OXFORD
SOT | Society of Toxicology
academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 181(1), 2021, 3–12

doi: 10.1093/toxsci/kfab022
Advance Access Publication Date: 2 March 2021
Contemporary Review

CONTEMPORARY REVIEW

The Impact of Environmental Factors on Monogenic Mendelian Diseases

Anke M. Tukker ,* Charmaine D. Royal,† Aaron B. Bowman ,* and Kimberly A. McAllister ‡,1

*School of Health Sciences, Purdue University, West Lafayette, Indiana 47907-2051; †Departments of African and African American Studies, Biology, Global Health, and Family Medicine and Community Health and Center on Genomics, Race, Identity, Difference, Duke University, Durham, North Carolina 27708; and ‡Genes Environment and Health Branch, Division of Extramural Research and Training, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709

[1]To whom correspondence should be addressed at Genes Environment and Health Branch, Division of Extramural Research and Training, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. E-mail: mcallis2@niehs.nih.gov.

ABSTRACT

Environmental factors and gene-environment interactions modify the variable expressivity, progression, severity, and onset of some classic (monogenic) Mendelian-inherited genetic diseases. Cystic fibrosis, Huntington disease, Parkinson's disease, and sickle cell disease are examples of well-known Mendelian disorders that are influenced by exogenous exposures. Environmental factors may act by direct or indirect mechanisms to modify disease severity, timing, and presentation, including through epigenomic influences, protein misfolding, miRNA alterations, transporter activity, and mitochondrial effects. Because pathological features of early-onset Mendelian diseases can mimic later onset complex diseases, we propose that studies of environmental exposure vulnerabilities using monogenic model systems of rare Mendelian diseases have high potential to provide insight into complex disease phenotypes arising from multi-genetic/multi-toxicant interactions. Mendelian disorders can be modeled by homologous mutations in animal model systems with strong recapitulation of human disease etiology and natural history, providing an important advantage for study of these diseases. Monogenic high penetrant mutations are ideal for toxicant challenge studies with a wide variety of environmental stressors, because background genetic variability may be less able to alter the relatively strong phenotype driving disease-causing mutations. These models promote mechanistic understandings of gene-environment interactions and biological pathways relevant to both Mendelian and related sporadic complex disease outcomes by creating a sensitized background for relevant environmental risk factors. Additionally, rare disease communities are motivated research participants, creating the potential of strong research allies among rare Mendelian disease advocacy groups and disease registries and providing a variety of translational opportunities that are under-utilized in genetic or environmental health science.

Key words: monogenic mendelian diseases; gene-environment interactions; cystic fibrosis; parkinson's disease; huntington disease; sickle cell disease.

Although "monogenic" Mendelian disorders are defined as typically rare diseases arising from single gene defects with high penetrance, it has become increasingly apparent that these diseases frequently exhibit much more complex and diverse phenotypic presentations than originally appreciated (O'Neal and Knowles, 2018). Some Mendelian monogenic diseases show variable onset

and expression of clinical manifestations of disease traits (Peltonen *et al.* 2006), whereas other individuals who carry known Mendelian deleterious mutations appear to be completely healthy or resilient (Chen *et al.*, 2016). The variable expressivity and alterations in progression, severity, onset, and penetrance of some rare Mendelian diseases could be due to environmental factors and gene-environment interactions (Chao *et al.*, 2018; Noyce *et al.*, 2012). Individuals with monogenic diseases may be the most genetically susceptible or vulnerable to a variety of environmental exposures (Chung and Karlsen, 2017; Kannarkat *et al.*, 2015). Moreover, many common human diseases have both a Mendelian and more complex polygenic class of disease and are often described as a continuum from "extreme" Mendelian forms to complex disease phenotypes (Freund *et al.*, 2018). Although the focus on genome-wide association studies and the rapid reduction in sequencing costs have moved many researchers away from Mendelian diseases, we argue here for the continued value of studying monogenic diseases in revealing critical pathways for both rare Mendelian and more common complex disease types. As one example, the Centers for Mendelian Genomics is one large-scale effort that is currently identifying genes underlying Mendelian diseases (Chong *et al.*, 2015). Many molecular and pathological insights about common human diseases have originated from the rare familial (usually early onset) forms of these diseases (Peltonen *et al.*, 2006). The identification of genes for Mendelian and rare familial forms of common diseases have in many cases identified new biological pathways or protein interactions that had not previously been associated with a particular disease phenotype (Peltonen *et al.*, 2006). These discoveries have helped pave the way for new diagnostic or therapeutic options relevant to both rare and common diseases (Chong *et al.*, 2015). For example, insights into more common forms of Parkinson's disease have come from studying Gaucher disease, and molecular insights relevant to Alzheimer's disease have come from studying the rare Niemann-Pick disease type C (Hassan *et al.*, 2017). Recent studies suggest biological pathways are shared between Mendelian and complex diseases and that in many cases, genetic coding variant mutations may lead to Mendelian disease and noncoding variants in the same gene(s) may produce complex traits (Freund *et al.*, 2018). In a similar fashion, exploration of environmental influences on these Mendelian diseases with common disease counterparts may also uncover unique mechanistic understandings of gene-environment interactions and biological pathways relevant to related common disease outcomes.

In this review, we use examples of classic well-defined Mendelian disorders where environmental factors strongly impact disease onset and pathogenesis to argue the value of this approach to understanding more complex human chronic diseases. Table 1 lists some of the key environmental risk factors for these particular Mendelian diseases. We will highlight some potential broad processes and molecular mechanisms whereby exposures have an impact on Mendelian disease outcomes and address what can be learned from further research endeavors in this field.

MONOGENIC MENDELIAN DISEASES WITH SUBSTANTIAL ENVIRONMENTAL INFLUENCES

Cystic Fibrosis

Cystic fibrosis is one of the most common Mendelian diseases. It is characterized by progressive damage to the respiratory system. Although mutations in only one gene, the cystic fibrosis transmembrane conductance regulator (CFTR), generally determine the presence or absence of cystic fibrosis, clinical outcomes vary greatly in individuals even with the same CFTR genotype (Drumm *et al.*, 2012). In general, there is a genotype-phenotype correlation with disease features (Wolfenden and Schechter, 2009). Nongenetic factors may account for approximately half of the clinical variation in cystic fibrosis (Collaco *et al.*, 2010). The clinical course of cystic fibrosis has been shown to be affected by pathogenic microorganisms, environmental tobacco smoke, e-cigarette vaping, air pollutants including ozone (O_3) and particulate matter ($PM_{2.5\ or\ 10}$), as well as dietary factors such as high fat and high calorie intake (Collaco *et al.*, 2010; Garcia-Arcos *et al.*, 2016; Gotts *et al.*, 2019; Hooper and Kaufman, 2018; Ong *et al.*, 2017; Schindler *et al.*, 2015; Wolfenden and Schechter, 2009). The exact CFTR mutation appears to affect the impact of some of these environmental risk factors, particularly secondhand smoke, on lung disease severity (Collaco and Cutting, 2008). Specifically, several studies have shown an association between ambient air pollution and pulmonary exacerbations in patients with cystic fibrosis (Brugha *et al.*, 2018). Researchers have determined that cystic fibrosis patients' lungs are particularly vulnerable to the impacts of air pollution in the form of particulate deposition (Goss *et al.*, 2004). Infection by *Pseudomonas aeruginosa* in the airway is associated with a more rapid decline in lung function in patients with cystic fibrosis as well (Psoter *et al.*, 2015). In addition, temperature appears to affect lung disease and infection in cystic fibrosis patients with patients living in areas with warmer ambient temperatures having a higher prevalence and an earlier initial age for *P. aeruginosa* acquisition (Collaco *et al.*, 2011).

Huntington Disease

Huntington disease is a progressive brain disorder viewed as a classic Mendelian autosomal dominant disease caused by a CAG triplet repeat expansion in the *huntingtin* gene with high penetrance of 40 or higher (to 120) tandem repeats (McColgan and Tabrizi, 2018). However, Huntington disease progression was found to be delayed in transgenic Huntington disease mice harboring a long CAG repeat by enriched housing conditions and a variety of environmental stimulations (Mazarakis *et al.*, 2014). Animal and human preclinical studies have found environmental interventions that can delay the common motor, cognitive, and other neurodegenerative symptoms of Huntington disease. These environmental alterations in Huntington disease mouse models included the addition of novel objects of varied textures and shapes, stimulating structures for climbing, and increased nesting and bedding materials. Various physical, cognitive, and occupational therapies have now been applied to Huntington disease patients which have improved motor function as well. Physical activity, stress, and dietary interventions or caloric restriction also appear to modulate Huntington disease progression (Mo *et al.*, 2015). In addition, a prominent neuroprotective gene-environment interaction with the *huntingtin* mutant gene and manganese (Mn) has been identified. Mn exposure reduces Huntington disease phenotypes and the Huntington disease genotype reduces effects of toxic Mn exposures (Bichell *et al.*, 2017; Bryan *et al.*, 2019, 2020; Pfalzer *et al.*, 2020; Williams *et al.*, 2010). The presence of a heavy metal modifier substantially affecting a classic Mendelian disease pathology in animal and rodent models sets the stage for many other explorations of previously unidentified environmental factors in other Mendelian diseases. In the case of Huntington disease, further research into the interaction of Mn and the Huntingtin protein has led to a better mechanistic understanding of the etiology of this neurodegenerative disease

Table 1. Environmental Factors Affecting Classic Mendelian Disease Presentations

Disease	Environmental risk factor	Reference
Cystic fibrosis	Pathogenic microorganisms Tobacco smoking E-cigarette vaping Air pollution Dietary factors Temperature	Wolfenden and Schechter (2009), Collaco *et al.* (2010), Collaco *et al.* (2011), Schindler *et al.* (2015), Garcia-Arcos *et al.* (2016), Ong *et al.* (2017), Brugha *et al.* (2018), Hooper and Kaufman (2018), Gotts *et al.* (2019)
Huntington disease	Housing conditions Environmental stimulations Physical activity Stress Caloric restrictions Dietary factors Manganese bioavailability	Williams *et al.* (2010), Mazarakis *et al.* (2014), Mo *et al.* (2015), Bichell *et al.* (2017), Bryan *et al.* (2019), Bryan *et al.* (2020), Pfalzer *et al.* (2020)
Parkinson's disease	Tobacco smoking Coffee/tea Dietary factors β2-adrenoreceptor agonists/antagonists Physical activity Vitamin E Gout NSAIDs Manganese Copper Pesticides	Chen *et al.* (2015), Ascherio and Schwarzschild (2016), Brouwer *et al.* (2017), Hughes *et al.* (2017), Simon *et al.* (2017), Cao *et al.* (2019), Kochmanski *et al.* (2019), Belvisi *et al.* (2020)
Sickle cell disease	Climate-related factors (temperature, humidity, high altitudes, etc.) Air pollution Tobacco smoking Physical exercise SES-related factors Dietary factors	Hyacinth *et al.* (2010), Tewari *et al.* (2015), Piel *et al.* (2017a,b), Yarboi *et al.* (2017), Crouch *et al.* (2018), Martin *et al.* (2018), Parriault *et al.* (2019), Xu and Frenette (2019), Bills *et al.* (2020), Blumberg *et al.* (2020), Karlson *et al.* (2020), Wachnian *et al.* (2020)

and the mechanisms of Mn neurotoxicity (Bichell *et al.*, 2017; Stansfield *et al.*, 2014; Tidball *et al.*, 2014; Warren *et al.*, 2020).

Parkinson's Disease

Parkinson's disease is a prevalent chronic, progressive neurodegenerative disease caused by selective dopaminergic neurodegeneration within the substantia nigra and the presence of protein aggregates known as Lewy bodies. Mutated forms of α-synuclein (SNCA) and leucine-rich repeat kinase 2 (LRRK2) are found in Lewy bodies which cause genetic forms of inherited Parkinson's disease. Parkinson's disease is intriguing in that it has both rare monogenic forms that are associated with highly penetrant gene variants in SNCA, LRRK2, and other genes but also much more common idiopathic forms that have strong contributions from both low penetrant genetic risk factors and environmental risk factors that elicit a "parkinsonism" phenotype. There are also rare forms on the opposite side of the spectrum induced by high doses of single neurotoxicants, such as manganese (Chen *et al.*, 2015; Petrucci *et al.* 2014), though even single neurotoxicants, like manganese, may be environmental risk factors for multiple diseases (Balachandran *et al.*, 2020). Thus, the monogenic and single environmental/toxicant forms in Parkinson's disease are contrasted by the more common complex disease presentations. This complex disease form is generally attributed to the interaction of many genetic and environmental variants (Petrucci *et al.*, 2014). Prospective longitudinal studies suggest that a variety of environmental factors impact Parkinson's disease. Cigarette smoking, coffee, tea, β2-adrenoreceptor agonists/antagonists, physical activity, intake of milk and dairy products, vitamin E, gout, and some nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, can be considered as probable or possible risk/protective factors for Parkinson's disease (Ascherio and Schwarzschild, 2016; Belvisi *et al.*, 2020; Hughes *et al.*, 2017; Simon *et al.*, 2017). In addition, there is reasonably strong epidemiological evidence for the association of some specific environmental toxins/toxicants and pesticides with Parkinson's disease monogenic-associated disease genes, particularly rotenone, paraquat, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), Cu, Mn, dieldrin, maneb, and zieram (Brouwer *et al.*, 2017; Cao *et al.*, 2019; Kochmanski *et al.*, 2019). Various modifiable environmental protective factors for Parkinson's disease are beginning to be explored as potential effective interventions or preventions (Belvisi *et al.*, 2020).

Sickle Cell Disease

Sickle cell disease has a heterogeneous presentation, typically characterized by recurrent pain and organ damage caused by the formation of sickled erythrocytes (Piel *et al.*, 2017a; Tewari *et al.*, 2015). Although the genetic basis for this disorder, a point mutation in the β-globin chain of the hemoglobin gene, is well understood, the sickle cell disease genotype only accounts for a small portion of the variation in phenotype and clinical presentation of the disease (Piel *et al.*, 2017b; Tewari *et al.*, 2015). Studies have shown that the range of sickle cell disease severity is associated with exposures to diverse environmental factors, including temperature, wind, humidity, high altitudes, and air pollutants, among other climate-related phenomena (Parriault *et al.*, 2019; Piel *et al.*, 2017b; Tewari *et al.*, 2015; Wachnian *et al.*,

2020; Xu and Frenette, 2019). The clinical hallmark of sickle cell disease, pain episodes (vasoocclusive crises—VOCs), are associated with wind exposure, large temperature fluctuations, cold temperatures, and decreased air humidity (Parriault *et al.*, 2019). Interestingly, higher concentrations of atmospheric carbon monoxide and lower atmospheric pressure may be beneficial for individuals with sickle cell disease. Physical exercise is associated with variations in sickle cell disease outcomes, with intense acute exercise sometimes leading to death (Martin *et al.*, 2018), whereas low to moderate exercise sometimes helps to reduce VOC-related pain (Karlson *et al.*, 2020). Active and passive smoking have been found to be detrimental to individuals with sickle cell disease (Tewari *et al.*, 2015). Social factors such as socioeconomic status and neighborhood can influence exposure to urban air pollution including traffic-related pollutants and have been found to exacerbate sickle cell disease symptoms as well (Bills *et al.*, 2020; Blumberg *et al.*, 2020; Piel, Steinberg, *et al.*, 2017; Yarboi *et al.*, 2017). Lastly, some dietary factors have also been implicated in sickle cell disease outcomes, although more research is needed to explore this link (Crouch *et al.*, 2018; Hyacinth *et al.* 2010).

POTENTIAL AVENUES FOR TOXICANT VULNERABILITY IN MENDELIAN DISEASE

The mechanisms by which environmental agents might affect Mendelian disease onset, severity, or phenotypic presentation may be directly or indirectly related to the pathogenic mutation. These mechanisms include gene-environment interactions (altered genetic susceptibility to toxicants that themselves directly lead to disease), or convergence of additive impacts by environmental risk factors on the biological pathways that are directly altered by monogenic Mendelian disease genes. Examples of direct gene-environment interactions have been identified in the case of rotenone, paraquat, and MPTP impacting Parkinson's disease risk via particular Parkinson's disease gene mutations (Belvisi *et al.*, 2020; Helley *et al.*, 2017). Genetic mutations allow for substantially increased susceptibility or sensitivity to environmental risk factors in some cases. For example, genetic susceptibility to environmental factors linked to human leukocyte antigen (HLA) variants that alter HLA expression and immune responses seem to increase Parkinson's disease risk (Kannarkat *et al.*, 2015). Paraquat and other environmental toxicants have also been directly implicated in causing the primary dopamine cell death associated with Parkinson's disease as dopamine active transporters take up this herbicide (Atsushi and Tamano, 2020; Richter *et al.*, 2017). Many other environmental risk or protective factors for Parkinson's disease have shown biological plausibility for impacting the nigrostriatal dopaminergic system as well (Aboud *et al.*, 2012, 2015; Belvisi *et al.*, 2020). In other cases, the environmental factors may indirectly affect biological pathways or networks previously implicated with genetic variant effects that ultimately converge to lead to the same pathophysiology related to the disease. For example, a number of conserved transcriptional pathways have been implicated for pesticide-induced neurotoxicity in Parkinson's disease (Cao *et al.*, 2019). The pesticides maneb, rotenone, and paraquat all affect ALDH2, TH, and SLC18A2 genes that contribute to dopamine metabolism. Further, these pesticides alter the number of transcripts of the SNCA and TNF (tumor necrosis factor; Cao *et al.*, 2019). These data support the hypothesis that reducing pesticide exposure may reduce Parkinson's disease risk. With regard to cystic fibrosis, environmental exacerbation through secondhand smoke may occur through regulation of fatty acid metabolism and activation of mitogen-activated protein kinase pathways in human airway epithelial cells (Kopp *et al.*, 2016; Zielen and Fussbroich, 2019). For sickle cell disease, environmental factors such as wind speed and temperature are known to alter central and neural pain mechanisms, resulting in increased heat and cold sensitivity through central nervous pain sensitization (Brandow *et al.*, 2013). In the sections below, we highlight five specific molecular mechanisms that have been explored in recent research. These general mechanisms may explain some of the ways in which environmental factors may impact monogenic disease.

Alterations in Epigenetic Machinery

The dynamic epigenetic regulation is widely seen as the interface between the stable coding portion of the genome and the ever-changing environment, with epigenetic mechanisms contributing in a variety of ways to how environmental influences might contribute to disease development (Bakulski and Fallin, 2014). Some Mendelian genetic disorders have now been identified that are associated with various alterations in specific epigenetic machinery that are caused by either genetic mutations, environmental factors, or both (Bakulski and Fallin, 2014). Specifically, disruptions of histone lysine acetylation and methylation, as well as DNA cytosine methylation, have been shown for Mendelian diseases (Leppert and Matarazzo, 2014). Some environmental influences have been found to affect these epigenetic marks in some Mendelian disorders as well (Fahrner and Bjornsson, 2014; Harris *et al.*, 2019). The exploration of these Mendelian disorders of epigenetic machinery have led to insights into the imbalance of chromatin states and the levels of methylation and their possible role in human disease pathogenesis in general. Epigenomic changes have also been indirectly linked to numerous neurodegenerative disorders. Parkinson's and Huntington disease, for example, both illustrate disturbances in various epigenetic marks (including methylation, chromatin remodeling, and histone marks; Wassouf and Schulze-Hentrich, 2019). Recent evidence suggests that Mn may play a role in neurotoxicity and susceptibility to Parkinson's disease through epigenetic mechanisms as well (Tarale *et al.*, 2016). Potential pharmaceutical therapeutic applications for restoring balance of chromatin states and alteration of methylation patterns with DNA methyltransferases are starting to be explored in these Mendelian disorders of epigenetic machinery, which may contribute to a better understanding of epigenomic manipulations that might have broad applicability for epigenetic-based therapies for many human diseases (Fahrner and Bjornsson, 2014; Leppert and Matarazzo, 2014). The reversibility of epigenetic regulations offers a potential for targeted therapies and intervention in the future (Wassouf and Schulze-Hentrich, 2019). One example is the use of several pharmacological therapies to affect epigenetic regulation to control polymerization of mutated sickle hemoglobin in red blood cells in sickle cell disease (Molokie *et al.*, 2017).

MicroRNA

MicroRNAs (miRNAs) may be one specific RNA-based epigenetic feature that provides a mechanistic link for how environmental exposures may impact certain Mendelian diseases, unappreciated until recently. These small noncoding single-stranded RNAs are transcribed as a stem-loop structure and bind in a sequence-specific manner at the 3′-UTR of mRNAs (Singh and Yadav, 2020). miRNA dysregulation is becoming increasingly recognized as a mechanism relevant to some Mendelian disease

development. miRNAs can regulate gene expression post-transcriptionally in a versatile manner because 1 miRNA can target numerous mRNAs, and 1 mRNA can be targeted by different miRNAs (Wallace *et al.*, 2020). Several recent reports have implicated alterations in miRNAs to explain the extreme variability in onset, progression, and severity of some Mendelian disease presentations, particularly for lysosomal storage disorders and Mendelian inflammasome-associated autoinflammatory diseases (Hassan *et al.*, 2017; Surace and Hedrich, 2019). It also appears that many environmental factors can affect miRNAs, and these miRNA changes can in turn lead to the pathology of both complex and monogenic human diseases. For example, some miRNAs appear to regulate neurotoxicant-induced neurodegeneration in the brain in Parkinson's disease, spinocerebellar ataxias, and other neurodegenerative diseases (Singh and Yadav, 2020; Wallace *et al.*, 2020). There is a growing body of evidence suggesting that environmental exposures often impact gene expression through alteration of miRNAs, and miRNAs are currently being explored as promising biomarkers for environmental exposures due to their stability, tissue specificity, and ease of measurement (Kotsyfakis and Patelarou, 2019; Vrijens *et al.*, 2015; Wallace *et al.*, 2020).

Transporter Activity

Cellular transporter activity has been shown to impact onset of some Mendelian diseases. Individuals with mutations in the Mn efflux transporter SLC30A10 and uptake transporter SLC39A14 are especially sensitive or susceptible to exposure to environmental Mn (Anagianni and Tuschl, 2019). Familial Parkinson's disease has also been reported as a result of a mutation in SLC30A10. These mutations prevent this transporter from travelling to its location on the cell surface, thereby preventing it from fulfilling its role in Mn efflux mediation (Leyva-Illades *et al.*, 2014). Patients with a mutation in SLC39A14 accumulate excessive Mn, resulting in rapid progressive childhood-onset parkinsonism dystonia (Tuschl *et al.*, 2016). Thus, inherited mutations in manganese transporters are a genetic predisposition for the development of Parkinson's disease. In addition, altered systemic metal levels can lead to changes in metal transporters that shift vulnerability to toxicity of co-transported metals (Smith *et al.*, 2013; Venkataramani *et al.*, 2018). For example, excess or deficient iron diets and excess Mn exposures can all affect the expression and function of transferrin receptor and divalent metal transporter 1 to influence tissue and cellular levels of the other metal (Amos-Kroohs *et al.*, 2015; Garcia *et al.*, 2006; Thompson *et al.*, 2007; Wang *et al.*, 2008). Research into these transporter mutations and environmental factors that modify transporter activity is likely to reveal new information on the role of Mn in the development of Parkinson's disease, related disorders, or Mn-related diseases.

Protein Misfolding

Protein misfolding is another mechanism whereby environmental exposure may impact monogenic disease development. Recent research has focused on the induction by environmental exposures of protein unfolding/misfolding and/or proteasomal degradation in some rare Mendelian diseases. Specifically, exposures such as cigarette smoke, air pollution, and some infectious agents and pathogens originating from the air have been shown to be associated with endoplasmic reticulum (ER) stress and protein misfolding in some chronic lung diseases (including CF) and may contribute to both the initiation and progression of lung disease by activation of the unfolded protein response (UPR; Wei *et al.*, 2013). The UPR is a highly conserved biological pathway that attempts to restore cellular homeostasis when unfolded protein accumulation leads to the activation of ER transmembrane transducers (Wei *et al.*, 2013). Additionally, abnormal S-nitrosylation caused by environmentally induced nitrosative and oxidative stress triggers protein misfolding and may contribute to the great majority of sporadic cases of neurodegenerative diseases having rare familial forms, including in Huntington and Parkinson's disease (Nakamura *et al.*, 2015). In the case of Parkinson's disease, both genetically and environmentally induced forms of the disease have been found to be strongly linked to altered post-translational modifications of α-synuclein and LRRK2 (Harischandra, Ghaisas, *et al.*, 2019; Harischandra, Rokad, *et al.*, 2019). Research suggests that phosphorylation, ubiquitination, nitration, and/or truncation (all potentially impacted by environmental exposures) appear to affect the structure, stability, localization, and function of SNCA and LRRK2 proteins (Pajarillo *et al.*, 2019). A variety of pesticides also appear to accelerate the onset of Huntington disease by influencing the aggregation of the mutant Huntingtin protein (Deshmukh *et al.*, 2012). Studying the direct effects of exposures on protein misfolding in some of these rare diseases may lead to a greater understanding of gene-environment interactions relevant to many disease phenotypes that are associated with functional protein conformational changes.

Mitochondrial Effects

Mitochondrial dysfunction is also seen as a common target that can be implicated in both genetic mutations and environmental risk factors relevant to many monogenic Mendelian diseases (Zhang et al., 2020). This is specifically true for Parkinson's disease, where α-synuclein is known to directly induce mitochondrial dysfunction *in vivo*. Many of the gene variants implicated in familiar Parkinson's disease play a role in autophagy and mitophagy and thus affect mitochondrial dysfunction indirectly as well. In fact, mitochondrial dysfunction appears to be a common route for the link or convergence of both genetic variants and environmental neurotoxicants to Parkinson's disease through multiple interconnected direct and indirect molecular mechanisms, including impacts on mitochondrial dynamics and function (fission, fusion, and transport), increased apoptosis, impaired autophagy, ubiquitin-proteasome systems, increased ROS production, and mitochondrial DNA damage (Helley *et al.*, 2017). Mitochondrial dysfunction in general is a hallmark feature of many Mendelian neurodegenerative diseases (including Huntington disease) and understanding the impact of environmental factors on mitochondrial dysfunction mechanisms could lead to a variety of therapeutic treatments (Panchal and Tiwari, 2019).

FUTURE DIRECTIONS

Well-established Mendelian animal models can be used as a tool to study perturbances caused by environmental exposures on the molecular or biochemical pathways affecting many complex diseases. Many animal models of Mendelian diseases are already thoroughly characterized, readily available, and often recapitulate the human disease phenotype better than most complex common disease model organisms. Because both phenotypes and molecular mechanisms of some early-onset Mendelian diseases mimic later-onset complex diseases, insights gained from future studies with Mendelian model organisms will logically be applicable to biological pathways that are disrupted in complex human diseases. Also, these Mendelian animal models are ideal for environmental challenge

studies, because all other variables can be more easily controlled in monogenic disease models than in complex models. Moreover, some of the genetic mutations render these models more susceptible to environmental insults. For example, physical activity, as well as stress, have been explored in both neurotoxicant-induced and genetic rodent Parkinson's disease models. These studies contributed to a greater understanding of the impact of these exposures on dopaminergic neurons (Wassouf and Schulze-Hentrich, 2019). Recently, the mechanism whereby rapid influx of divalent Zn cation with extracellular glutamate accumulation causes nigrostriatal dopaminergic degeneration has been explored in a paraquat-induced Parkinson's disease rat model (Tamano *et al.*, 2019). A combined MPTP neurotoxin with a genetic model for Parkinson's disease is now being investigated as a promising animal model to provide insights into the complex multifactorial nature of Parkinson's disease (Kin *et al.*, 2019).

In addition to established mammalian (eg, rodent) models, many other *in vivo*, *in vitro*, and *in silico* models have utility to further understand the impact of environmental exposures or genetic and environmental modifiers on Mendelian disease onset and progress. A variety of lower model organisms, including Drosophila, *C. elegans*, and zebrafish are being explored. Population-based model organisms such as the Collaborative Cross and Diversity Outbred, combined with recent advances in a variety of *in vitro* approaches (especially genome editing tools such as CRISPR/Cas9, high-throughput toxicity screens, embryonic stem cells, and [human] induced pluripotent stem cells [iPSCs]), could allow the introduction of a Mendelian disease variant to be explored across a range of genetic and environmental backgrounds. Recent advances in human iPSCs have allowed them to be a strong tool for *in vitro* disease modeling by duplicating the human gene variant and the corresponding disease phenotypes in an *in vitro* setting (Tobe *et al.*, 2011). Recent efforts have utilized human iPSCs to specifically model Mendelian diseases in a cell-specific context (Kouroupi *et al.*, 2017), or in a 3D environment to more closely resemble the *in vivo* brain (Chlebanowska *et al.*, 2020; Kim *et al.*, 2019; Smits *et al.*, 2019). These efforts could be further exploited to incorporate environmental toxicants. Computational toxicology is also starting to be utilized to probe how environmental toxicants may perturb interacting signaling and molecular pathways leading to Mendelian disease (Cao *et al.*, 2019).

CONCLUSIONS

Rare disease communities and broad-based coalitions (eg, the Genetic Alliance) comprise motivated research participants and drivers of research who could accelerate strong research partnerships with environmental health scientists that have not been explored extensively. Rare disease networks could provide powerful human research cohorts of sufficient power for meaningful analysis of gene-environment interactions for rare monogenic diseases. Certainly, many untapped collaborations exist for interactions with several NIH Institutes, as well as the Office of Rare Diseases Research and the National Organization of Rare Diseases, that focus and/or award both basic and translational rare disease research.

The ability for environmental exposures to impact Mendelian disease outcomes can also have regulatory consequences. A recent policy (the Frank R. Lautenberg Chemical Safety for the 21st Century Act) requires the U.S. Environmental Protection Agency to evaluate chemicals with specific consideration to susceptible populations of all types (including genetic susceptibility). People with certain Mendelian disease variants that may be more susceptible to the impacts of environmental toxicants may therefore constitute a susceptible subpopulation of higher risk to be considered in regulations limiting exposures. Recently, an adverse outcome pathway (AOP) approach was proposed to potentially identify and integrate human genetic susceptibility in human health risk assessment (Mortensen *et al.*, 2018). This methodology utilizes publicly available human genetic datasets to acquire mechanistic understanding of molecular pathways that might inform human susceptibility to an adverse outcome. This AOP-framed approach uses functional genomic and human polymorphism data to characterize individual and population-level genetic variation that may impact susceptibilities to environmental chemicals. The application of this approach may help to connect existing knowledge of both Mendelian and complex disease genetics to environmental toxicant susceptibility and further contribute to the understanding of the etiology of both monogenic and complex human disease outcomes.

A greater mechanistic understanding of the role of environmental exposures in Mendelian diseases may ultimately result in valuable public health translations. Recent focus on attempting to translate results of the genomic era into health benefits have shown limited value to date. Rather than focus on primarily genetic or pharmaceutical targets for intervention, current strategies need to also exploit environmental or behavioral modifications. Emphasis on precision medicine can incorporate environmental measures of human disease and utilize unique susceptibilities of individual patients based on their particular genetic makeup and past environmental exposures. Therapeutic or environmental interventions and preventions can then be tailored based on this knowledge (Groopman, 2019; Topol, 2014). Particularly in the absence of effective treatments to slow the course of Huntington's and other classic Mendelian diseases, environmental interventions offer feasible approaches to delay disease onset or reduce the disease severity.

ACKNOWLEDGMENTS

The authors acknowledge the thoughtful comments of Dr Leroy Worth, Dr Jon Hollander, and Dr Cindy Lawler in the preparation of this manuscript.

FUNDING

National Institutes of Health National Institute of Environmental Health Sciences (ES010563 to A.B.B., A.M.T., ES016931 to A.B.B.).

DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

Aboud, A. A., Tidball, A. M., Kumar, K. K., Neely, M. D., Ess, K. C., Erikson, K. M., and Bowman, A. B. (2012). Genetic risk for Parkinson's disease correlates with alterations in neuronal manganese sensitivity between two human subjects. *Neurotoxicology* **33**, 1443–1449.

Aboud, A. A., Tidball, A. M., Kumar, K. K., Neely, M. D., Han, B., Ess, K. C., Hong, C. C., Erikson, K. M., Hedera, P., and Bowman,

A. B. (2015). PARK2 patient neuroprogenitors show increased mitochondrial sensitivity to copper. *Neurobiol. Dis.* **73**, 204–212.

Amos-Kroohs, R. M., Bloor, C. P., Qureshi, M. A., Vorhees, C. V., and Williams, M. T. (2015). Effects of developmental exposure to manganese and/or low iron diet: Changes to metal transporters, sucrose preference, elevated zero-maze, open-field, and locomotion in response to fenfluramine, amphetamine, and MK-801. *Toxicol. Rep.* **2**, 1046–1056.

Anagianni, S., and Tuschl, K. (2019). Genetic disorders of manganese metabolism. *Curr. Neurol. Neurosci. Rep.* **19**, 33.

Ascherio, A., and Schwarzschild, M. A. (2016). The epidemiology of Parkinson's disease: Risk factors and prevention. *Lancet Neurol.* **15**, 1257–1272.

Atsushi, T., and Tamano, H. (2020). New insight into Parkinson's disease pathogenesis from reactive oxygen species-mediated extracellular Zn2+ influx. *J. Trace Elem. Med. Biol.* **61**, 126545.

Bakulski, K. M., and Fallin, M. D. (2014). Epigenetic epidemiology: Promises for public health research. *Environ. Mol. Mutagen.* **55**, 171–183.

Balachandran, R. C., Mukhopadhyay, S., McBride, D., Veevers, J., Harrison, F. E., Aschner, M., Haynes, E. N., and Bowman, A. B. (2020). Brain manganese and the balance between essential roles and neurotoxicity. *J. Biol. Chem.* **295**, 6312–6329.

Belvisi, D., Pellicciari, R., Fabbrini, G., Tinazzi, M., Berardelli, A., and Defazio, G. (2020). Modifiable risk and protective factors in disease development, progression and clinical subtypes of Parkinson's disease: What do prospective studies suggest? *Neurobiol. Dis.* **134**, 104671.

Bichell, T. J. V., Wegrzynowicz, M., Tipps, K. G., Bradley, E. M., Uhouse, M. A., Bryan, M., Horning, K., Fisher, N., Dudek, K., Halbesma, T., *et al.* (2017). Reduced bioavailable manganese causes striatal urea cycle pathology in Huntington's disease mouse model. *Biochim. Biophys. Acta Mol. Basis Dis.* **1863**, 1596–1604.

Bills, S. E., Schatz, J., Hardy, S. J., and Reinman, L. (2020). Social-environmental factors and cognitive and behavioral functioning in pediatric sickle cell disease. *Child Neuropsychol.* **26**, 83–99.

Blumberg, A. H., Ebelt, S. T., Liang, D., Morris, C. R., and Sarnat, J. A. (2020). Ambient air pollution and sickle cell disease-related emergency department visits in Atlanta, GA. *Environ. Res.* **184**, 109292.

Brandow, A. M., Stucky, C. L., Hillery, C. A., Hoffmann, R. G., and Panepinto, J. A. (2013). Patients with sickle cell disease have increased sensitivity to cold and heat. *Am. J. Hematol.* **88**, 37–43.

Brouwer, M., Huss, A., van der Mark, M., Nijssen, P. C. G., Mulleners, W. M., Sas, A. M. G., van Laar, T., de Snoo, G. R., Kromhout, H., and Vermeulen, R. C. H. (2017). Environmental exposure to pesticides and the risk of Parkinson's disease in the Netherlands. *Environ. Int.* **107**, 100–110.

Brugha, R., Edmondson, C., and Davies, J. C. (2018). Outdoor air pollution and cystic fibrosis. *Paediatr. Respir. Rev.* **28**, 80–86.

Bryan, M. R., Nordham, K. D., Rose, D. I. R., O'Brien, M. T., Joshi, P., Foshage, A. M., Gonçalves, F. M., Nitin, R., Uhouse, M. A., Aschner, M., *et al.* (2020). Manganese acts upon insulin/IGF receptors to phosphorylate AKT and increase glucose uptake in Huntington's disease cells. *Mol. Neurobiol.* **57**, 1570–1593.

Bryan, M. R., O'brien, M. T., Nordham, K. D., Rose, D. I. R., Foshage, A. M., Joshi, P., Nitin, R., Uhouse, M. A., Di, P. A., Zhang, Z., *et al.* (2019). Acute manganese treatment restores defective autophagic cargo loading in Huntington's disease cell lines. *Hum. Mol. Genet.* **28**, 3825–3841.

Cao, F., Souders, C. L., Perez-Rodriguez, V., and Martyniuk, C. J. (2019). Elucidating conserved transcriptional networks underlying pesticide exposure and Parkinson's disease: A focus on chemicals of epidemiological relevance. *Front. Genet.* **10**. doi:10.3389/fgene.2018.00701.

Chao, M. J., Kim, K. H., Shin, J. W., Lucente, D., Wheeler, V. C., Li, H., Roach, J. C., Hood, L., Wexler, N. S., Jardim, L. B., *et al.* (2018). Population-specific genetic modification of Huntington's disease in Venezuela. *PLoS Genet.* **14**, e1007274.

Chen, P., Chakraborty, S., Mukhopadhyay, S., Lee, E., Paoliello, M. M. B., Bowman, A. B., and Aschner, M. (2015). Manganese homeostasis in the nervous system. *J. Neurochem.* **134**, 601–610.

Chen, R., Shi, L., Hakenberg, J., Naughton, B., Sklar, P., Zhang, J., Zhou, H., Tian, L., Prakash, O., Lemire, M., *et al.* (2016). Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases. *Nat. Biotechnol.* **34**, 531–538.

Chlebanowska, P., Tejchman, A., Sułkowski, M., Skrzypek, K., and Majka, M. (2020). Use of 3D organoids as a model to study idiopathic form of Parkinson's disease. *Int. J. Mol. Sci.* **21**, 694.

Chong, J. X., Buckingham, K. J., Jhangiani, S. N., Boehm, C., Sobreira, N., Smith, J. D., Harrell, T. M., McMillin, M. J., Wiszniewski, W., Gambin, T., Centers for Mendelian Genomics., *et al.* (2015). The genetic basis of Mendelian phenotypes: Discoveries, challenges, and opportunities. *Am. J. Hum. Genet.* **97**, 199–215.

Chung, B. K., and Karlsen, T. H. (2017). Genetic discoveries highlight environmental factors as key drivers of liver disease. *Dig. Dis.* **35**, 323–333.

Collaco, J. M., Blackman, S. M., McGready, J., Naughton, K. M., and Cutting, G. R. (2010). Quantification of the relative contribution of environmental and genetic factors to variation in cystic fibrosis lung function. *J. Pediatr.* **157**, 802–807.

Collaco, J. M., and Cutting, G. R. (2008). Update on gene modifiers in cystic fibrosis. *Curr. Opin. Pulm. Med.* **14**, 559–566.

Collaco, J. M., McGready, J., Green, D. M., Naughton, K. M., Watson, C. P., Shields, T., Bell, S. C., Wainwright, C. E., and Cutting, G. R., for the ACFBAL Study Group, Cutting, G. R. (2011). Effect of temperature on cystic fibrosis lung disease and infections: A replicated cohort study. *PLoS One* **6**, e27784.

Crouch, E. M., Bonham, V. L., Abdallah, K., Buscetta, A., Vinces, G., Heo, M., and Minniti, C. P. (2018). Nutritional supplement profile of adults with sickle cell disease. *Am. J. Hematol.* **93**, E187–E188.

Deshmukh, R. S., Chaudhary, R. K., and Roy, I. (2012). Effect of pesticides on the aggregation of mutant huntingtin protein. *Mol. Neurobiol.* **45**, 405–414.

Drumm, M. L., Ziady, A. G., and Davis, P. B. (2012). Genetic variation and clinical heterogeneity in cystic fibrosis. *Annu. Rev. Pathol. Mech. Dis.* **7**, 267–282.

Fahrner, J. A., and Bjornsson, H. T. (2014). Mendelian disorders of the epigenetic machinery: Tipping the balance of chromatin states. *Annu. Rev. Genomics Hum. Genet.* **15**, 269–293.

Freund, M. K., Burch, K. S., Shi, H., Mancuso, N., Kichaev, G., Garske, K. M., Pan, D. Z., Miao, Z., Mohlke, K. L., Laakso, M., *et al.* (2018). Phenotype-specific enrichment of Mendelian disorder genes near GWAS regions across 62 complex traits. *Am. J. Hum. Genet.* **103**, 535–552.

Garcia, S. J., Gellein, K., Syversen, T., and Aschner, M. (2006). A manganese-enhanced diet alters brain metals and transporters in the developing rat. *Toxicol. Sci.* **92**, 516–525.

Garcia-Arcos, I., Geraghty, P., Baumlin, N., Campos, M., Dabo, A. J., Jundi, B., Cummins, N., Eden, E., Grosche, A., Salathe, M., *et al.* (2016). Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. *Thorax* **71**, 1119–1129.

Goss, C. H., Newsom, S. A., Schildcrout, J. S., Sheppard, L., and Kaufman, J. D. (2004). Effect of ambient air pollution on pulmonary exacerbations and lung function in cystic fibrosis. *Am. J. Respir. Crit. Care Med.* **169**, 816–821.

Gotts, J. E., Jordt, S. E., McConnell, R., and Tarran, R. (2019). What are the respiratory effects of e-cigarettes? *BMJ* **366**, l5275.

Groopman, J. D. (2019). Highlight Article: Environmental health in the biology century: Transitions from population to personalized prevention. *Exp. Biol. Med.* **244**, 728–733.

Harischandra, D. S., Ghaisas, S., Zenitsky, G., Jin, H., Kanthasamy, A., Anantharam, V., and Kanthasamy, A. G. (2019). Manganese-induced neurotoxicity: New insights into the triad of protein misfolding, mitochondrial impairment, and neuroinflammation. *Front. Neurosci.* **13**. doi:10.3389/fnins.2019.00654.

Harischandra, D. S., Rokad, D., Neal, M. L., Ghaisas, S., Manne, S., Sarkar, S., Panicker, N., Zenitsky, G., Jin, H., Lewis, M., *et al.* (2019). Manganese promotes the aggregation and prion-like cell-to-cell exosomal transmission of α-synuclein. *Sci. Signal.* **12**, aau4543.

Harris, J., Mahone, E. M., and Bjornsson, H. T. (2019). Molecularly confirmed Kabuki (Niikawa-Kuroki) syndrome patients demonstrate a specific cognitive profile with extensive visuospatial abnormalities. *J. Intellect. Disabil. Res.* **63**, 489–497.

Hassan, S., Sidransky, E., and Tayebi, N. (2017). The role of epigenetics in lysosomal storage disorders: Uncharted territory. *Mol. Genet. Metab.* **122**, 10–18.

Helley, M. P., Pinnell, J., Sportelli, C., and Tieu, K. (2017). Mitochondria: A common target for genetic mutations and environmental toxicants in Parkinson's disease. *Front. Genet.* **8**, 177.

Hooper, L. G., and Kaufman, J. D. 2018. Ambient air pollution and clinical implications for susceptible populations. *Ann. Am. Thoracic Soc.* **15**, S64–S68.

Hughes, K. C., Gao, X., Kim, I. Y., Wang, M., Weisskopf, M. G., Schwarzschild, M. A., and Ascherio, A. (2017). Intake of dairy foods and risk of Parkinson disease. *Neurology* **89**, 46–52.

Hyacinth, H. I., Gee, B. E., and Hibbert, J. M. (2010). The role of nutrition in sickle cell disease. *Nutr. Metab. Insights* **3**, NMI.S5048.

Kannarkat, G. T., Cook, D. A., Lee, J. K., Chang, J., Chung, J., Sandy, E., Paul, K. C., Ritz, B., Bronstein, J., Factor, S. A., *et al.* (2015). Common genetic variant association with altered HLA expression, synergy with pyrethroid exposure, and risk for Parkinson's disease: An observational and case-control study. *Parkinsons Dis.* **1**, 15002.

Karlson, C. W., Delozier, A. M., Seals, S. R., Britt, A. B., Stone, A. L., Reneker, J. C., Jackson, E. A., McNaull, M. M., Credeur, D. P., and Welsch, M. A. (2020). Physical activity and pain in youth with sickle cell disease. *Fam. Commun. Heal.* **43**, 1–9.

Kim, H., Park, H. J., Choi, H., Chang, Y., Park, H., Shin, J., Kim, J., Lengner, C. J., Lee, Y. K., and Kim, J. (2019). Modeling G2019S-LRRK2 sporadic Parkinson's disease in 3D midbrain organoids. *Stem Cell Rep.* **12**, 518–531.

Kin, K., Yasuhara, T., Kameda, M., and Date, I. (2019). Animal models for Parkinson's disease research: Trends in the 2000s. *Int. J. Mol. Sci.* **20**, 5402.

Kochmanski, J., Vanoeveren, S. E., Patterson, J. R., and Bernstein, A. I. (2019). Developmental dieldrin exposure alters DNA methylation at genes related to dopaminergic neuron development and Parkinson's disease in mouse midbrain. *Toxicol. Sci.* **169**, 593–607.

Kopp, B., Ortega-García, J., Sadreameli, S., Wellmerling, J., Cormet-Boyaka, E., Thompson, R., McGrath-Morrow, S., and Groner, J. (2016). The impact of secondhand smoke exposure on children with cystic fibrosis: A review. *Int. J. Environ. Res. Public Health* **13**, 1003.

Kotsyfakis, M., and Patelarou, E. (2019). MicroRNAs as biomarkers of harmful environmental and occupational exposures: A systematic review. *Biomarkers* **24**, 623–630.

Kouroupi, G., Taoufik, E., Vlachos, I. S., Tsioras, K., Antoniou, N., Papastefanaki, F., Chroni-Tzartou, D., Wrasidlo, W., Bohl, D., Stellas, D., *et al.* (2017). Defective synaptic connectivity and axonal neuropathology in a human iPSC-based model of familial Parkinson's disease. *Proc. Natl. Acad. Sci. U.S.A.* **114**, E3679–E3688.

Leppert, S., and Matarazzo, M. (2014). De novo DNMTs and DNA methylation: Novel Insights into disease pathogenesis and therapy from epigenomics. *Curr. Pharm. Des.* **20**, 1812–1818.

Leyva-Illades, D., Chen, P., Zogzas, C. E., Hutchens, S., Mercado, J. M., Swaim, C. D., Morrisett, R. A., Bowman, A. B., Aschner, M., and Mukhopadhyay, S. (2014). SLC30A10 is a cell surface-localized manganese efflux transporter, and parkinsonism-causing mutations block its intracellular trafficking and efflux activity. *J. Neurosci.* **34**, 14079–14095.

Martin, C., Pialoux, V., Faes, C., Charrin, E., Skinner, S., and Connes, P. (2018). Does physical activity increase or decrease the risk of sickle cell disease complications? *Br. J. Sports Med.* **52**, 214–218.

Mazarakis, N. K., Mo, C., Renoir, T., Van Dellen, A., Deacon, R., Blakemore, C., and Hannan, A. J. (2014). "Super-enrichment" reveals dose-dependent therapeutic effects of environmental stimulation in a transgenic mouse model of Huntington's disease. *J. Huntingtons Dis.* **3**, 299–309.

McColgan, P., and Tabrizi, S. J. (2018). Huntington's disease: A clinical review. *Eur. J. Neurol.* **25**, 24–34.

Mo, C., Hannan, A. J., and Renoir, T. (2015). Environmental factors as modulators of neurodegeneration: Insights from gene-environment interactions in Huntington's disease. *Neurosci. Biobehav. Rev.* **52**, 178–192.

Molokie, R., Lavelle, D., Gowhari, M., Pacini, M., Krauz, L., Hassan, J., Ibanez, V., Ruiz, M. A., Ng, K. P., Woost, P., *et al.* (2017). Oral tetrahydrouridine and decitabine for non-cytotoxic epigenetic gene regulation in sickle cell disease: A randomized phase 1 study. *PLoS Med.* **14**, e1002382.

Mortensen, H. M., Chamberlin, J., Joubert, B., Angrish, M., Sipes, N., Lee, J. S., and Euling, S. Y. (2018). Leveraging human genetic and adverse outcome pathway (AOP) data to inform susceptibility in human health risk assessment. *Mamm. Genome* **29**, 190–204.

Nakamura, T., Prikhodko, O. A., Pirie, E., Nagar, S., Akhtar, M. W., Oh, C. K., McKercher, S. R., Ambasudhan, R., Okamoto, S. i., and Lipton, S. A. (2015). Aberrant protein S-nitrosylation contributes to the pathophysiology of neurodegenerative diseases. *Neurobiol. Dis.* **84**, 99–108.

Noyce, A. J., Bestwick, J. P., Silveira-Moriyama, L., Hawkes, C. H., Giovannoni, G., Lees, A. J., and Schrag, A. (2012). Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Ann. Neurol.* **72**, 893–901.

O'Neal, W. K., and Knowles, M. R. (2018). Cystic fibrosis disease modifiers: Complex genetics defines the phenotypic diversity in a monogenic disease. *Annu. Rev. Genomics Hum. Genet.* **19**, 201–222.

Ong, T., Schechter, M., Yang, J., Peng, L., Emerson, J., Gibson, R. L., Morgan, W., and Rosenfeld, M, for the EPIC Study Group (2017). Socioeconomic status, smoke exposure, and health outcomes in young children with cystic fibrosis. *Pediatrics* **139**, e20162730.

Pajarillo, E., Rizor, A., Lee, J., Aschner, M., and Lee, E. (2019). The role of posttranslational modifications of α-synuclein and LRRK2 in Parkinson's disease: Potential contributions of environmental factors. *Biochim. Biophys. Acta Mol. Basis Dis.* **1865**, 1992–2000.

Panchal, K., and Tiwari, A. K. (2019). Mitochondrial dynamics, a key executioner in neurodegenerative diseases. *Mitochondrion* **47**, 151–173.

Parriault, M.-C., Cropet, C., Fahrasmane, A., Rogier, S., Parisot, M., Nacher, M., and Elenga, N. (2019). Air Drep—A retrospective study evaluating the influence of weather conditions and viral epidemics on vaso-occlusive crises in patients with sickle cell disease living in French Guiana. *Int. J. Environ. Res. Public Health* **16**, 2724.

Peltonen, L., Perola, M., Naukkarinen, J., and Palotie, A. (2006). Lessons from studying monogenic disease for common disease. *Hum. Mol. Genet.* **15**, R67–R74.

Petrucci, S., Consoli, F., and Valente, E. M. (2014). Parkinson disease genetics: A "continuum" from Mendelian to multifactorial inheritance. *Curr. Mol. Med.* **14**, 1079–1088.

Pfalzer, A. C., Wilcox, J. M., Codreanu, S. G., Totten, M., Bichell, T. J. V., Halbesma, T., Umashanker, P., Yang, K. L., Parmalee, N. L., Sherrod, S. D., *et al.* (2020). Huntington's disease genotype suppresses global manganese-responsive processes in premanifest and manifest YAC128 mice. *Metallomics* **12**, 1118–1130.

Piel, F. B., Steinberg, M. H., and Rees, D. C. (2017a). Sickle cell disease. *N. Engl. J. Med.* **376**, 1561–1573.

Piel, F. B., Tewari, S., Brousse, V., Analitis, A., Font, A., Menzel, S., Chakravorty, S., Thein, S. L., Inusa, B., Telfer, P., *et al.* (2017b). Associations between environmental factors and hospital admissions for sickle cell disease. *Haematologica* **102**, 666–675.

Psoter, K. J., De Roos, A. J., Mayer, J. D., Kaufman, J. D., Wakefield, J., and Rosenfeld, M. (2015). Fine particulate matter exposure and initial *Pseudomonas aeruginosa* acquisition in cystic fibrosis. *Ann. Am. Thorac. Soc.* **12**, 385–391.

Richter, F., Gabby, L., McDowell, K. A., Mulligan, C. K., De La Rosa, K., Sioshansi, P. C., Mortazavi, F., Cely, I., Ackerson, L. C., Tsan, L., *et al.* (2017). Effects of decreased dopamine transporter levels on nigrostriatal neurons and paraquat/maneb toxicity in mice. *Neurobiol. Aging* **51**, 54–66.

Schindler, T., Michel, S., and Wilson, A. W. M. (2015). Nutrition management of cystic fibrosis in the 21st century. *Nutr. Clin. Pract.* **30**, 488–500.

Simon, D. K., Wu, C., Tilley, B. C., Lohmann, K., Klein, C., Payami, H., Wills, A. M., Aminoff, M. J., Bainbridge, J., Dewey, R., *et al.* (2017). Caffeine, creatine, GRIN2A and Parkinson's disease progression. *J. Neurol. Sci.* **375**, 355–359.

Singh, T., and Yadav, S. (2020). Role of microRNAs in neurodegeneration induced by environmental neurotoxicants and aging. *Ageing Res. Rev.* **60**, 101068.

Smith, E. A., Newland, P., Bestwick, K. G., and Ahmed, N. (2013). Increased whole blood manganese concentrations observed in children with iron deficiency anaemia. *J. Trace Elem. Med. Biol.* **27**, 65–69.

Smits, L. M., Reinhardt, L., Reinhardt, P., Glatza, M., Monzel, A. S., Stanslowsky, N., Rosato-Siri, M. D., Zanon, A., Antony, P. M., Bellmann, J., *et al.* (2019). Modeling Parkinson's disease in midbrain-like organoids. *NPJ Park. Dis.* **5**, 1–8.

Stansfield, K. H., Bichell, T. J., Bowman, A. B., and Guilarte, T. R. (2014). BDNF and Huntingtin protein modifications by manganese: Implications for striatal medium spiny neuron pathology in manganese neurotoxicity. *J. Neurochem.* **131**, 655–666.

Surace, A. E. A., and Hedrich, C. M. (2019). The role of epigenetics in autoimmune/inflammatory disease. *Front. Immunol.* **10**, 1525.

Tamano, H., Nishio, R., Morioka, H., Furuhata, R., Komata, Y., and Takeda, A. (2019). Paraquat as an environmental risk factor in Parkinson's disease accelerates age-related degeneration via rapid influx of extracellular Zn2+ into nigral dopaminergic neurons. *Mol. Neurobiol.* **56**, 7789–7799.

Tarale, P., Chakrabarti, T., Sivanesan, S., Naoghare, P., Bafana, A., and Krishnamurthi, K. (2016). Potential role of epigenetic mechanism in manganese induced neurotoxicity. *Biomed. Res. Int.* **2016**, 1–18.

Tewari, S., Brousse, V., Piel, F. B., Menzel, S., and Rees, D. C. (2015). Environmental determinants of severity in sickle cell disease. *Haematologica* **100**, 1108–1116.

Thompson, K., Molina, R. M., Donaghey, T., Schwob, J. E., Brain, J. D., and Wessling-Resnick, M. (2007). Olfactory uptake of manganese requires DMT1 and is enhanced by anemia. *Faseb J.* **21**, 223–230.

Tidball, A. M., Bryan, M. R., Uhouse, M. A., Kumar, K. K., Aboud, A. A., Feist, J. E., Ess, K. C., Diana, N. M., Aschner, M., and Bowman, A. B. (2014). A novel manganese-dependent ATM-p53 signaling pathway is selectively impaired in patient-based neuroprogenitor and murine striatal models of Huntington's disease. *Hum. Mol. Genet.* doi:10.1093/hmg/ddu609.

Tobe, B. T. D., Snyder, E. Y., and Nye, J. S. (2011). Modeling complex neuropsychiatric disorders with human induced pluripotent stem cells. *Curr. Opin. Pharmacol.* **11**, 521–527.

Topol, E. J. (2014). Individualized medicine from prewomb to tomb. *Cell* **157**, 241–253.

Tuschl, K., Meyer, E., Valdivia, L. E., Zhao, N., Dadswell, C., Abdul-Sada, A., Hung, C. Y., Simpson, M. A., Chong, W. K., Jacques, T. S., *et al.* (2016). Mutations in SLC39A14 disrupt manganese homeostasis and cause childhood-onset parkinsonism-dystonia. *Nat. Commun.* **7**, 1–16.

Venkataramani, V., Doeppner, T. R., Willkommen, D., Cahill, C. M., Xin, Y., Ye, G., Liu, Y., Southon, A., Aron, A., Au-Yeung, H. Y., *et al.* (2018). Manganese causes neurotoxic iron accumulation via translational repression of amyloid precursor protein and H-Ferritin. *J. Neurochem.* **147**, 831–848.

Vrijens, K., Bollati, V., and Nawrot, T. S. (2015). MicroRNAs as potential signatures of environmental exposure or effect: A systematic review. *Environ. Health Perspect.* **123**, 399–411.

Wachnian, C., Tompkins, N., Corriveau-Bourque, C., Belletrutti, M., and Bruce, A. A. K. (2020). Cold external temperatures and sickle cell morbidity in children. *J. Pediatr. Hematol. Oncol.* **42**, 8–11.

Wallace, D. R., Taalab, Y. M., Heinze, S., Tariba Lovaković, B., Pizent, A., Renieri, E., Tsatsakis, A., Farooqi, A. A., Javorac, D., Andjelkovic, M., *et al.* (2020). Toxic-metal-induced alteration in miRNA expression profile as a proposed mechanism for disease development. *Cells* **9**, 901.

Wang, X., Miller, D. S., and Zheng, W. (2008). Intracellular localization and subsequent redistribution of metal transporters in a rat choroid plexus model following exposure to manganese or iron. *Toxicol. Appl. Pharmacol.* **230**, 167–174.

Warren, E. B., Bryan, M. R., Morcillo, P., Hardeman, K. N., Aschner, M., and Bowman, A. B. (2020). Manganese-induced mitochondrial dysfunction is not detectable at exposures below the acute cytotoxic threshold in neuronal cell types. *Toxicol. Sci.* **176**, 446–459.

Wassouf, Z., and Schulze-Hentrich, J. M. (2019). Alpha-synuclein at the nexus of genes and environment: The impact of

environmental enrichment and stress on brain health and disease. *J. Neurochem.* **150**, 591–604.

Wei, J., Rahman, S., Ayaub, E. A., Dickhout, J. G., and Ask, K. (2013). Protein misfolding and endoplasmic reticulum stress in chronic lung disease. *Chest* **143**, 1098–1105.

Williams, B. B., Li, D., Wegrzynowicz, M., Vadodaria, B. K., Anderson, J. G., Kwakye, G. F., Aschner, M., Erikson, K. M., and Bowman, A. B. (2010). Disease-toxicant screen reveals a neuroprotective interaction between Huntington's disease and manganese exposure. *J. Neurochem.* **112**, 227–237.

Wolfenden, L. L., and Schechter, M. S. (2009). Genetic and non-genetic determinants of outcomes in cystic fibrosis. *Paediatr. Respir. Rev.* **10**, 32–36.

Xu, C., and Frenette, P. S. (2019). Seasonal manifestations of sickle cell disease activity. *Nat. Med.* **25**, 536–537.

Yarboi, J., Compas, B. E., Brody, G. H., White, D., Rees Patterson, J., Ziara, K., and King, A. (2017). Association of social-environmental factors with cognitive function in children with sickle cell disease. *Child Neuropsychol.* **23**, 343–360.

Zhang, Z., Yan, J., Bowman, A. B., Bryan, M. R., Singh, R., and Aschner, M. (2020). Dysregulation of TFEB contributes to manganese-induced autophagic failure and mitochondrial dysfunction in astrocytes. *Autophagy* **16**, 1506–1523.

Zielen, S., and Fussbroich, D. (2019). Impact of secondhand smoke on cystic fibrosis: Is there a link to fatty acid metabolism? *Thorax* **74**, 529–530.