined on the basis of symptoms, and treatments rely on a one-size-fits-all approach. The accumulation of omics and health-related data opens a new avenue for the identification of endophenotype-specific treatments. **b**, In the Fang et al. study[1], drugs are ranked for their potential to target endophenotypes defined using omics data, enabling the repurposing of existing drugs for endophenotypes in neurodegenerative disorders such as Alzheimer's disease (AD). Colours of the clusters relate to endophenotypes in **a**. **c**, Patient-subgroup-stratified propensity analyses on medical claims data using sex, age, and co-occurring conditions such as type 2 diabetes (T2D), hypertension (HT) and coronary artery disease (CAD) associate sildenafil with decreased AD risk. In vitro experiments offer insights into possible mechanisms-of-action for sildenafil in AD, such as inhibiting lipopolysaccharide-induced activation of glycogen synthase kinase 3β (GSK3β) and cyclin-3-dependent kinase 5 (CDK5) in human microglia (HMC3) cells.

tau protein accumulation), the authors leveraged genetics, transcriptomics and proteomics data. They integrated data on genes and proteins from large-scale genetic datasets, together with data from in vivo knockdown or overexpression models of AD-like pathology and transgenic mouse models with amyloidosis or tauopathy. The genes, grouped on the basis of their relevance to amyloidosis, tauopathy and general AD pathology, were used to generate endophenotype and disease modules in the interactome, the molecular network of known protein–protein interactions in humans. These modules (gene sets connected to each other within the interactome) were then examined algorithmically for their potential to be targeted by FDA-approved drugs using network-based proximity[5].

The network-based analysis ranked sildenafil among the top candidates and pointed to glycogen synthase kinase 3β (GSK3β) and cyclin-3-dependent kinase 5 (CDK5) as the closest proteins to the targets of sildenafil. Indeed, sildenafil use was associated with a 69% reduction in AD risk compared with matched individuals who did not use sildenafil (hazard ratio (HR) 0.31, 95% confidence interval (CI) 0.25–0.39, $P < 1 \times 10^{-8}$) within 6 years of follow-up in the longitudinal claims data. Additional cohort-based analyses, stratified by propensity score, that investigated the use of sildenafil versus comparative drugs (such as diltiazem, glimepiride, losartan and metformin) revealed a significant reduction in AD risk with sildenafil as compared to each of these drugs (HR of 0.35, 0.36, 0.45 and 0.37, respectively; all with $P < 1 \times 10^{-8}$). The potential benefit of sildenafil compared to the other drugs in reducing AD risk was also observed in both mid-older (65–74 years) (HR of 0.38 for sildenafil users versus non-users) and older individuals (75–100 years) (HR of 0.49 for sildenafil users versus non-users). On the other hand, sex-specific subgroup analysis showed that the potential protective effect of sildenafil against AD was more apparent among men than women (HR of 0.27 and 0.65 for male and female sildenafil users versus non-users), a finding that the authors attribute to most sildenafil users being men who are receiving treatment for erectile dysfunction at daily dosages higher than those of women who are receiving treatment for pulmonary hypertension.

The authors further explored in vitro a possible mechanism-of-action that relates the phosphorylation levels of the two implicated proteins, GSK3β and CDK5, to sildenafil. Treatment of human microglia cells (the HMC3 cell line) with sildenafil showed a downregulation of GSK3β and CDK5 phosphorylation in a concentration-dependent manner. Microglia cells have an important role in active immune defense in the central nervous system, help to maintain homeostasis in healthy tissue and promote inflammation in injured tissue. Regulating microglia activity may provide therapeutic benefits that slow down inflammatory-mediated neurodegeneration. Using induced pluripotent stem cells derived from patients with AD, the authors showed that neurite growth was increased and phosphorylated tau expression was decreased in sildenafil-treated forebrain neuron cells obtained from progenitor cells of a patient with AD. Further experiments investigating the potential mechanism for the effect of sildenafil through inhibition of PDE5 will help to better characterize the protective role of sildenafil in AD.

Transforming diseases into multiple genetically related endophenotypes and representing them as modular components inside the cellular interaction network constitute a powerful modeling approach. For example, recent graph theoretical analyses in the human interactome have highlighted crosstalk between the endophenotype modules involved in inflammatory responses[6], the molecular similarities and comorbidities across disease modules[7] and the potential role of lipid metabolism endophenotype involved in the common pathology of AD and type 2 diabetes[8]. Network-based modeling of disease and endophenotype modules has also helped to shift from serendipity-based drug repurposing to mechanism-based characterization of the effects of drugs[5,8–11].

The study by Fang et al.[1] is a timely addition to the recent applications of endophenotype-based drug repurposing by combining multi-omics data analysis and real-world pharmaco-epidemiological data from patients. The study design considers various confounding factors, such as sex, race, age and co-occurring conditions, to ensure that the decrease in AD risk is significant independent of these factors when compared to diltiazem, glimepiride, losartan and metformin (other drugs that are used for hypertension and diabetes). In fact, the authors find that the decrease in AD risk is rather modest in women compared to men, calling for caution and sex-based stratification for follow-up studies that use biomedical and healthcare data to avoid biases[12].

However, there may be additional confounding factors, such as socioeconomic status and education level, that were not available in the claims dataset used by the authors. Although the claims data have a crucial role in validating the potential benefit of sildenafil for AD, they also introduce a bottleneck as they are far from complete and are probably biased for more frequently prescribed treatments in the USA. Moreover, the analysis presented in the study fails to demonstrate the causality between sildenafil and the decrease in the AD risk.

Another important limitation of this study is the lack of a clear link between the endophenotypes characterized at the cellular level and the patients analyzed using the claims data. Genotyping information, such as the *APOE* status of the patient, would be needed to be able to validate endophenotype-specific drug-repurposing hypotheses identified by network-based analyses. Therefore, increasing the availability and accessibility of de-identified patient data such as medical records and genetic information for this kind of meta-analysis remains a key challenge in identifying novel therapeutic options for neurodegenerative disorders. There is also a clear need for agreeing on the definition of the endophenotypes in AD and other neurodegenerative disorders[13,14].

Although the concept of endophenotypes is not new, its application to drug repurposing through data-driven approaches is relatively recent. As there are different mechanisms involved in the pathology of complex, polygenic and pleiotropic neurodegenerative disorders such as AD[15], there are possibly numerous other needles to be found and to be validated in properly designed randomized clinical trials: the best treatment options might be found in the haystacks of large repositories of patient data. ❐

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Competing interests

E.G. is an employee of STALICLA, a clinical-stage biopharmaceutical company leading omics-based precision medicine drug development for patients with neurodevelopmental disorders through endophenotyping and artificial intelligence. A.A. is an employee of Accenture.