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Gene-by-environment interactions in Alzheimer's disease and Parkinson's disease

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Abstract

Diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) arise from complex interactions of genetic and environmental factors, with genetic variants regulating individual responses to environmental exposures (i.e. gene-by-environment interactions). Identifying gene-by-environment interactions will be critical to fully understanding disease mechanisms and developing personalized therapeutics, though these interactions are still poorly understood and largely under-studied. Candidate gene approaches have shown that known disease risk variants often regulate response to environmental factors. However, recent improvements in exposome-and genome-wide association and interaction studies in humans and mice are enabling discovery of novel genetic variants and pathways that predict response to a variety of environmental factors. Here, we highlight recent approaches and ongoing developments in human and rodent studies to identify genetic modulators of environmental factors using AD and PD as exemplars. Identifying gene-by-environment interactions in disease will be critical to developing personalized intervention strategies and will pave the way for precision medicine.

Keywords

gene-environment; genetic reference panel; genome; exposome; Alzheimer's disease; Parkinson's disease

Introduction

Complex neurological diseases arise from interactions between genetic (G) and environmental (E) factors (GxE interactions, (Patel 2016)). Significant advances in genomic technologies have enabled the robust identification of genetic modulators of disease risk and susceptibility in humans; current approaches are now underway to develop standardized definitions and analyses of environmental exposures (the "exposome") throughout the lifespan (Wild 2005; Niedzwiecki et al. 2019; Vineis et al. 2017). A critical next step is to integrate genome and exposome information in order to understand how genetic variants

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regulate response to environmental factors related to human disease (Rappaport 2011). GxE interactions will perhaps prove most important in aging and age-related neurodegenerative diseases because they arise after a lifetime of interactions between environmental exposures and genetic risk factors to cumulatively alter disease risk and progression on a population level. For example, both Alzheimer's disease (AD) and Parkinson's disease (PD) have significant genetic components (Gatz et al. 1997; Gatz et al. 2006; Pedersen et al. 2003; Shulman, De Jager, and Feany 2011; Lunati, Lesage, and Brice 2018; Bandres-Ciga et al. 2017; Douglas, Lewthwaite, and Nicholl 2007). However, risk for these diseases are also significantly affected by a plethora of environmental factors throughout a person's lifespan (Caudle 2012; Hatcher 2008; Di Monte, Lavasani, and Manning-Bog 2002; Livingston et al. 2017; Barnes and Yaffe 2011), although how these factors interact is not well understood.

Extracting GxE interactions is a difficult task (Patel 2016). GxE effects may have relatively small effect sizes, and given the complexity of the human genome, population-based human studies require an uncommonly large number of participants to attain the statistical power needed for valid analyses (Ahmad et al. 2013). In those studies that are sufficiently well-powered to extract GxE interactions, the complexity and quality of data available to quantify a lifetime of environmental exposures may reduce the ability to identify true GxE interactions. Indeed, accuracy in retrospective environment-wide association studies ("EWAS") is challenged by several factors, including: i) participants' incomplete recall or reporting of exposures, ii) confounds produced by related exposures, iii) inconsistent timing, dose, and duration of exposures within the population, and iv) sampling biases such as attrition and selective survival. Additional complexity is introduced because environmental factors and exposures evolve across time, such that exposures that are particularly important mediators of AD and PD in the current at-risk population may not be present or relevant in subsequent generations.

Use of laboratory rodent models of disease allow some of the difficulties associated with human studies to be circumvented. Researchers are able to carefully control environmental exposures, and in age-related diseases like AD and PD, rodents' shorter natural lifespan allows for more efficient studies of lifelong exposures and pathogenic processes. Rodent models will be invaluable in confirming and exploring mechanism of modifiers of GxE interactions identified in humans (Ermann and Glimcher 2012). However, the utility of traditional inbred rodent models for identification of novel genetic variants contributing to GxE interactions is limited.

To overcome these barriers, novel tools and approaches are in development and in early stages of use. In humans, genomic wide association and interaction studies (GWAIS) are gaining traction (Hamza et al. 2011; Hill-Bums 2012; Thomas 2010). New analysis algorithms are available that boost the predictive power of these studies without significantly increasing study size and that allow adjustment for incomplete "E" data (Lin et al. 2015). In parallel, other groups are exploring epigenetic changes following environmental exposures to identify potential GxE interactions (Maloney et al. 2012). Significant advances in wearable and smartphone-based technologies are allowing for accurate, real-time readouts of health, exposures and lifestyle factors (Ueberham and Schlink 2018; Dunn, Runge, and Snyder 2018; Wanigatuna et al. 2018; Vasan and Benjamin 2016). New large-scale studies

such as the UK Biobank and NIH's "All of Us" program are beginning to generate the depth and breadth of data that will be required to identify GxE interactions in a truly genome-wide, exposome-wide manner with outputs relevant to a wide variety of diseases. In mice, recombinant inbred genetic reference panels consisting of a set of genetically diverse (yet reproducible) strains, such as the Collaborative Cross (CC) and BXD panels, have allowed us to enhance genetic complexity while maintaining our ability to systematically vary environmental exposures under controlled conditions for GxE studies (Jones et al. 2013; French et al. 2015; Schoenrock et al. 2017; Williams et al. 2016). In GxE research, human and mouse studies can be particularly synergistic. Mouse studies will not only function to validate findings in humans, but will help to generate hypotheses to inform and improve future analyses of human data-analogous to the use of current mouse models for both forward and reverse genetics approaches (Ermann and Glimcher 2012; Nadeau and Auwerx 2019). Still, despite the importance of understanding GxE interactions and recent development of tools to facilitate these investigations, there are relatively few published studies using unbiased, genome-wide analyses to identify novel genetic modulators of environmental factors in neurodegenerative diseases. Nonetheless, such studies of GxE interactions will be critical to understanding disease mechanisms and improving personalized, precision therapeutic strategies for age-related neurodegenerative diseases.

Genetic and environmental contributors to Alzheimer's disease and Parkinson's disease

AD is the most common neurodegenerative disease and the sixth most common cause of death in the US (Alzheimer's Association, 2016). Neuropathologically, AD is characterized by hippocampal and cortical neuron loss, aggregation of amyloid-beta in extracellular neuritic plaques, and accumulation of tau in intracellular neurofibrillary tangles. Current pharmacological treatment strategies in use and development are largely limited to acetylcholinesterase inhibitors, NMDA receptor antagonists, or drugs that reduce amyloid beta aggregation (Anand, Gill, and Mahdi 2014). Unfortunately, no therapeutic that prevents or slows progression of AD has yet been found, highlighting the desperate need for a more complete understanding of disease mechanisms as well as new avenues for treatment. Although AD is highly heritable (Gatz et al. 1997; Gatz et al. 2006; Pedersen et al. 2003), only a small minority of cases (<2%) are familial and can be attributed to causal mutations in the amyloid precursor protein (*APP*) and presenilin (*PSEN1/PSEN2*) genes. The majority of AD cases are sporadic, late-onset AD (LOAD) and GWAS have identified over 25 genetic regulators of LOAD (Karch, Cruchaga, and Goate 2014; Van Cauwenberghe, Van Broeckhoven, and Sleegers 2016; Barber 2012; Jansen et al. 2019). *APOE* is the strongest genetic determinant of LOAD risk, with APOEε2 conferring resistance to AD and APOEε4 homozygotes having a 4- to 10-fold increased risk of AD. The known risk variants for sporadic AD only account for about 25-30% (Ridge et al. 2013; Lee et al. 2013) of the variation in AD risk, indicating that there is a substantial amount of "missing heritability" factors yet to be identified. One potential source for this missing heritability may lie in gene-environment interactions, whereby specific environmental conditions may potentiate the effects of otherwise low-impact genetic vulnerability to AD (or vice-versa). In addition to its various genetic contributors, AD also has a significant environmental component. Meta-analyses have found that up to one-third of dementia and AD cases may be attributed to modifiable environmental factors throughout a person's life (Livingston et al. 2017; Barnes

and Yaffe 2011). Of these, lifestyle factors such as lifetime cognitive activity and early life education, late-life social interaction, as well as diet, smoking and alcohol consumption, physical activity, and comorbidities such as cardiovascular disease, diabetes, and hearing loss have well-characterized impacts on AD risk.

After AD, Parkinson's disease (PD) is the second-most common neurodegenerative disease and is characterized neuropathologically by degeneration of the dopamine-producing neurons in the substantia nigra pars compacta and aggregation of the protein alpha-synuclein (α-syn; *SNCA*) in extracellular Lewy bodies throughout the brain. While the vast majority (>95%) of PD cases are classified as idiopathic, there is a strong genetic component to the disease. Causal mutations have been identified in at least seven genes (*SNCA, LRRK2, PARK2, DJ-1, PINK1, VPS35, ATP13A2*) and around 20 other genes have been found to harbor risk variants (Shulman, De Jager, and Feany 2011; Lunati, Lesage, and Brice 2018; Bandres-Ciga et al. 2017; Douglas, Lewthwaite, and Nicholl 2007). Several environmental exposures increase risk for PD, including pesticides, polychlorinated biphenyls, manganese and other metals (reviewed in (Caudle 2012; Hatcher 2008)), traumatic brain injury and repeated concussions (Crane PK 2016; Rumalla 2017), and vitamin D deficiency (reviewed in (Newmark 2007)). Intriguingly, there are also multiple environmental factors that are robustly protective against PD. Caffeine consumption is protective against PD, with a dose-dependent level of protection (Ascherio A 2001; Checkoway 2002; Hernan 2002). Non-steroidal anti-inflammatory drug (NSAID) treatments have also been found to reduce PD incidence (Chen H 2005; Chen H 2003; Hernan 2006). Nicotine is the strongest environmental factor influencing PD risk: people who smoke cigarettes, use chewing tobacco, or consume high levels of nicotine-containing produce are robustly protected against the development of PD (Checkoway 2002; Godwin-Austen 1982; Grandinetti 1994; Hernán 2001; Kelton MC 2000; Nielsen 2013; O'Reilly et al. 2005).

In both AD and PD, however, there is substantial variability in the impact of environmental factors on disease risk in human and animal studies. How genetic variants regulate response to these environmental factors is poorly understood, but several strategies to identify these gene-by-environment interactions are underway, including candidate gene analyses, GWAIS, and genome-wide by exposome-wide association studies (see Figure 1A).

Candidate gene approaches in GxE studies in AD and PD: one-gene, one-exposure with a focus on APOE

Many studies have taken advantage of a candidate gene approach to identify whether known disease risk variants alter susceptibility to environmental risks and protective factors. In candidate gene approaches, researchers typically evaluate human carriers and noncarriers of disease risk alleles (e.g., APOEε4) and assess their relative odds ratio given a particular environmental exposure. These studies may be addressing the "multi-hit" hypothesis of neurodegenerative disease, in which genetic vulnerability and environmental risk factors accumulate to promote disease development and progression. For example, individuals with ε4 alleles experience greater changes in total cholesterol, LDL, and HDL in response to reductions in dietary fat, and have a varied response to different levels of physical activity compared to ε3/2 carriers (Head et al. 2012; Masson, McNeill, and Avenell 2003).

Transgenic animals are also valuable in candidate-gene GxE experiments, where animals harboring known risk or protective variants (e.g., humanized APOEε2/3/4) can be exposed to various environmental contexts to determine if these risk variants are sufficient to alter susceptibility to known environmental insults. These studies allow researchers to determine if people who are at increased risk genetically for disease will be disproportionately affected by environmental risk factors, or perhaps particularly benefitted by protective factors. This may be clinically useful especially for carriers of common risk variants, such as APOEε4.

APOEε4 is the strongest genetic risk factor for sporadic AD and it also affects PD risk (Pankratz and Foroud 2007). Human and animal studies have consistently shown that *APOE* genotype affects the response to environmental risk factors in both diseases (summarized in Table 1). In some cases, APOEε4 carrier status potentiates the negative effects of environmental risk factors. For example, the pathogenic effects of poor diet, obesity, chronic stress, sedentary lifestyle, and exposure to heavy metals have all been reported to be worsened in APOEε4 carriers in both human and rodent studies. (Ghebranious et al. 2011; Lee et al. 2008; Engstrom et al. 2017; Head et al. 2012). These studies lend support to a "multi-hit" hypothesis, where known genetic vulnerability factors (APOEε4) coupled with a known environmental insult may act synergistically on AD risk.

On the other hand, several studies have shown that APOEε4 status may confer protection against environmental factors. Some evidence suggests that lifetime cognitive activity is particularly protective against AD-related neuropathology in APOEε4 carriers with minimal benefit for APOEε2/3 carriers (Wirth et al. 2014), and that higher educational attainment may be sufficient to negate increased risk for AD associated with APOEε4 status (Cook and Fletcher 2015). Interestingly, this suggests that those who are at genetic risk for AD based on their APOEε4 carrier status, may particularly benefit from increased cognitive activity or education. Another study found that an elevated BMI in late life may be protective against cognitive decline specifically in APOEε4 carriers but not in APOEε2/3 individuals (Rajan et al. 2014). APOE status also determines the effects of tobacco and alcohol on AD risk: APOE genotype determines the direction of the effect of smoking, with smoking being detrimental to AD risk in APOEε2/3carriers, but apparently protective in APOEε4 carriers (Ghebranious et al. 2011). However, other data suggest that certain environmental protective factors cannot counteract the increased risk associated with APOEε4 carrier status. In humans and rodents, protective factors like polyunsaturated fat consumption and strong social support are associated with better cognitive function in aging at a population level; however, this relationship is not seen in APOEε4 carriers (Whalley et al. 2008; Zuelsdorff et al. 2013; Levi et al. 2003; Levi and Michaelson 2007; Lestaevel et al. 2014). A limitation to these approaches, however, is that these studies are not designed to discover *new* genetic factors and are therefore likely to miss novel genetic regulators of environmental factors not previously associated with the disease. Another limitation to using significant GWAS hits to inform GxE analyses is that some variants may only be high-impact under certain exposures, and are therefore not significantly associated with the disease at a population level. Certainly, conducting GWAIS or otherwise hypothesis-*generating* studies to identify novel genetic modulators of environmental factors in an unbiased manner will be critical to more fully understanding GxE interactions.

Candidate gene approaches in GxE studies in AD and PD: beyond one-gene, one-exposure

In the absence of genome-wide, unbiased GWAIS, some groups have taken the approach of evaluating the interactions of a large number of known genetic and environmental risk factors in human datasets. One study assessed the association between 27 AD-associated genes and a variety of lifestyle factors on AD risk (Lin et al. 2017) and found that *SLC24A4* genotype interacted with smoking, as well as alcohol consumption and social support, to determine the effects on AD risk of those modifiable factors. Wang, et al. (2017) conducted a similarly thorough evaluation of the interaction of cardiovascular disease (CVD) and CVD risk factors with 21 AD risk genes in mediating brain structure volume as a proxy for brain health. Interestingly, they found that an association between *ABCA7* and right parietal volume differed between CVD patients and controls, suggesting that *ABCA7* genotype may affect individual susceptibility to the effects of CVD-related factors on cognitive decline. The strategies employed in these studies are less biased than traditional, one-gene/one-exposure candidate gene approaches in that assumptions are not made about which candidate genes may interact with known environmental factors. They may also provide clues regarding the particular pathways in which environmental factors mediate disease risk, and thereby offer insights into biological processes that are thought to be involved in disease pathogenesis (Ahmad et al. 2018; Holmans et al. 2013). However, like all candidate gene studies, they still do not allow the discovery of novel disease-relevant genes or pathways.

Genome-wide approaches in GxE studies

GWAIS: genome-wide, one exposure—The major limitations of candidate gene approaches include the inability to identify potential genetic modulators of environmental risk factors that have not previously been associated with the disease. In studies that have conducted genome-wide association and interaction studies in neurodegenerative diseases few, if any, of the novel identified genetic modulators of environmental effects have been previously established as disease-related genes. This is striking, because it strongly suggests that expanding GxE analyses beyond disease GWAS hits even further will inform us of novel disease mechanisms, unexplored disease-relevant pathways, and potential therapeutic targets, and even more importantly will accelerate the path to personalized precision treatment strategies. Genome-wide approaches to identify GxE interactions have successfully identified novel genetic mediators of environmental insults in non-neurological disease, particularly in alcohol consumption and cardiovascular disease outcomes (Lin et al. 2018), as well as asbestos and tobacco smoke exposure in lung cancer susceptibility (Wei et al. 2012; Zhang et al. 2014). Each of these studies highlighted genes that had not been previously associated with the disease, providing strong support for the value of taking a genome-wide, rather than candidate-gene approach in identifying GxE interactions.

A handful of groups have employed the GWAIS strategy to identify novel genetic modulators of known environmental factors in PD and AD. A GWAIS identified *GRIN2A*, a gene encoding for a glutamate NMDA receptor subunit, as the determinate of the neuroprotective effects of caffeine in PD. Among coffee drinkers, those homozygous for the minor allele at the rs4998386 SNP of *GRIN2A* showed a particularly strong benefit of caffeine, with heavy coffee consumption being associated with a 70-80% reduction in PD risk in comparison to a ~30% reduction in PD risk at the population level and irrespective of

GRIN2A genotype (Hamza et al. 2011). A second study replicated this finding in an independent cohort, though a third was unable to replicate this relationship (Ahmed et al. 2014; Yamada-Fowler, Fredrikson, and Soderkvist 2014). Together, this suggests that the interaction may depend on additional, unknown factors. Indeed, the association between *GRIN2A*, caffeine, and PD is likely more complicated. In patients who are high-caffeine consumers and also taking creatine supplements, the minor allele at this *GRIN2A* SNP is actually associated with more rapid PD progression (Simon et al. 2017).

A GWAIS approach has also been used to identify a genetic regulator of the effects of smoking on PD risk. On average, cigarette smoking reduces risk of PD by about half, though this varies depending genetic context. Variants in the synaptic vesicle glycoprotein 2C (*SV2C*) gene were found to regulate the protective effects of smoking and nicotine in humans and drosophila. Individuals homozygous for the major alleles were the most protected by smoking, while smokers homozygous for the minor alleles were at a 3.5-fold increased risk for PD compared to non-smokers (Hill-Burns 2012). The modulatory relationship between SV2C and PD-relevant phenotypes was further validated in mice lacking SV2C: SV2C-knockout mice displayed a dramatically altered dopamine response to nicotine in the dorsal striatum (Dunn 2017). The fact that SV2C had not previously been associated with PD serves to again highlight that unbiased GxE discovery analyses will be indispensable for identifying potentially novel, disease-modifying pharmacological targets that are not identified by traditional GWAS. Nonetheless, the challenge that is presented by poor or incomplete data on environmental exposures in human studies will likely persist for some time.

Mouse genetic reference panels—Laboratory animals provide a clear advantage in studies of environmental factors in disease because, compared to human studies, researchers are able to precisely control environmental variables and minimize biases introduced by selection, survival, and attrition. Recently developed genetic reference panels augment this advantage by offering genetic diversity not found in traditionally inbred rodent strains. Strains are now available that provide a range of genetic diversity from moderate (e.g., BXD genetic reference panel, ~5 million variants across the genome) to highly complex (e.g., CC genetic reference panel, > 50 million variants), with the genomes of the CC mice matching or exceeding the genetic diversity present in humans. These populations are well-characterized and their genomes are stable and reproducible, which positions them as an ideal tool to study genome-wide GxE effects in a controlled laboratory setting across a wide variety of exposures and disease models (Jones et al. 2013; Shea et al. 2015; Williams et al. 2016; Brinkmeyer-Langford et al. 2017; Cichocki et al. 2017; Gralinski et al. 2015; Gatti et al. 2018). These populations allow for tuning of genetic and phenotypic diversity of relevant traits to lend the statistical power needed to identify novel GxE factors. Moreover, there are rich resources associated with these mouse models, including publicly-available tools and databases covering a wide range of strains and species and PD- and AD-relevant phenotypes on platforms such as GeneNetwork.org, the Mouse Phenome Database, and the AMP-AD Knowledge Portal (Parker et al. 2018; Hodes and Buckholtz 2016; Bogue, Churchill, and Chesler 2015; Bogue et al. 2018). These data may be leveraged for pilot analyses to extract

potential GxE-relevant targets, exposures, and optimal mouse models for further experiments.

An example of the utility of these panels is provided by our recent work examining the effects of diet on AD. A high-fat, high-sugar or “Western” diet has been associated with greater risk and earlier onset of AD, whereas a diet low in sugar, high in unsaturated fats, fiber, and protein, a so-called “Mediterranean” diet, is associated with lower rates of AD. However, inconsistent results in human and animal literature regarding the effects of diet on AD pathogenesis suggest that while a subset of at-risk individuals may benefit from low-fat, low-sugar diets, this diet may not be ideal for all patients (Singh et al. 2014; Yusufov, Weyandt, and Piryantinsky 2015; Otaegui-Arrazola et al. 2013; Cherbuin and Annstey 2012). Few studies have attempted to identify genetic modulators of the effect of diet on cognitive decline and AD due to the unreliable and complex nature of retrospective dietary reporting by participants. As a result, the source of the variable response in human studies remains unclear.

To circumvent some of the challenges present in the human studies, our lab recently developed a genetically diverse population of mice harboring the 5XFAD transgene (AD-BXDs, (Neuner et al. 2018)). This mouse strain allows us to explore, among other topics, GxE interactions in AD in an unbiased manner and in a controlled laboratory setting. We evaluated the effects of genetic background, diet, and gene-by-diet interactions in AD-related metabolic and cognitive traits by feeding a high fat, high sugar diet (HFD; Research Diets D12451i) to 10 strains of AD-BXD and nontransgenic littermates (Ntg-BXD) for eight weeks. Metabolic and cognitive functions were monitored before and throughout HFD administration. Working memory was assessed by measuring spontaneous alternations on a y-maze (Neuner et al. 2018). Weight and body composition was assessed using an EchoMRI Whole Body Nuclear Magnetic Resonance (NMR) analyzer. Glucose tolerance was determined by measuring blood glucose levels at 15, 30, 60, 90, and 120 minutes following a 1.0g/kg intraperitoneal injection of glucose and calculating the area under the curve (Ayala et al. 2010). Food intake and energy expenditure were determined using indirect calorimetry (Sable, Las Vegas, NV). To determine the relative contribution of genetic background (AD-BXD strain), diet, and a gene-by-diet interaction on each of these traits, we performed analysis of variance (ANOVA). After removing the unknown sources of variance contributed by residual effects, we calculated the remaining percent variance in each trait that was determined by genetic background (BXD strain), diet, or a gene-by-diet interaction (Figure 1B). Interestingly, the contribution of gene-by-diet interactions to trait variance was dramatically different depending on the trait. In general, energy expenditure was highly dependent on genetic background, whereas food intake and weight were highly dependent on diet. Other traits, such as glucose tolerance and working memory showed a substantial interaction between genetic background and diet, suggesting that the effects of diet on these traits are dependent on genetic variants within this population. Additionally, some differences between AD-BXD and Ntg-BXD mice were observed. For example, in AD-BXD mice, gene-by-diet interactions accounted for about twice as much variance in glucose tolerance than in Ntg-BXD animals, suggesting that the 5XFAD transgene may alter relative contributions of genetic and dietary influences on glucose metabolism. Finally, these analyses may indicate that certain phenotypes share common patterns genetic and

environmental regulation, and by extension may be regulated by similar disease-relevant pathways. Our findings indicate that the use of these specialized mouse strains will allow researchers to narrow their focus in human GxE analyses and facilitate the identification of similar interactions in human populations.

Future of GxE

While current approaches are currently being refined for genome-wide GxE investigations, studies thus far lack unbiased, exposome-wide analyses. In part, this is due to incomplete reporting of exposures across the lifetime and a lack of prospective studies that systematically gather exposure data. Multiple large-scale studies have recently been established to allow for of genome-wide, exposome-wide GxE analyses. The UK Biobank is a 500,000-participant prospective longitudinal study that is collecting genomic data as well as a broad range of behavioral and exposure data via activity monitoring, questionnaires, health records and blood chemistry. Ultimately, the UK Biobank will be sufficiently well-powered to identify GxE interactions within their comprehensive dataset of genome-wide and potentially exposome-wide risk factors as they associate with a variety of common diseases, including a predicted 30,000 AD and 14,000 PD cases (Collins 2012; Sudlow et al. 2015). Similarly, the NIH program “All of Us” began in 2018 with the goal of collecting genetic, environmental, behavioral, and health data from one million participants. Like with the UK Biobank, the ultimate goal of All of Us is to establish a comprehensive dataset to allow researchers to determine how complex factors contribute to a wide range of diseases (Lyles et al. 2018). An important feature of these studies is the large degree of diversity in the genetics and exposures of participants which will allow for generalizability of results to the whole population. Additionally, improved informatics tools will allow for detection of GxE interactions with small effect sizes or in datasets with incomplete exposure data (Lin et al. 2015). As human studies will invariably be affected by problems such as selection and survival bias, study attrition, and unforeseen confounding variables, they will be well-complemented by parallel advancements in research utilizing mouse populations that model the genetic diversity of human populations. Mouse research will be critical for our ability to experimentally elucidate and validate the complex architecture of GxE interactions in human populations.

Additional factors beyond simple GxE contributions to disease will also be important to consider. The length of exposure, as well as age at exposure to environmental factors, likely interact with genetic variants and changing gene expression over time. A gene-by-environment-by-time model has been proposed for other neurodegenerative diseases such as ALS (Bradley 2018, Al-Chalabi 2013), and is likely relevant to AD, PD, and various other neurological diseases. Both the UK Biobank and the All of Us initiative collect longitudinal exposure and lifestyle data which will help to address the temporal and longitudinal factor in GxE interactions.

Fundamentally, aging and disease risk are dependent on the interaction of genetic factors and environmental exposures across the lifespan that are currently largely unknown, and the UK Biobank and All of Us initiative will provide the first, most complete picture of these

interactions for large cohorts of humans and animal models in order to improve disease risk calculations, as well as individualized prevention and therapeutic strategies.

Conclusions

Characterization of GxE interactions will provide critical insight to disease mechanisms, personalized intervention strategies, and help pave the way toward precision medicine. Currently, multi-scale intervention strategies like the FINGER trial for AD are underway to reduce dementia incidence in at-risk individuals by altering lifestyle factors that are known to modulate AD risk, such as diet and physical activity (Ngandu et al. 2015). Identifying those genetic factors that regulate the beneficial effects of these lifestyle interventions will better help us to identify the patients who will benefit the most from such an intervention, as well as exclude patients who are expected to be non-responders or poor responders based on their GxE profile. To date, few whole-genome analyses of genetic modulators of environmental exposures in AD and PD have been conducted due to the challenges associated with complex exposure measurement and statistical power insufficient to detect interactions with small effect sizes. Computational tools for extracting GxE effects from complex and incomplete data are currently being developed, but researchers have yet to widely apply these strategies to AD GWAIS. As a cursory approach to identifying GxE interactions, a wide range of candidate-gene studies have been conducted. However, most genome wide GxE studies have identified novel genetic factors, suggesting that current established disease-related variants may not be major contributors to GxE. As relevant techniques improve (computational, genomic, exposomic), and as genomic, exposomic, and diseasomic data collection is expanded and standardized, the challenges associated with GxE interaction detection in human data will diminish. In parallel, novel mouse resources such as the BXD and AD-BXD, and CC reference panels will allow for more precise control of both exposures and genetic diversity to better power GxE analyses, and will be critical to help to inform, support, and interpret human studies.

Identifying novel GxE interactions will elucidate disease mechanisms, identify novel therapeutic targets, improve personalized therapeutic strategies, and better inform multi-scale intervention trials in at-risk individuals. Complex, age-related neurodegenerative diseases such as PD and AD are neither all “nature” nor all “nurture”, and approaching disease mechanisms from a GxE perspective will be critical to our full understanding of the disease and development of successful disease-modifying therapies.

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Highlights:

- Gene-environment interactions (GxE) are important in disease pathogenesis
- Few studies have explored GxE in a genome-wide or exposome-wide manner
- Recent advances will improve identification of GxE interactions in humans and mice
- GxE interactions will elucidate novel disease pathways and mechanisms
- Identification of GxE interactions will facilitate personalized precision medicine

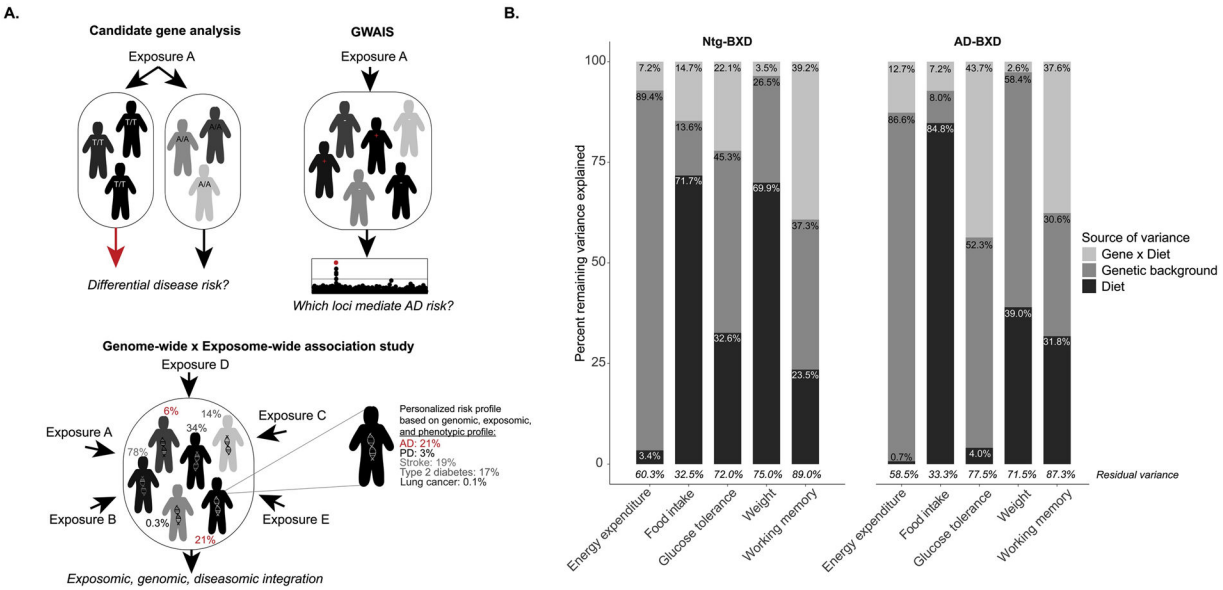

Figure 1. Recent approaches to identify GxE interactions in neurological disease.

(A) Candidate gene analyses, genome-wide interaction and association studies (GWAIS), and genome-wide and exposome-wide association studies (GxEWAS) are valuable in approaching GxE analyses. Candidate gene analyses ask whether an exposure or exposures results in differential disease risk in carriers (e.g. “T/T” individuals) or non-carriers (e.g. “A/A” individuals) of a particular known disease risk allele. GWAIS ask which genetic variants and genomic loci correlate with disease risk given individuals’ exposure to a known disease-relevant environmental factor. Finally, GxEWAS take an integrated approach of measuring and determining which exposome-wide and genome-wide factors contribute to risk of a variety of diseases, and how these factors interact across time in order to determine individual risk for any number of diseases. (B) AD-BXD and Ntg-BXD mice underwent extensive cognitive and metabolic phenotyping on chow and after eight weeks of high-fat diet. We performed ANOVA and removed the residual variation resulting from unknown sources to calculate the remaining relative contribution of diet, genetic background, and gene-by-diet interactions on each of these traits. Interestingly, we found a wide range of contributions from genetic background, diet, and gene-by-diet interactions depending on phenotype. In general, energy expenditure is highly dependent on genetic background, whereas food intake and weight are highly dependent on diet. Other traits, such as glucose tolerance and working memory show a substantial interaction between genetic background and diet, suggesting that the effects of diet on these traits are dependent on genetic variants within this population.

Table 1.

Summary of effects of APOEε4 carrier status on environmental factors in AD and PD.

	Risk	Details	Protective	Details
Potentiation of effects	Poor diet/obesity (Moser and Pike 2017)	(Mice) APOEε4 carriers with AD mutations have worse neuropathological outcomes following western diet compared to APOEε3 carriers.	Higher cognitive activity (Wirth et al. 2014)	(Human) APOEε4, but not APOEε3, carriers with higher lifetime cognitive activity had lower AB burden in late life
	Low physical activity (Luck et al. 2014)	(Humans >75yr) Low physical activity and APOEε4 status resulted in an additively increased risk for AD	Educational attainment (Cook and Fletcher 2015)	(Humans—siblings) Increased AD risk in APOEε4 carriers was eliminated in individuals with >16yrs education
	Heavy metal exposure (Engstrom et al. 2017)	(Mice) Lead treatment in adulthood impaired cognitive function in APOEε4 but not APOEε3 knock-ins	Late-life weight maintenance (Rajan et al. 2014)	(Human) The negative impact of APOEε4 status on late-life cognitive decline was reduced in overweight and obese patients
	Mood/sleep disturbances (Burke et al. 2016)	(Human) APOEε4 carriers with depression have up to a 20.26 OR for AD, APOEε4 carriers with sleep disturbance have up to a 12.05 OR for AD.		
Negation of effects	Smoking (Ghebranious et al. 2011)	(Human) APOEε2 or 3, but not APOEε4, carriers show increased risk for AD with smoking.	Polyunsaturated fat consumption (Whalley et al. 2008)	(Human) Polyunsaturated fat consumption in late life is protective only in APOEε2 or 3 carriers.
			Social support (Zuelsdorff et al. 2013)	(Human) Social support was associated with better cognitive performance except in APOEε4 carriers.
			Estrogen (Yaffe et al. 2000)	(Human) Estrogen use was protective against cognitive decline in APOEε2/3 carriers but not APOEε4 carriers
			Coffee consumption (McCulloch et al. 2008)	(Human) Increased coffee consumption is less protective in APOEε4 carriers compared to APOEε2/3 carriers.