



Association Between Parkinson's Disease and Melanoma: Putting the Pieces Together

Qing Ye^{1†}, Ya Wen^{1,2†}, Nasser Al-Kuwari¹ and Xiqun Chen^{1*}

¹Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States,

²letheory Institute, Burlington, MA, United States

Patients with Parkinson's disease (PD) generally have reduced risk of developing many types of cancers, except melanoma—a malignant tumor of melanin-producing cells in the skin. For decades, a large number of epidemiological studies have reported that the occurrence of melanoma is higher than expected among subjects with PD, and the occurrence of PD is reciprocally higher than expected among patients with melanoma. More recent epidemiological studies further indicated a bidirectional association, not only in the patients themselves but also in their relatives. This association between PD and melanoma offers a unique opportunity to understand PD. Here, we summarize epidemiological, clinical, and biological evidence in regard to shared risk factors and possible underlying mechanisms for these two seemingly distinct conditions.

OPEN ACCESS

Edited by:

Nicola Simola,
University of Cagliari, Italy

Reviewed by:

Rivka Inzelberg,
Tel Aviv University, Israel
Roberta Marongiu,
Cornell University, United States

*Correspondence:

Xiqun Chen
xchen17@mgh.harvard.edu

[†]These authors have contributed
equally to this work

Received: 28 November 2019

Accepted: 20 February 2020

Published: 10 March 2020

Citation:

Ye Q, Wen Y, Al-Kuwari N and
Chen X (2020) Association Between
Parkinson's Disease and Melanoma:
Putting the Pieces Together.
Front. Aging Neurosci. 12:60.
doi: 10.3389/fnagi.2020.00060

Keywords: Parkinson's disease, melanoma, cancer, risk factors, pigmentation

INTRODUCTION

Epidemiological studies have provided substantial insight into our understanding of Parkinson's disease (PD). Many risks and inverse risk factors have been identified to play important roles in the development and progression of the disease (Ascherio and Schwarzschild, 2016). The association between PD and melanoma discovered by epidemiological studies appears to be particularly intriguing. Melanoma is a form of cancer that develops from melanocytes, which produce melanin, the pigment that colors skin, eyes, and hair. Melanoma is among the most aggressive and treatment-resistant human cancers and it accounts for 75% of all skin cancer deaths. PD and cancer are distinct diseases, with cancer resulting from uncontrolled cell growth and proliferation whereas PD is characterized by the premature death of dopaminergic neurons. Epidemiological evidence indeed supports an overall reduced risk of total cancer in patients with PD (Zhang and Liu, 2019), and reduced risk of developing PD in cancer patients (Bajaj et al., 2010; Fois et al., 2010; Tacik et al., 2016; Cui et al., 2019; Zhang and Liu, 2019). This is, however, not the case with melanoma. A large number of epidemiological studies have reported that the occurrence of melanoma was higher than expected among subjects with PD, and melanoma patients were reciprocally more likely to develop PD (Huang et al., 2015; Bose et al., 2018). A meta-analysis showed that the risk of developing melanoma in individuals with PD was 3.6-fold higher than expected, with a pooled odds ratio of 2.1 from 12 studies (Liu et al., 2011). A more recent meta-analysis reported a 2.4-fold increased risk of melanoma in PD and an overall pooled odds ratio of 1.83 from 22 studies (Huang et al., 2015).

SHARED RISK FACTORS AND INVERSE RISK FACTORS BETWEEN PD AND MELANOMA

Both PD and melanoma are considered multifaceted disorders that result from complex interactions of genetic and environmental factors. Growing evidence suggests that there are shared risk factors between PD and melanoma, which include:

Age. The risk of developing PD or melanoma increases with age. People typically develop PD around age 60 or older, while about half of melanomas occur in people over the age of 50.

Family History and Genetics. Having a close relative with PD increases the risk of developing PD, and having a close relative with melanoma also increases the risk of developing melanoma (Ward et al., 2017). The finding that a family history of melanoma in first-degree relatives was associated with a higher risk of PD suggests shared genetic predispositions (Gao et al., 2009a).

Gender. Men are 1.5 times more likely to develop PD (Wooten et al., 2004) or melanoma (National Cancer Institute, 2019; Rastrelli et al., 2014) than women.

Ethnicity. PD is more common in the white population than in black or Asian population (Van Den Eeden et al., 2003; Dahodwala et al., 2009; Wright Willis et al., 2010). Melanoma is also more common in the white population (Wooten et al., 2004).

Red Hair and Fair Skin. Melanoma is strongly linked to fair skin and red hair, the phenotype of the gene MC1R (melanocortin 1 receptor) polymorphisms. Red hair color has also been associated with an increased risk of developing PD (Chen et al., 2017b).

Toxins. Continuous exposure to environmental toxins such as pesticides has been reported to increase the risk of developing both PD (Goldman, 2014; Nandipati and Litvan, 2016) and melanoma (Dennis et al., 2010).

PD and melanoma also share inverse risk factors, such as:

Smoking. Many epidemiologic studies have consistently reported that PD was less common in people who smoke cigarette (Hernán et al., 2001, 2002; Ritz et al., 2007; Li et al., 2015), use smokeless tobacco (Benedetti et al., 2000; O'Reilly et al., 2005), and even only with environmental tobacco exposure (O'Reilly et al., 2009; Searles Nielsen et al., 2012). Smoking is usually associated with an increased risk of developing many types of cancer. Though surprisingly, studies have suggested that smokers had lower risks of melanoma than nonsmokers (Kessides et al., 2011; Dusingize et al., 2018). However, smoking was linked to an increased risk of melanoma metastases (Jones et al., 2017).

Coffee Consumption. Coffee consumption is associated with a decreased risk of developing PD, suggested by a large number of studies (Benedetti et al., 2000; Hernán et al., 2002; Hu et al., 2007; Costa et al., 2010). The risk of developing melanoma was also reported among different populations to be decreased in

individuals who drink coffee (Loftfield et al., 2015; Wu et al., 2015; Lukic et al., 2016; Caini et al., 2017).

COMMON CLINICAL FEATURES OF PD AND MELANOMA

Although their major symptoms are distinct, PD and melanoma share some common clinical features:

Vitamin D Deficiency

Both PD and melanoma have lower serum vitamin D levels, which are associated with more severe symptoms. Lower serum vitamin D levels were found in patients with PD (Sleeman et al., 2017), and vitamin D deficiency was associated with increased risk of the disease (Sato et al., 1997; Evatt et al., 2008). Studies also found that in PD patients, vitamin D levels significantly correlated with falls and some non-motor symptoms such as insomnia, depression, and anxiety (Zhang et al., 2019), and lower serum 25-hydroxy vitamin D in early PD may predict greater disease severity (Sleeman et al., 2017). Conversely, higher plasma vitamin D levels were associated with lower symptom severity, better cognition, and less depression in PD patients without dementia (Peterson et al., 2013). Decreased serum vitamin level was also detected in patients with melanoma (Field and Newton-Bishop, 2011; Field et al., 2013), and lower levels of vitamin D were associated with thicker tumors and reduced patient survival (Slominski et al., 2017), tumor ulceration, and high tumor mitotic rate (Timerman et al., 2016; Moreno-Arrones et al., 2019).

Sleep Disorders

Patients with PD often have sleep disorders (Menza et al., 2010). Sleep disturbance such as sleep apnea correlates with a higher risk of PD (Chen J.-C. et al., 2015; Yeh et al., 2016; Chou et al., 2017). The risk of melanoma was significantly higher in patients with sleep apnea as well (Gozal et al., 2016). Additionally, sleep apnea was reported to be associated with aggressive melanoma (Martínez-García et al., 2014; Martínez-García et al., 2018).

Extended Echogenic SN Area

Abnormally extended echogenic SN area was observed in both PD and melanoma patients by transcranial sonography (Rumpf et al., 2013). Later, a prospective observational study revealed that patients with melanoma had increased frequency of SN hyperechogenicity and prodromal motor and non-motor features of PD. This study also showed that larger echogenicity of SN correlated with lower serum iron in patients with melanoma, consistent with prior findings in PD (Walter et al., 2016).

POSSIBLE UNDERLYING MECHANISMS FOR THE PD AND MELANOMA ASSOCIATION

The epidemiological and clinical associations between PD and melanoma suggest common underlying mechanisms. Known PD- and melanoma-related genes/gene products and pathways have been implicated in the PD and melanoma associations.

PD-RELATED GENES IN MELANOMA

PRKN gene encodes protein parkin, which belongs to a group of proteins called E3 ubiquitin ligases, and is involved in the maintenance of mitochondria, and also act as a tumor suppressor protein (Wahabi et al., 2018). More than 200 PRKN gene mutations were identified to cause PD, especially early-onset PD. PRKN mutations were also identified in melanoma cases, and its expression level was found to decrease in melanoma cell lines. PRKN somatic mutations were found in ~13% melanomas (Inzelberg et al., 2016b). Expression of PRKN in melanoma cells attenuated cell proliferation and conversely, inhibition of PRKN in melanocytes induced cell proliferation (Hu et al., 2016).

SNCA encodes protein alpha-synuclein (α -Syn), which is abundant in the brain. It plays a role in controlling the mobility of synaptic vesicles, regulating the release of neurotransmitters such as dopamine. α -Syn may interact with tyrosinase (TYR) and tyrosine hydroxylase (TH; Pan et al., 2012), which are enzymes involved in the biosynthesis of melanin and dopamine, respectively. Mutations in SNCA cause dementia with Lewy bodies, as well as PD. Elevated expression levels of α -Syn were indicated in skin cells from PD patients (Rodríguez-Leyva et al., 2014; Rodríguez-Leyva et al., 2017) and metastatic tissues from melanoma patients (Matsuo and Kamitani, 2010; Welinder et al., 2014). A study using melanoma cells showed that α -Syn might have inhibitory effects on melanin synthesis in melanoma cells (Pan et al., 2012). Some researchers proposed that neuromelanin might have direct interaction with α -Syn (Xu and Chan, 2015). However, whether α -Syn has a direct role in dermal melanin synthesis or melanoma is uncertain (Inzelberg et al., 2016a).

LRRK2 encodes protein dardarin, which is involved in protein-protein interactions, kinase activity, and GTPase activity. LRRK2 mutations are the most common genetic cause of familial as well as sporadic PD. PD patients carrying LRRK2 G2019S mutation had a higher overall cancer risk (Agalliu et al., 2015) Although LRRK2 somatic mutations were demonstrated in human melanomas (Inzelberg et al., 2016b), melanoma is not among specific cancers that have been associated with LRRK2 mutations, which include leukemia, colon and skin cancer (Agalliu et al., 2019), breast cancer in women (Agalliu et al., 2015), and non-skin cancers (Inzelberg et al., 2012).

PARK7 encodes protein DJ-1, with functions in regulating protein folding and oxidative stress. PARK7 mutations are associated with early-onset PD. DJ-1 is also considered as an oncogene (Vasseur et al., 2009). In melanoma cell lines, PARK7 expression is positively correlated with migratory ability (Cecconi et al., 2017), and patients with metastatic uveal melanoma had significantly higher levels of serum DJ-1 (Chen L.-L. et al., 2015).

PINK1 encodes the protein PTEN induced kinase 1, a mitochondrial serine/threonine-protein kinase and a tumor suppressor. Mutations in this gene cause early-onset PD. PINK1 appears to protect mitochondria from stress-induced malfunctioning. PINK1 targets parkin to depolarized mitochondria to induce autophagy (Arena and Valente, 2017).

Altered expression levels of PINK1 were detected in melanoma cells (Brown et al., 2017).

PLA2G6 encodes the enzyme A2 phospholipase, which is involved in metabolizing phospholipids. Mutations in PLA2G6 cause early-onset parkinsonism (Tomiyama et al., 2011; Lin et al., 2018). PLA2G6 variants were associated with increased nevus counts, a major indicator for melanoma risk (Law et al., 2012).

HTRA2 encodes a serine protease localized in the endoplasmic reticulum (ER) and mitochondria. It is regulated by PINK1 and is involved in apoptosis in PD (Strauss et al., 2005; Plun-Favreau et al., 2007; Desideri and Martins, 2012). It is reported that HTRA2 expression levels were changed in melanoma cells (Su et al., 2009).

UCHL1 encodes a deubiquitinating enzyme called ubiquitin carboxy-terminal hydrolase L1, abundantly presents in all neurons. It is a PD susceptibility gene (Maraganore et al., 2004) and may link to alpha-synucleinopathy (Cartier et al., 2012). The aberrant expression level of UCHL1 was detected in melanoma cells (Wulfänger et al., 2013). It appeared to regulate melanin production and distribution in melanocytes (Seo et al., 2017).

CANCER-OR MELANOMA-RELATED GENES IN PD

TRPM7 encodes protein Trpm7, which is an essential ion channel and serine/threonine-protein kinase. It regulates cellular calcium and magnesium levels. In melanocytes and melanoma cells, TRPM7 functions as a protector and detoxifier (Guo et al., 2012). TRPM7 channel was shown to regulate dopamine-dependent developmental transition and dopaminergic cell survival (Sun et al., 2015). Decreased TRPM7 expression was found in the SN area of PD patients (Sun et al., 2015).

TP53 encodes p53 protein, a well-known tumor suppressor. It binds to DNA and triggers DNA damage repair or apoptosis. It is the most frequently mutated gene in human cancers and it plays broad roles in many types of cancers including melanoma. In PD, it may be responsible for inducing the death of dopaminergic neurons (Alves da Costa and Checler, 2011).

PTEN encodes protein Pten, which is also a major tumor suppressor. It involves in signaling pathways that regulate cell death. Similar to p53, PTEN is related to many cancers including melanoma (Aguissa-Touré and Li, 2012). *De novo* variants of PTEN were implicated in PD (Kun-Rodrigues et al., 2015), and PTEN was proposed to be a potential therapeutic target for the disease.

GPNMB encodes the protein transmembrane glycoprotein NMB, which is a transmembrane protein enriched on the cell surface of various cancer cells, including melanoma cells. It appears to have both inhibitory and tumor-promoter roles in different cancers (Taya and Hammes, 2018). Increased brain GPNMB expression may explain the association between the GPNMB gene locus and PD risk (Murthy et al., 2017).

MC1R encodes the melanocortin 1 receptor. In melanocytes, MC1R determines the relative amount of brown-black eumelanin and yellow-red pheomelanin by facilitating eumelanin production. Loss-of-function MC1R variants are associated

with red hair, fair skin, poor tanning and increased risk of melanoma. Red hair color and loss-of-function MC1R R151C variant have also been associated with PD (Gao et al., 2009a; Chen et al., 2017b). Further, MC1R was reported to be expressed in dopaminergic neurons and it influenced dopaminergic neuron survival (Chen et al., 2017a).

OTHER GENES THAT MAY BE INVOLVED IN BOTH PD AND MELANOMA

CYP2D6 encodes the enzyme cytochrome P450 2D6, which catalyzes many reactions involved in drug metabolism. CYP2D6 polymorphisms have been associated with increased susceptibility to melanoma (Strange et al., 1999), as well as increased susceptibility to PD (Lu et al., 2014; Aslam et al., 2017).

GSTM1 encodes a human glutathione s-transferase. It functions in the detoxification of electrophilic compounds including drugs and environmental toxins. Its association with PD is still up for debate (Wang et al., 2016), some suggested that it linked to PD *via* pesticide exposures (Pinhel et al., 2013). GSTM1 was linked to melanoma (Kanetsky et al., 2001), and the protective effect of coffee consumption was reported to be particularly high for subjects with GSTM1 null polymorphisms (Fortes et al., 2013).

VDR encodes the vitamin D receptor, a member of the nuclear receptor family of transcription factors, which binds to the active form of vitamin D. VDR expression was decreased in melanoma (Brozyna et al., 2014), and VDR variants were associated with a higher risk of PD (Butler et al., 2011; Meamar et al., 2017). Its role in PD and melanoma is likely linked to vitamin D deficiency.

GRIN2A encodes the regulatory GluN2A subunit of the glutamate-gated N-methyl-d-aspartate receptor (NMDAR). NMDA receptors are a class of ionotropic glutamate receptors found in neurons. Variants of GRIN2A were associated with the protective effect of coffee against PD (Hamza et al., 2011; Yamada-Fowler et al., 2014), and mutations of GRIN2A in melanoma correlate with decreased survival (D'Mello et al., 2014).

The genes discussed above have varied strengths of evidence for their involvement in PD and melanoma, from multidisciplinary studies. To understand their pleiotropic roles in both conditions, it is important to further investigate their biological functions, interactions, and involvements in molecular pathways.

THE PIGMENTATION PATHWAY

Dopaminergic neurons and melanocytes share common pathways or cascades that control the final fate of the cells, including cell cycle, DNA repair, oxidative stress, and immune responses. They are both pigmented, and L-dopa is an intermediate product for the synthesis of both dopamine in dopaminergic neurons and melanin in melanocytes.

The associations between red hair color, redhead-related MC1R variants, and risk for both melanoma and PD support

a possible role of systemic pigmentation in the PD-melanoma link (Gao et al., 2009b; Edwards et al., 2011; Rumpf et al., 2015; Chen et al., 2017b). In addition, light skin/hair pigmentation was related to abnormal SN echogenicity (Rumpf et al., 2015), and the TYR melanogenesis pathway was identified in the GWAS database as the top significant pathway for PD (Edwards et al., 2011). Furthermore, vitamin D regulates cutaneous pigmentation by enhancing melanogenesis (Pavlovitch et al., 1982; Watabe et al., 2002). PD and melanoma both have vitamin D insufficiency (Sato et al., 1997; Evatt et al., 2008; Field and Newton-Bishop, 2011; Field et al., 2013), and a lower expression level of VDR was found in melanoma (Slominski et al., 2017). These findings suggest that systemic melanogenesis may be compromised in both conditions.

In addition to eumelanin and pheomelanin in the periphery, there is the third melanin—neuromelanin in the human brain. Neuromelanin may be synthesized from dopamine precursor L-dopa, or it could derive from non-enzymatic oxidation in mitochondria from excess cytosolic dopamine accumulated by synaptic vesicles (Zecca et al., 2001). Evidence supports both the protective and cytotoxic effects of neuromelanin (Enochs et al., 1994). PD patients have significantly less neuromelanin in the brain (Zecca et al., 2002). It is unclear whether the decreased level of neuromelanin is a result of the loss of neurons, or the death of neurons is triggered by loss of neuromelanin as its protective function may be compromised. A new study showed the age-dependent production of neuromelanin in rat SN overexpressing TYR. Neuromelanin accumulation was associated with Lewy body-like inclusions and nigrostriatal neurodegeneration (Carballo-Carbajal et al., 2019). The findings that neuromelanin structurally consisted of a pheomelanin core and a eumelanin surface led to a hypothesis that thinning eumelanin surface and exposing pheomelanin core may be responsible for the selective vulnerability of pigmented dopaminergic neurons in PD (Bush et al., 2006; Ito, 2006). Excessive pheomelanin in the periphery (e.g., in red-haired individuals) plays a causal role in melanomagenesis (Roider and Fisher, 2016). It is unknown how neuromelanin might be related to skin melanin or whether MC1R has any role in neuromelanin synthesis. Albino humans with TYR were reported to have pigmented SN (Foley and Baxter, 1958). Further studies should aim to elucidate the exact role of the periphery pigmentation and the central nervous system (CNS) pigmentation in the PD-melanoma association.

A related question is whether L-dopa is involved in high melanoma occurrence in PD. Although bidirectional, the risk ratio for PD preceding melanoma has overall consistently been higher than that for melanoma preceding PD (Liu et al., 2011; Huang et al., 2015), indicating that there might be additional factors contributing to the former. L-dopa as the mainstay therapy for PD and common rate-limiting intermediate products for the biosynthesis of both dopamine in dopaminergic neurons and melanin in melanocytes has long been proposed to be such a contributing factor. In fact, the very first reported melanoma cases in PD were from patients taking

levodopa (Skibba et al., 1972). However, subsequent findings that rates of melanoma increased among early PD patients not yet taking L-dopa argue against levodopa's involvement in this link (Zanetti et al., 2006; Vermeij et al., 2009). This issue has not been fully settled as there have been so far only a few observational studies (Fiala et al., 2003; Constantinescu et al., 2007; Olsen et al., 2007). Melanoma history is still listed as a contraindication to L-dopa use. With the identification of the possible genetic risk factors for both PD and melanoma, it may be necessary to reevaluate L-dopa's role in melanoma development in PD, especially in populations at risk.

THE IMMUNE SYSTEM

The immune systems are often weakened in cancers including melanoma (Rangwala and Tsai, 2011). In fact, melanoma is considered the immunogenic tumor, and cell proliferation, as well as apoptosis, are associated with immune system dysfunctions during melanomagenesis (Passarelli et al., 2017). Further, immunotherapy is in use to treat advanced melanoma (Passarelli et al., 2017). Once considered immune-privileged, the CNS, in fact, possesses abilities to elicit immune responses. Neuroinflammation plays a role in the pathogenesis as well as disease progression of PD (Tansey and Goldberg, 2010; Vivekanantham et al., 2015; Gelders et al., 2018). Post-mortem studies found elevated levels of pro-inflammatory factors in the brains of PD patients. Glial cell activation was detected in the brains of PD patients or the animal models of PD. As the disease progresses, α -Syn and other molecules released from the degenerating dopamine neurons may further activate microglia, which may result in more neuron death and thus forming a vicious cycle of neurodegeneration (Wang et al., 2015). Emerging evidence supports the involvement of peripheral inflammation and the peripheral immune system in PD pathogenesis and progression (Garretti et al., 2019; Kustrimovic et al., 2019). Constipation is often a symptom of PD, and PD patients have altered gut microbiome, which may increase inflammation (Garretti et al., 2019). T cells from PD patients respond to α -Syn to a greater degree when compared to the control subjects (Sulzer et al., 2017). A study using human induced pluripotent stem cell (iPSC)-based PD model showed increased neuronal death induced by upregulation of IL-17 receptor (IL-17R) and NF- κ B activation, and the neuronal death could be rescued by

blockage of IL-17 or IL-17R or the use of an IL-17 antibody (Sommer et al., 2018). More studies are needed to explore immune dysregulation, particularly the systemic immune system and its interactions with the central immune system in the PD-melanoma link.

CONCLUSION AND FUTURE PERSPECTIVES

PD patients have a significantly higher risk of developing melanoma, and vice versa. The association is well-documented by epidemiological studies and supported by clinical and biological studies. PD and melanoma share several risk factors, inverse risk factors, as well as some common clinical features. Genetic studies have identified genes that may be associated with both conditions. Studies using cellular and animal models further provided evidence for a possibly critical role of the pigmentation pathway in this association. As complex as the two pathologies separately, their association is likely a result of complex interactions between environmental and genetic factors. The immune dysregulation may represent one of the convergent mechanisms leading to neurodegeneration in dopaminergic neurons and tumorigenesis in melanocytes. Future studies using detailed systems analysis focusing on the multi-level interactions between PD and melanoma may lead to a more comprehensive understanding of the mechanisms underlying the PD-melanoma link, thus shed fresh insight on both pathologies and help develop treatment strategies.

AUTHOR CONTRIBUTIONS

QY, YW, NA-K, and XC wrote the article.

FUNDING

This work was supported by National Institutes of Health (NIH), Grant No. R01NS102735 and The Farmers Family Foundation.

ACKNOWLEDGMENTS

We thank all the authors who contributed to the publications we cited here and apologize to those whose studies are relevant to this topic but are not cited due to the space limit.

REFERENCES

- Agalliu, I., Ortega, R. A., Luciano, M. S., Mirelman, A., Pont-Sunyer, C., Brockmann, K., et al. (2019). Cancer outcomes among Parkinson's disease patients with leucine rich repeat kinase 2 mutations, idiopathic Parkinson's disease patients, and nonaffected controls. *Mov. Disord.* 34, 1392–1398. doi: 10.1002/mds.27807
- Agalliu, I., San Luciano, M., Mirelman, A., Giladi, N., Waro, B., Aasly, J., et al. (2015). Higher frequency of certain cancers in LRRK2 G2019S mutation carriers with Parkinson disease: a pooled analysis. *JAMA Neurol.* 72, 58–65. doi: 10.1001/jamaneurol.2014.1973
- Aguisa-Touré, A.-H., and Li, G. (2012). Genetic alterations of PTEN in human melanoma. *Cell. Mol. Life Sci.* 69, 1475–1491. doi: 10.1007/s00018-011-0878-0
- Alves da Costa, C., and Checler, F. (2011). Apoptosis in Parkinson's disease: is p53 the missing link between genetic and sporadic Parkinsonism? *Cell. Signal.* 23, 963–968. doi: 10.1016/j.cellsig.2010.10.020
- Anwarullah, Aslam, M., Badshah, M., Abbasi, R., Sultan, A., Khan, K., et al. (2017). Further evidence for the association of CYP2D6*4 gene polymorphism with Parkinson's disease: a case control study. *Genes Environ.* 39:18. doi: 10.1186/s41021-017-0078-8
- Arena, G., and Valente, E. M. (2017). PINK1 in the limelight: multiple functions of an eclectic protein in human health and disease. *J. Pathol.* 241, 251–263. doi: 10.1002/path.4815
- Ascherio, A., and Schwarzschild, M. A. (2016). The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol.* 15, 1257–1272. doi: 10.1016/S1474-4422(16)30230-7

- Bajaj, A., Driver, J. A., and Schernhammer, E. S. (2010). Parkinson's disease and cancer risk: a systematic review and meta-analysis. *Cancer Causes Control* 21, 697–707. doi: 10.1007/s10552-009-9497-6
- Benedetti, M. D., Bower, J. H., Maraganore, D. M., McDonnell, S. K., Peterson, B. J., Ahlskog, J. E., et al. (2000). Smoking, alcohol and coffee consumption preceding Parkinson's disease: a case-control study. *Neurology* 55, 1350–1358. doi: 10.1212/wnl.55.9.1350
- Bose, A., Petsko, G. A., and Eliezer, D. (2018). Parkinson's disease and melanoma: co-occurrence and mechanisms. *J. Parkinsons Dis.* 8, 385–398. doi: 10.3233/JPD-171263
- Brożyna, A. A., Józwicki, W., and Slominski, A. T. (2014). Decreased VDR expression in cutaneous melanomas as marker of tumor progression: new data and analyses. *Anticancer Res.* 34, 2735–2743.
- Brown, K., Yang, P., Salvador, D., Kulikauskas, R., Ruohola-Baker, H., Robitaille, A. M., et al. (2017). WNT/ β -catenin signaling regulates mitochondrial activity to alter the oncogenic potential of melanoma in a PTEN-dependent manner. *Oncogene* 36, 3119–3136. doi: 10.1038/ncr.2016.450
- Bush, W. D., Garguilo, J., Zucca, F. A., Albertini, A., Zecca, L., Edwards, G. S., et al. (2006). The surface oxidation potential of human neuromelanin reveals a spherical architecture with a pheomelanin core and a eumelanin surface. *Proc. Natl. Acad. Sci. U S A* 103, 14785–14789. doi: 10.1073/pnas.0604010103
- Butler, M. W., Burt, A., Edwards, T. L., Zuchner, S., Scott, W. K., Martin, E. R., et al. (2011). Vitamin D receptor gene as a candidate gene for Parkinson disease. *Ann. Hum. Genet.* 75, 201–210. doi: 10.1111/j.1469-1809.2010.00631.x
- Caini, S., Masala, G., Saieva, C., Kvaskoff, M., Savoye, I., Sacerdote, C., et al. (2017). Coffee, tea and melanoma risk: findings from the European Prospective Investigation into Cancer and Nutrition. *Int. J. Cancer* 140, 2246–2255. doi: 10.1002/ijc.30659
- Carballo-Carbajal, I., Laguna, A., Romero-Giménez, J., Cuadros, T., Bové, J., Martínez-Vicente, M., et al. (2019). Brain tyrosinase overexpression implicates age-dependent neuromelanin production in Parkinson's disease pathogenesis. *Nat. Commun.* 10:973. doi: 10.1038/s41467-019-08858-y
- Cartier, A. E., Ubhi, K., Spencer, B., Vazquez-Roque, R. A., Kosberg, K. A., Fourgeaud, L., et al. (2012). Differential effects of UCHL1 modulation on α -synuclein in PD-like models of α -synucleinopathy. *PLoS One* 7:e34713. doi: 10.1371/journal.pone.0034713
- Cecconi, D., Carbonare, L. D., Mori, A., Cheri, S., Deiana, M., Brandi, J., et al. (2017). An integrated approach identifies new oncotargets in melanoma. *Oncotarget* 9, 11489–11502. doi: 10.18632/oncotarget.23727
- Chen, X., Chen, H., Cai, W., Maguire, M., Ya, B., Zuo, F., et al. (2017a). The melanoma-linked “redhead” MC1R influences dopaminergic neuron survival. *Ann. Neurol.* 81, 395–406. doi: 10.1002/ana.24852
- Chen, X., Feng, D., Schwarzschild, M. A., and Gao, X. (2017b). Red hair, MC1R variants, and risk for Parkinson's disease—a meta-analysis. *Ann. Clin. Transl. Neurol.* 4, 212–216. doi: 10.1002/acn3.381
- Chen, L.-L., Tian, J. J., Su, L., Jing, Y., Zhang, S. C., Zhang, H. X., et al. (2015). DJ-1: a promising marker in metastatic uveal melanoma. *J. Cancer Res. Clin. Oncol.* 141, 315–321. doi: 10.1007/s00432-014-1804-2
- Chen, J.-C., Tsai, T.-Y., Li, C.-Y., and Hwang, J.-H. (2015). Obstructive sleep apnea and risk of Parkinson's disease: a population-based cohort study. *J. Sleep Res.* 24, 432–437. doi: 10.1111/jsr.12289
- Chou, P.-S., Lai, C.-L., Chou, Y.-H., and Chang, W.-P. (2017). Sleep apnea and the subsequent risk of Parkinson's disease: a 3-year nationwide population-based study. *Neuropsychiatr. Dis. Treat.* 13, 959–965. doi: 10.2147/NDT.S134311
- Constantinescu, R., Romer, M., Kieburz, K., and DATATOP Investigators of the Parkinson Study Group. (2007). Malignant melanoma in early Parkinson's disease: the DATATOP trial. *Mov. Disord.* 22, 720–722. doi: 10.1002/mds.21273
- Costa, J., Lunet, N., Santos, C., Santos, J., and Vaz-Carneiro, A. (2010). Caffeine exposure and the risk of Parkinson's disease: a systematic review and meta-analysis of observational studies. *J. Alzheimers Dis.* 20, S221–S238. doi: 10.3233/JAD-2010-091525
- Cui, X., Liew, Z., Hansen, J., Lee, P. C., Arah, O. A., and Ritz, B. (2019). Cancers preceding Parkinson's disease after adjustment for bias in a danish population-based case-control study. *Neuroepidemiology* 52, 136–143. doi: 10.1159/000494292
- D'Mello, S. A. N., Flanagan, J. U., Green, T. N., Leung, E. Y., Askarian-Amiri, M. E., Joseph, W. R., et al. (2014). Evidence that GRIN2A mutations in melanoma correlate with decreased survival. *Front. Oncol.* 3:333. doi: 10.3389/fonc.2013.00333
- Dahodwala, N., Siderowf, A., Xie, M., Noll, E., Stern, M., and Mandell, D. S. (2009). Racial differences in the diagnosis of Parkinson's disease. *Mov. Disord.* 24, 1200–1205. doi: 10.1002/mds.22557
- Dennis, L. K., Lynch, C. F., Sandler, D. P., and Alavanja, M. C. R. (2010). Pesticide use and cutaneous melanoma in pesticide applicators in the agricultural health study. *Environ. Health Perspect.* 118, 812–817. doi: 10.1289/ehp.0901518
- Desideri, E., and Martins, L. M. (2012). Mitochondrial stress signalling: HTRA2 and Parkinson's disease. *Int. J. Cell Biol.* 2012:607929. doi: 10.1155/2012/607929
- Dusingize, J. C., Olsen, C. M., Pandeya, N., Thompson, B. S., Webb, P. M., Green, A. C., et al. (2018). Smoking and cutaneous melanoma: findings from the QSkin sun and health cohort study. *Cancer Epidemiol. Biomarkers Prev.* 27, 874–881. doi: 10.1158/1055-9965.epi-17-1056
- Edwards, Y. J. K., Beecham, G. W., Scott, W. K., Khuri, S., Bademci, G., Tekin, D., et al. (2011). Identifying consensus disease pathways in Parkinson's disease using an integrative systems biology approach. *PLoS One* 6:e16917. doi: 10.1371/journal.pone.0016917
- Enochs, W. S., Sarna, T., Zecca, L., Riley, P. A., and Swartz, H. M. (1994). The roles of neuromelanin, binding of metal ions, and oxidative cytotoxicity in the pathogenesis of Parkinson's disease: a hypothesis. *J. Neural Transm. Park. Dis. Dement. Sect.* 7, 83–100. doi: 10.1007/bf02260963
- Evatt, M. L., Delong, M. R., Khazai, N., Rosen, A., Triche, S., and Tangpricha, V. (2008). Prevalence of vitamin D insufficiency in patients with parkinson disease and Alzheimer disease. *Arch. Neurol.* 65, 1348–1352. doi: 10.1001/archneur.65.10.1348
- Fiala, K. H., Whetteckey, J., and Manyam, B. V. (2003). Malignant melanoma and levodopa in Parkinson's disease: causality or coincidence? *Phys. Med. Biol.* 9, 321–327. doi: 10.1016/s1353-8020(03)00040-3
- Field, S., Davies, J., Bishop, D. T., and Newton-Bishop, J. A. (2013). Vitamin D and melanoma. *Dermatoendocrinol.* 5, 121–129. doi: 10.4161/derm.25244
- Field, S., and Newton-Bishop, J. A. (2011). Melanoma and vitamin D. *Mol. Oncol.* 5, 197–214. doi: 10.1016/j.molonc.2011.01.007
- Fois, A. F., Wotton, C. J., Yeates, D., Turner, M. R., and Goldacre, M. J. (2010). Cancer in patients with motor neuron disease, multiple sclerosis and Parkinson's disease: record linkage studies. *J. Neurol. Neurosurg. Psychiatry* 81, 215–221. doi: 10.1136/jnnp.2009
- Foley, J. M., and Baxter, D. (1958). On the nature of pigment granules in the cells of the locus coeruleus and substantia nigra. *J. Neuropathol. Exp. Neurol.* 17, 586–598. doi: 10.1097/00005072-195810000-00005
- Fortes, C., Mastroeni, S., Boffetta, P., Antonelli, G., Pilla, M. A., Bottà, G., et al. (2013). The protective effect of coffee consumption on cutaneous melanoma risk and the role of GSTM1 and GSTT1 polymorphisms. *Cancer Causes Control* 24, 1779–1787. doi: 10.1007/s10552-013-0255-4
- Gao, X., Simon, K. C., Han, J., Schwarzschild, M. A., and Ascherio, A. (2009a). Family history of melanoma and Parkinson disease risk. *Neurology* 73, 1286–1291. doi: 10.1212/WNL.0b013e3181bd13a1
- Gao, X., Simon, K. C., Han, J., Schwarzschild, M. A., and Ascherio, A. (2009b). Genetic determinants of hair color and Parkinson's disease risk. *Ann. Neurol.* 65, 76–82. doi: 10.1002/ana.21535
- Garretti, F., Agalliu, D., Lindestam Arlehamn, C. S., Sette, A., and Sulzer, D. (2019). Autoimmunity in Parkinson's disease: the role of α -synuclein-specific T cells. *Front. Immunol.* 10:303. doi: 10.3389/fimmu.2019.00303
- Gelders, G., Baekelandt, V., and Van der Perren, A. (2018). Linking neuroinflammation and neurodegeneration in Parkinson's disease. *J. Immunol. Res.* 2018:4784268. doi: 10.1155/2018/4784268
- Goldman, S. M. (2014). Environmental toxins and Parkinson's disease. *Annu. Rev. Pharmacol. Toxicol.* 54, 141–164. doi: 10.1146/annurev-pharmtox-011613-135937
- Gozal, D., Ham, S. A., and Mokhlesi, B. (2016). Sleep apnea and cancer: analysis of a nationwide population sample. *Sleep* 39, 1493–1500. doi: 10.5665/sleep.6004
- Guo, H., Carlson, J. A., and Slominski, A. (2012). Role of TRPM in melanocytes and melanoma. *Exp. Dermatol.* 21, 650–654. doi: 10.1111/j.1600-0625.2012.01565.x
- Hamza, T. H., Chen, H., Hill-Burns, E. M., Rhodes, S. L., Montimurro, J., Kay, D. M., et al. (2011). Genome-wide gene-environment study identifies glutamate receptor gene GRIN2A as a Parkinson's disease modifier gene via

- interaction with coffee. *PLoS Genet.* 7:e1002237. doi: 10.1371/journal.pgen.1002237
- Hernán, M. A., Takkouche, B., Caamaño-Isorna, F., and Gestal-Otero, J. J. (2002). A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann. Neurol.* 52, 276–284. doi: 10.1002/ana.10277
- Hernán, M. A., Zhang, S. M., Rueda-deCastro, A. M., Colditz, G. A., Speizer, F. E., and Ascherio, A. (2001). Cigarette smoking and the incidence of Parkinson's disease in two prospective studies. *Ann. Neurol.* 50, 780–786. doi: 10.1002/ana.10028
- Hu, G., Bidel, S., Jousilahti, P., Antikainen, R., and Tuomilehto, J. (2007). Coffee and tea consumption and the risk of Parkinson's disease. *Mov. Disord.* 22, 2242–2248. doi: 10.1002/mds.21706
- Hu, H.-H., Kannengiesser, C., Lesage, S., André, J., Mourah, S., Michel, L., et al. (2016). PARKIN inactivation links Parkinson's disease to melanoma. *J. Natl. Cancer Inst.* 108:djv340. doi: 10.1093/jnci/djv340
- Huang, P., Yang, X.-D., Chen, S.-D., and Xiao, Q. (2015). The association between Parkinson's disease and melanoma: a systematic review and meta-analysis. *Transl. Neurodegener.* 4:21. doi: 10.1186/s40035-015-0044-y
- Inzelberg, R., Cohen, O. S., Aharon-Peretz, J., Schlesinger, I., Gershoni-Baruch, R., Djaldetti, R., et al. (2012). The LRRK2 G2019S mutation is associated with Parkinson disease and concomitant non-skin cancers. *Neurology* 78, 781–786. doi: 10.1212/wnl.0b013e318249f673
- Inzelberg, R., Flash, S., Friedman, E., and Azizi, E. (2016a). Cutaneous malignant melanoma and Parkinson disease: common pathways? *Ann. Neurol.* 80, 811–820. doi: 10.1002/ana.24802
- Inzelberg, R., Samuels, Y., Azizi, E., Qutob, N., Inzelberg, L., Domany, E., et al. (2016b). Parkinson disease (PARK) genes are somatically mutated in cutaneous melanoma. *Neurol. Genet.* 2:e70. doi: 10.1212/nxg.0000000000000070
- Ito, S. (2006). Encapsulation of a reactive core in neuromelanin. *Proc. Natl. Acad. Sci. U S A* 103, 14647–14648. doi: 10.1073/pnas.0606879103
- Jones, M. S., Jones, P. C., Stern, S. L., Elashoff, D., Hoon, D. S. B., Thompson, J., et al. (2017). The impact of smoking on sentinel node metastasis of primary cutaneous melanoma. *Ann. Surg. Oncol.* 24, 2089–2094. doi: 10.1245/s10434-017-5775-9
- Kanetsky, P. A., Holmes, R., Walker, A., Najarian, D., Swoyer, J., Guerry, D., et al. (2001). Interaction of glutathione S-transferase M1 and T1 genotypes and malignant melanoma. *Cancer Epidemiol. Biomarkers Prev.* 10, 509–513.
- Kessides, M. C., Wheless, L., Hoffman-Bolton, J., Clipp, S., Alani, R. M., and Alberg, A. J. (2011). Cigarette smoking and malignant melanoma: a case-control study. *J. Am. Acad. Dermatol.* 64, 84–90. doi: 10.1016/j.jaad.2010.10.041
- Kun-Rodrigues, C., Ganos, C., Guerreiro, R., Schneider, S. A., Schulte, C., Lesage, S., et al. (2015). A systematic screening to identify *de novo* mutations causing sporadic early-onset Parkinson's disease. *Hum. Mol. Genet.* 24, 6711–6720. doi: 10.1093/hmg/ddv376
- Kustrimovic, N., Marino, F., and Cosentino, M. (2019). Peripheral immunity, immunoenvironment and neuroinflammation in Parkinson's disease. *Curr. Med. Chem.* 26, 3719–3753. doi: 10.2174/0929867325666181009161048
- Law, M. H., MacGregor, S., and Hayward, N. K. (2012). Melanoma genetics: recent findings take us beyond well-traveled pathways. *J. Invest. Dermatol.* 132, 1763–1774. doi: 10.1038/jid.2012.75
- Li, X., Li, W., Liu, G., Shen, X., and Tang, Y. (2015). Association between cigarette smoking and Parkinson's disease: a meta-analysis. *Arch. Gerontol. Geriatr.* 61, 510–516. doi: 10.1016/j.archger.2015.08.004
- Lin, G., Lee, P. T., Chen, K., Mao, D., Tan, K. L., Zuo, Z., et al. (2018). Phospholipase PLA2G6, a Parkinsonism-associated gene, affects Vps26 and Vps35, retromer function, and ceramide levels, similar to α -synuclein gain. *Cell Metab.* 28, 605.e6–618.e6. doi: 10.1016/j.cmet.2018.05.019
- Liu, R., Gao, X., Lu, Y., and Chen, H. (2011). Meta-analysis of the relationship between Parkinson disease and melanoma. *Neurology* 76, 2002–2009. doi: 10.1212/wnl.0b013e31821e554e
- Loftfield, E., Freedman, N. D., Graubard, B. I., Hollenbeck, A. R., Shebl, F. M., Mayne, S. T., et al. (2015). Coffee drinking and cutaneous melanoma risk in the NIH-AARP diet and health study. *J. Natl. Cancer Inst.* 107:dju421. doi: 10.1093/jnci/dju421
- Lu, Y., Peng, Q., Zeng, Z., Wang, J., Deng, Y., Xie, L., et al. (2014). CYP2D6 phenotypes and Parkinson's disease risk: a meta-analysis. *J. Neurol. Sci.* 336, 161–168. doi: 10.1016/j.jns.2013.10.030
- Lukic, M., Jareid, M., Weiderpass, E., and Braaten, T. (2016). Coffee consumption and the risk of malignant melanoma in the Norwegian Women and Cancer (NOWAC) study. *BMC Cancer* 16:562. doi: 10.1186/s12885-016-2586-5
- Maraganore, D. M., Lesnick, T. G., Elbaz, A., Chartier-Harlin, M. C., Gasser, T., Krüger, R., et al. (2004). UCHL1 is a Parkinson's disease susceptibility gene. *Ann. Neurol.* 55, 512–521. doi: 10.1002/ana.20017
- Martínez-García, M.-Á., Martorell-Calatayud, A., Nagore, E., Valero, I., Selma, M. J., Chiner, E., et al. (2014). Association between sleep disordered breathing and aggressiveness markers of malignant cutaneous melanoma. *Eur. Respir. J.* 43, 1661–1668. doi: 10.1183/09031936.00115413
- Martínez-García, M. A., Campos-Rodríguez, F., Nagore, E., Martorell, A., Rodríguez-Peralto, J. L., Riveiro-Falkenbach, E., et al. (2018). Sleep-disordered breathing is independently associated with increased aggressiveness of cutaneous melanoma: a multicenter observational study in 443 patients. *Chest* 154, 1348–1358. doi: 10.1016/j.chest.2018.07.015
- Matsuo, Y., and Kamitani, T. (2010). Parkinson's disease-related protein, α -synuclein, in malignant melanoma. *PLoS One* 5:e10481. doi: 10.1371/journal.pone.0010481
- Meamar, R., Javadirad, S. M., Chitsaz, N., Ghahfarokhi, M. A., Kazemi, M., and Ostadsharif, M. (2017). Vitamin D receptor gene variants in Parkinson's disease patients. *Egypt. J. Med. Hum. Genet.* 18, 225–230. doi: 10.1016/j.ejmhg.2016.08.004
- Menza, M., Dobkin, R. D., Marin, H., and Bienfait, K. (2010). Sleep disturbances in Parkinson's disease. *Mov. Disord.* 25, S117–S122. doi: 10.1002/mds.22788
- Moreno-Arrones, O. M., Zegeer, J., Gerbo, M., Manrique-Silva, E., Requena, C., Traves, V., et al. (2019). Decreased vitamin D serum levels at melanoma diagnosis are associated with tumor ulceration and high tumor mitotic rate. *Melanoma Res.* 29, 664–667. doi: 10.1097/cmr.0000000000000638
- Murthy, M. N., Blauwendraat, C., UKBEC, Gueffi, S., IPDGC, Hardy, J., et al. (2017). Increased brain expression of GPNMB is associated with genome wide significant risk for Parkinson's disease on chromosome 7p15.3. *Neurogenetics* 18, 121–133. doi: 10.1007/s10048-017-0514-8
- Nandipati, S., and Litvan, I. (2016). Environmental exposures and Parkinson's disease. *Int. J. Environ. Res. Public Health* 13:E881. doi: 10.3390/ijerph13090881
- National Cancer Institute. (2019). *SEER Cancer Stat Facts: Melanoma Skin Cancer Statistics*. Available online at: <https://www.cancer.org/cancer/melanoma-skin-cancer/about/key-statistics.html>. Accessed June 10, 2019.
- O'Reilly, E. J., Chen, H., Gardener, H., Gao, X., Schwarzschild, M. A., and Ascherio, A. (2009). Smoking and Parkinson's disease: using parental smoking as a proxy to explore causality. *Am. J. Epidemiol.* 169, 678–682. doi: 10.1093/aje/kwn388
- O'Reilly, E. J., McCullough, M. L., Chao, A., Henley, S. J., Calle, E. E., Thun, M. J., et al. (2005). Smokeless tobacco use and the risk of Parkinson's disease mortality. *Mov. Disord.* 20, 1383–1384. doi: 10.1002/mds.20587
- Olsen, J. H., Tangerud, K., Wermuth, L., Frederiksen, K., and Friis, S. (2007). Treatment with levodopa and risk for malignant melanoma. *Mov. Disord.* 22, 1252–1257. doi: 10.1002/mds.21397
- Pan, T., Zhu, J., Hwu, W.-J., and Jankovic, J. (2012). The role of α -synuclein in melanin synthesis in melanoma and dopaminergic neuronal cells. *PLoS One* 7:e45183. doi: 10.1371/journal.pone.0045183
- Passarelli, A., Mannavola, F., Stucci, L. S., Tucci, M., and Silvestri, F. (2017). Immune system and melanoma biology: a balance between immunosurveillance and immune escape. *Oncotarget* 8, 106132–106142. doi: 10.18632/oncotarget.22190
- Pavlovitch, J. H., Rizk, M., and Balsan, S. (1982). Vitamin D nutrition increases skin tyrosinase response to exposure to ultraviolet radiation. *Mol. Cell. Endocrinol.* 25, 295–302. doi: 10.1016/0303-7207(82)90085-5
- Peterson, A. L., Murchison, C., Zabetian, C., Leverenz, J. B., Watson, G. S., Montine, T., et al. (2013). Memory, mood, and vitamin D in persons with Parkinson's disease. *J. Parkinsons Dis.* 3, 547–555. doi: 10.3233/JPD-130206
- Pinhel, M. A. S., Sado, C. L., Longo Gdos, S., Gregório, M. L., Amorim, G. S., Florim, G. M., et al. (2013). Nullity of GSTT1/GSTM1 related to pesticides is associated with Parkinson's disease. *Arq. Neuropsiquiatr.* 71, 527–532. doi: 10.1590/0004-282x20130076
- Plun-Favreau, H., Klupsch, K., Moiso, N., Gandhi, S., Kjaer, S., Frith, D., et al. (2007). The mitochondrial protease HtrA2 is regulated by Parkinson's disease-associated kinase PINK1. *Nat. Cell Biol.* 9, 1243–1252. doi: 10.1038/ncb1644

- Rangwala, S., and Tsai, K. Y. (2011). Roles of the immune system in skin cancer. *Br. J. Dermatol.* 165, 953–965. doi: 10.1111/j.1365-2133.2011.10507.x
- Rastrelli, M., Tropea, S., Rossi, C. R., and Alaibac, M. (2014). Melanoma: epidemiology, risk factors, pathogenesis, diagnosis and classification. *In Vivo* 28, 1005–1011.
- Ritz, B., Ascherio, A., Checkoway, H., Marder, K. S., Nelson, L. M., Rocca, W. A., et al. (2007). Pooled analysis of tobacco use and risk of Parkinson disease. *Arch. Neurol.* 64, 990–997. doi: 10.1001/archneur.64.7.990
- Rodríguez-Leyva, I., Calderón-Garcidueñas, A. L., Jiménez-Capdeville, M. E., Rentería-Palomo, A. A., Hernández-Rodríguez, H. G., Valdés-Rodríguez, R., et al. (2014). α -synuclein inclusions in the skin of Parkinson's disease and parkinsonism. *Ann. Clin. Transl. Neurol.* 1, 471–478. doi: 10.1002/acn3.78
- Rodríguez-Leyva, I., Chi-Ahumada, E., Mejía, M., Castanedo-Cazares, J. P., Eng, W., Saikaly, S. K., et al. (2017). The presence of α -synuclein in skin from melanoma and patients with Parkinson's disease. *Mov. Disord. Clin. Pract.* 4, 724–732. doi: 10.1002/mdc3.12494
- Roider, E. M., and Fisher, D. E. (2016). Red hair, light skin, and UV-independent risk for melanoma development in humans. *JAMA Dermatol.* 152, 751–753. doi: 10.1001/jamadermatol.2016.0524
- Rumpf, J.-J., Schirmer, M., Fricke, C., Weise, D., Wagner, J. A., Simon, J., et al. (2015). Light pigmentation phenotype is correlated with increased substantia nigra echogenicity. *Mov. Disord.* 30, 1848–1852. doi: 10.1002/mds.26427
- Rumpf, J.-J., Weise, D., Fricke, C., Wetzig, T., Simon, J. C., and Classen, J. (2013). Sonographic abnormality of the substantia nigra in melanoma patients. *Mov. Disord.* 28, 219–223. doi: 10.1002/mds.25233
- Sato, Y., Kikuyama, M., and Oizumi, K. (1997). High prevalence of vitamin D deficiency and reduced bone mass in Parkinson's disease. *Neurology* 49, 1273–1278. doi: 10.1212/wnl.49.5.1273
- Searles Nielsen, S., Gallagher, L. G., Lundin, J. I., Longstreth, W. T. Jr., Smith-Weller, T., Franklin, G. M., et al. (2012). Environmental tobacco smoke and Parkinson's disease. *Mov. Disord.* 27, 293–296. doi: 10.1002/mds.24012
- Seo, E. Y., Jin, S. P., Sohn, K. C., Park, C. H., Lee, D. H., and Chung, J. H. (2017). UCHL1 regulates melanogenesis through controlling MITF Stability in human melanocytes. *J. Invest. Dermatol.* 137, 1757–1765. doi: 10.1016/j.jid.2017.03.024
- Skibba, J. L., Pinckley, J., Gilbert, E. F., and Johnson, R. O. (1972). Multiple primary melanoma following administration of levodopa. *Arch. Pathol.* 93, 556–561.
- Sleeman, I., Aspray, T., Lawson, R., Coleman, S., Duncan, G., Khoo, T. K., et al. (2017). The role of vitamin D in disease progression in early Parkinson's disease. *J. Parkinsons Dis.* 7, 669–675. doi: 10.3233/JPD-171122
- Slominski, A. T., Brożyna, A. A., Zmijewski, M. A., Józwicki, W., Jetten, A. M., Mason, R. S., et al. (2017). Vitamin D signaling and melanoma: role of vitamin D and its receptors in melanoma progression and management. *Lab. Invest.* 97, 706–724. doi: 10.1038/labinvest.2017.3
- Sommer, A., Marxreiter, F., Krach, F., Fadler, T., Grosch, J., Maroni, M., et al. (2018). Th17 lymphocytes induce neuronal cell death in a human iPSC-based model of Parkinson's disease. *Cell Stem Cell* 23, 123.e6–131.e6. doi: 10.1016/j.stem.2018.06.015
- Strange, R. C., Ellison, T., Ichii-Jones, F., Bath, J., Hoban, P., Lear, J. T., et al. (1999). Cytochrome P450 CYP2D6 genotypes: association with hair colour, Breslow thickness and melanocyte stimulating hormone receptor alleles in patients with malignant melanoma. *Pharmacogenetics* 9, 269–276. doi: 10.1097/00008571-199906000-00001
- Strauss, K. M., Martins, L. M., Plun-Favreau, H., Marx, F. P., Kautzmann, S., Berg, D., et al. (2005). Loss of function mutations in the gene encoding Omi/HtrA2 in Parkinson's disease. *Hum. Mol. Genet.* 14, 2099–2111. doi: 10.1093/hmg/ddi215
- Su, D. M., Zhang, Q., Wang, X., He, P., Zhu, Y. J., Zhao, J., et al. (2009). Two types of human malignant melanoma cell lines revealed by expression patterns of mitochondrial and survival-apoptosis genes: implications for malignant melanoma therapy. *Mol. Cancer Ther.* 8, 1292–1304. doi: 10.1158/1535-7163.mct-08-1030
- Sulzer, D., Alcalay, R. N., Garretti, F., Cote, L., Kanter, E., Agin-Liebes, J., et al. (2017). T cells from patients with Parkinson's disease recognize α -synuclein peptides. *Nature* 546, 656–661. doi: 10.1038/nature22815
- Sun, Y., Sukumaran, P., Schaar, A., and Singh, B. B. (2015). TRPM7 and its role in neurodegenerative diseases. *Channels* 9, 253–261. doi: 10.1080/19336950.2015.1075675
- Tacik, P., Curry, S., Fujioka, S., Strongosky, A., Uitti, R. J., van Gerpen, J. A., et al. (2016). Cancer in Parkinson's disease. *Parkinsonism Relat. Disord.* 31, 28–33. doi: 10.1016/j.parkreldis.2016.06.014
- Tansey, M. G., and Goldberg, M. S. (2010). Neuroinflammation in Parkinson's disease: its role in neuronal death and implications for therapeutic intervention. *Neurobiol. Dis.* 37, 510–518. doi: 10.1016/j.nbd.2009.11.004
- Taya, M., and Hammes, S. R. (2018). Glycoprotein non-metastatic melanoma protein B (GPNMB) and cancer: a novel potential therapeutic target. *Steroids* 133, 102–107. doi: 10.1016/j.steroids.2017.10.013
- Timerman, D., McEnery-Stonelake, M., Joyce, C. J., Nambudiri, V. E., Hodi, F. S., Claus, E. B., et al. (2016). Vitamin D deficiency is associated with a worse prognosis in metastatic melanoma. *Oncotarget* 8, 6873–6882. doi: 10.18632/oncotarget.14316
- Tomiyama, H., Yoshino, H., Ogaki, K., Li, L., Yamashita, C., Li, Y., et al. (2011). PLA2G6 variant in Parkinson's disease. *J. Hum. Genet.* 56, 401–403. doi: 10.1038/jhg.2011.22
- Van Den Eeden, S. K., Tanner, C. M., Bernstein, A. L., Fross, R. D., Leimpe, A., Bloch, D. A., et al. (2003). Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *Am. J. Epidemiol.* 157, 1015–1022. doi: 10.1093/aje/kwg068
- Vasseur, S., Afzal, S., Tardivel-Lacombe, J., Park, D. S., Iovanna, J. L., and Mak, T. W. (2009). DJ-1/PARK7 is an important mediator of hypoxia-induced cellular responses. *Proc. Natl. Acad. Sci. U S A* 106, 1111–1116. doi: 10.1073/pnas.0812745106
- Vermeij, J.-D., Winogrodzka, A., Trip, J., and Weber, W. E. J. (2009). Parkinson's disease, levodopa-use and the risk of melanoma. *Parkinsonism Relat. Disord.* 15, 551–553. doi: 10.1016/j.parkreldis.2009.05.002
- Vivekanantham, S., Shah, S., Dewji, R., Dewji, A., Khatri, C., and Ologunde, R. (2015). Neuroinflammation in Parkinson's disease: role in neurodegeneration and tissue repair. *Int. J. Neurosci.* 125, 717–725. doi: 10.3109/00207454.2014.982795
- Wahabi, K., Perwez, A., and Rizvi, M. A. (2018). Parkin in Parkinson's disease and cancer: a double-edged sword. *Mol. Neurobiol.* 55, 6788–6800. doi: 10.1007/s12035-018-0879-1
- Walter, U., Heilmann, E., Voss, J., Riedel, K., Zhivov, A., Schäd, S. G., et al. (2016). Frequency and profile of Parkinson's disease prodromi in patients with malignant melanoma. *J. Neurol. Neurosurg. Psychiatry* 87, 302–310. doi: 10.1136/jnnp-2014-310239
- Wang, Q., Liu, Y., and Zhou, J. (2015). Neuroinflammation in Parkinson's disease and its potential as therapeutic target. *Transl. Neurodegener.* 4:19. doi: 10.1186/s40035-015-0042-0
- Wang, D., Zhai, J.-X., and Liu, D.-W. (2016). Glutathione S-transferase M1 polymorphisms and Parkinson's disease risk: a meta-analysis. *Neurol. Res.* 38, 144–150. doi: 10.1080/01616412.2015.1126996
- Ward, W. H., Lambrette, F., Goel, N., Yu, J. Q., and Farma, J. M. (2017). "Chapter 6-Clinical presentation and staging of melanoma," in *Cutaneous Melanoma: Etiology and Therapy*, eds W. H. Ward and J. M. Farma (Brisbane, AU: Codon Publications), 79–89.
- Watabe, H., Soma, Y., Kawa, Y., Ito, M., Ooka, S., Ohsumi, K., et al. (2002). Differentiation of murine melanocyte precursors induced by 1,25-dihydroxyvitamin D3 is associated with the stimulation of endothelin B receptor expression. *J. Invest. Dermatol.* 119, 583–589. doi: 10.1046/j.1523-1747.2002.00116.x
- Welinder, C., Jönsson, G. B., Ingvar, C., Lundgren, L., Baldetorp, B., Olsson, H., et al. (2014). Analysis of α -synuclein in malignant melanoma—development of a SRM quantification assay. *PLoS One* 9:e110804. doi: 10.1371/journal.pone.0110804
- Wooten, G. F., Currie, L. J., Bovbjerg, V. E., Lee, J. K., and Patrie, J. (2004). Are men at greater risk for Parkinson's disease than women? *J. Neurol. Neurosurg. Psychiatry* 75, 637–639. doi: 10.1136/jnnp.2003.020982
- Wright Willis, A., Evanoff, B. A., Lian, M., Criswell, S. R., and Racette, B. A. (2010). Geographic and ethnic variation in Parkinson disease: a population-based study of US medicare beneficiaries. *Neuroepidemiology* 34, 143–151. doi: 10.1159/000275491
- Wu, S., Han, J., Song, F., Cho, E., Gao, X., Hunter, D. J., et al. (2015). Caffeine intake, coffee consumption, and risk of cutaneous malignant melanoma. *Epidemiology* 26, 898–908. doi: 10.1097/ede.0000000000000360

- Wulfänger, J., Biehl, K., Tetzner, A., Wild, P., Ikenberg, K., Meyer, S., et al. (2013). Heterogeneous expression and functional relevance of the ubiquitin carboxyl-terminal hydrolase L1 in melanoma. *Int. J. Cancer* 133, 2522–2532. doi: 10.1002/ijc.28278
- Xu, S., and Chan, P. (2015). Interaction between neuromelanin and α -synuclein in Parkinson's disease. *Biomolecules* 5, 1122–1142. doi: 10.3390/biom5021122
- Yamada-Fowler, N., Fredrikson, M., and Söderkvist, P. (2014). Caffeine interaction with glutamate receptor gene GRIN2A: Parkinson's disease in swedish population. *PLoS One* 9:e99294. doi: 10.1371/journal.pone.0099294
- Yeh, N.-C., Tien, K.-J., Yang, C.-M., Wang, J.-J., and Weng, S.-F. (2016). Increased risk of Parkinson's disease in patients with obstructive sleep apnea: a population-based, propensity score-matched, longitudinal follow-up study. *Medicine* 95:e2293. doi: 10.1097/MD.00000000000002293
- Zanetti, R., Loria, D., and Rosso, S. (2006). Melanoma, Parkinson's disease and levodopa: causal or spurious link? A review of the literature. *Melanoma Res.* 16, 201–206. doi: 10.1097/01.cmr.0000215043.61306.d7
- Zecca, L., Fariello, R., Riederer, P., Sulzer, D., Gatti, A., and Tampellini, D. (2002). The absolute concentration of nigral neuromelanin, assayed by a new sensitive method, increases throughout the life and is dramatically decreased in Parkinson's disease. *FEBS Lett.* 510, 216–220. doi: 10.1016/s0014-5793(01)03269-0
- Zecca, L., Tampellini, D., Gerlach, M., Riederer, P., Fariello, R. G., and Sulzer, D. (2001). Substantia nigra neuromelanin: structure, synthesis, and molecular behaviour. *Mol. Pathol.* 54, 414–418.
- Zhang, P., and Liu, B. (2019). Association between Parkinson's disease and risk of cancer: a PRISMA-compliant meta-analysis. *ACS Chem. Neurosci.* 10, 4430–4439. doi: 10.1021/acscchemneuro.9b00498
- Zhang, H.-J., Zhang, J. R., Mao, C. J., Li, K., Wang, F., Chen, J., et al. (2019). Relationship between 25-Hydroxyvitamin D, bone density, and Parkinson's disease symptoms. *Acta Neurol. Scand.* 140, 274–280. doi: 10.1111/ane.13141

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Ye, Wen, Al-Kuwari and Chen. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.