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Genetically Optimizing Parkinson's Medications

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ABSTRACT: The most common Parkinson's disease (PD) medication, L-DOPA, relieves motor symptoms of the disease but with significant side effects. Based on genetic differences, we use statistical tests to study the effectiveness of other Parkinson's medications used to lessen L-DOPA's side effects and improve Parkinson's symptoms. Our analyses suggest that PD patients with the GG genotype at *SNCA* rs356182 experience greater effectiveness across many symptoms when taking Amantadine. Contrarily, those with the AA genotype (versus AG or GG) at the gene locus experience decreased effectiveness across most studied symptoms when taking Rasagiline. Parkinson's patients with the CC genotype at *LRRK2* rs76904798 experience worse results following the administration of Lodosyn than those with the CT/TT genotype at this locus. However, these same CC patients experience better results for most symptoms when taking the medication Stalevo. At the *LRRK2* rs34637584 locus, our study confirms that the A allele is a known Parkinson's risk factor. Despite this, further investigation suggests that among Parkinson's patients, those with the GG genotype generally exhibit more severe symptoms. Ultimately, our research indicates the importance of considering genetic differences when prescribing Parkinson's medications. Despite relatively similar Parkinson's symptoms and shared dopamine deficiency, patients' differing backgrounds render a common medication ineffective.

KEYWORDS: Biomedical and Health Sciences; Genetics and Molecular Biology of Disease; Parkinson's Disease; *SNCA* and *LRRK2* Genes; Levodopa and Related Medications.

■ Introduction

Parkinson's disease (PD), one of the most common neurodegenerative diseases worldwide, is characterized by dopamine deficiency in the motor and cognitive regions of the brain.[1] There is no cure for PD despite its high frequency, especially in the elderly, and its common cause of degeneration of dopamine-producing neurons and the brain's basal ganglia.[2] Levodopa (L-DOPA), the most common current treatment, helps restore some dopamine and improve motor function in Parkinson's patients. The L-DOPA molecule, a precursor to dopamine, must be used rather than dopamine itself because the latter cannot cross the blood-brain barrier. At the same time, the former can enter the brain, where it converts into dopamine.[3] However, while L-DOPA significantly helps patients early on, high doses and ongoing treatment often come with many side effects, including motor fluctuations, orthostatic hypotension, nausea, sleepiness, and, most notably, L-DOPA-induced dyskinesias (involuntary movements), which usually restrict the dosage of L-DOPA.[4] To combat these side effects, patients often take L-DOPA in conjunction with other medications. For example, carbidopa decreases L-DOPA degradation outside the blood-brain barrier, allowing for a lower dosage of L-DOPA to produce better effects.[1]

Previously, we looked at how various genes and possible mutations in them affect the onset and cellular progression of Parkinson's disease.[5] Earlier research suggests that two genes, *SNCA* and *LRRK2*, are significant risk factors for Parkinson's disease. Specifically, *SNCA* contributes to Parkinson's due to its production of the *a*-synuclein protein, which plays a role in the release of neurotransmitters, proper functioning at synapses, and the ability of dopaminergic neurons to alter their connections. Mutated forms of *SNCA* can create defective forms of *a*-synuclein, an occurrence often linked to the formation of the toxic Lewy bodies present in the brains of Parkinson's patients. *a*-synuclein aggregation in Lewy bodies may damage mitochondria in dopamine-producing cells, resulting in the above dopamine deficiency.[5] Regarding *LRRK2*, the most common Parkinson's related mutation is called G2019S. G2019S can cause overactivity of the *LRRK2* (leucine-rich repeat kinase 2) protein which may also lead to mitochondrial damage in dopaminergic neurons.[5] Evidently, the current literature emphasizes the connection between these genes and dopamine deficiency related to Parkinson's. Recent research also investigates the development of new Parkinson's medications based on genetic risk factors.[6] In this paper, we seek to understand whether the genes and their protein products may also interact with existing Parkinson's treatments. Thus, we study how different genotypes in the two genes above create different responses to medications.

The rest of the paper is organized as follows: Section 2 details our statistical testing. Section 3 discusses the relationship between the gene locus *SNCA* rs356182 and the medicines amantadine (Symmetrel) and rasagiline (Azilect). Section 4 focuses on the relationships between the gene locus *LRRK2* rs76904798 and Lodosyn and Stalevo medicines. Section 5 investigates the relationship between *LRRK2* rs34637584 and overall Parkinson's symptoms. Finally, Section 6 concludes the paper.

■ Methods

Data used in the preparation of this article were obtained from the Fox Insight database (https://foxinsight-info.michaeljfox.org/insight/explore/insight.jsp) starting on 6/21/2021. For up-to-date information on the Fox study, visit https://

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insight.jsp. We first utilize mechanisms within the database to evaluate whether there is a connection between a specific symptom and a specific genotype in a cohort of Parkinson's patients taking a particular medication. If an association is found across multiple symptoms, we investigate further. Specifically, we conduct two-sample z-tests of proportions that compare the proportion of PD patients in a general Parkinson's cohort with the specified genotype who do or do not experience the symptom to the same proportion in a cohort of Parkinson's patients taking the medication. The calculation can be understood as follows:

$$Z(p_1, p_2, n_1, n_2) = \frac{\frac{p_1}{n_1} - \frac{p_2}{n_2}}{\sqrt{\frac{p_1\left(1-\frac{p_1}{n_1}\right)}{(n_1)^2} - \frac{p_2\left(1-\frac{p_2}{n_2}\right)}{(n_2)^2}}} \quad (1)$$

where Z is the z-score for the un-pooled 2-sample z-test for proportions, p1 is the number of people in the medicine group with the desired genotype experiencing a particular symptom, p2 is the number of people in the general PD group with the desired genotype experiencing a specific symptom, n1 is the total number of people in the medicine group with the desired genotype, and n2 is the total number of people in the general PD group with the desired genotype. The p-value, the probability of obtaining results as significant or more significant than the ones found in the samples due to chance alone, is calculated from the Z-score using a statistical calculator. If the p-value suggests substantial differences between the two proportions across numerous symptoms, we conclude that the medicine correlates with the difference. Z-scores yielding significant p-values are discussed below.

Results and Discussion

Results are provided for two medications at the *SNCA* rs356182 gene locus, two medications at the *LRRK2* rs76904798 gene locus, and general Parkinson's symptoms at the *LRRK2* rs34637584 gene locus.

SNCA rs356182:

This subsection consists of two parts. The first part discusses relationships between the GG genotype at *SNCA* rs356182 and the medication amantadine. The second part focuses on relationships between the AA genotype at *SNCA* rs356182 and the medication rasagiline.

Association with Amantadine:

Multiple studies have found that the GG genotype at SNCA rs356182 frequently associates with tremor-dominant Parkinson's (in which tremors emerge as the most prevalent symptom), slower motor decline, and less *a*-synuclein production in the brain.[7] Hence, we examine the rs356182 gene locus. The data set we study suggests multiple significant correlations regarding the GG genotype and the medicines amantadine (of the brand Symmetrel) and rasagiline (of the brand Azilect). Amantadine helps decrease dopamine-induced dyskinesias and also reduces tremors. It should be taken on its own to assist with rigidity and tremor or with L-DOPA to reduce L-DOPA's side effects. Amantadine's side effects include dizziness, vivid imagination, and nausea, among others.[8] Starting with ON/OFF periods (which describe alternating periods during which L-DOPA is effective in reducing Parkinson's symptoms and when it is not), the data suggest that amantadine is more effective in decreasing ON/OFF periods in patients with the GG genotype. Specifically, in a 125-person cohort of Parkinson's patients who take amantadine at an alpha level of 0.10, there is statistical evidence that ON/OFF periods depend on *SNCA* rs356182 being AA/AG vs. GG. Upon further examination, 89/103 (86.4%) of cohort members without the GG genotype experience ON/OFF periods, while only 15/22 (68.2%) of cohort members with the genotype GG experience ON/OFF periods. The genotype and symptom are also tested in a general Parkinson's cohort of 1264 people. In this cohort, the association between the genotype and ON/OFF periods yields a non-significant p-value of 0.16, suggesting that genotype-based difference emerges with amantadine. In addition, 842/1050 (80.2%) of cohort members without the genotype experience ON/OFF periods, while 181/214 (84.6%) of cohort members with GG experience ON/OFF periods. For example, a visual representation of these percentages can be seen in Figure 1.

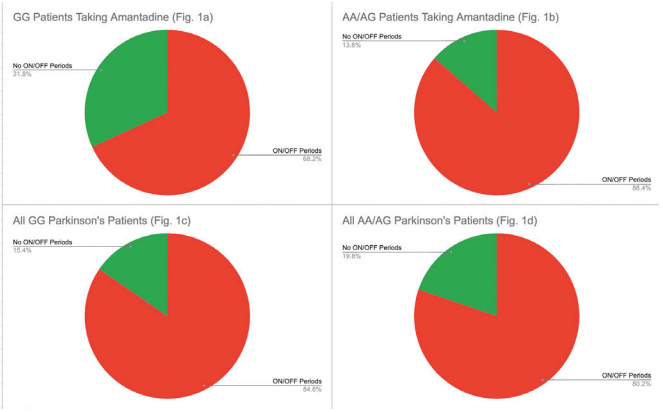

Figure 1: (a) Percentage of PD patients that take amantadine with the GG genotype at *SNCA* rs356182 who experience ON/OFF periods vs. those who do not experience ON/OFF periods. (b) Percentage of PD patients that take amantadine with the AA or AG genotype at *SNCA* rs356182 who experience ON/OFF periods vs. those who do not experience ON/OFF periods. (c) Percentage of all PD patients with the GG genotype at *SNCA* rs356182 who experience ON/OFF periods vs. those who do not experience ON/OFF periods. (d) Percentage of all PD patients with the AA or AG genotype at *SNCA* rs356182 who experience ON/OFF periods vs. those who do not experience ON/OFF periods.

These results imply that the percentage of AA/AG patients who experience ON/OFF periods actually increases with the administration of amantadine. In contrast, ON/OFF periods decrease in those with the GG genotype. A two-sample z-test of proportions using equation (1),

$Z(15{,}181{,}22{,}214) = -1.6025$, p-value = 0.05 (improvement in ON/OFF periods among rs356182 GG genotype when taking amantadine)

suggests a trend that the proportion of GG patients in the amantadine cohort with ON/OFF periods is less than that in the no-amantadine cohort (improvement), unlike the result for the AG/AA genotypes. Similarly, we find statistically significant evidence (p-value = 0.02) that experiencing tremmors

depends on the genotype at rs356182 in a cohort of 696 Parkinson's patients who take amantadine. 39/118 (33.1%) of the GG patients in the group experience tremors that affect daily activity, while 261/578 (45.2%) of AA/AG patients in the group experience tremors that affect daily activity. In contrast, the relationship between tremors and the genotype does not yield significant results in the general Parkinson's cohort of 8539 patients. To further contrast the results of the amantadine cohort, 492/1392 (35.3%) of these general GG patients experience worse than mild tremors, while 2649/7147 (37.1%) of these AG/AA patients experience worse than mild tremors. Yet again, we see a possible increase in tremors for non-GG patients after taking amantadine and the opposite result for GG patients. Evidence of this claim emerges when comparing the non-GG patients in the amantadine and general cohorts: a p-value of 0.000057 < a = 0.05 is calculated from

$Z(261,2649,578,7147) = 3.768$ (worsening in daily activity-affecting tremors among rs356182 AA/AG genotypes when taking amantadine)

which supports an increase in the proportion of those with tremors for non-GG patients following amantadine administration. The experience of excess saliva/drooling brings similar results. With a p-value of 0.05, this third symptom shows dependence on the genotype of rs356182 in a cohort of 709 people that take amantadine. 39/120 (32.5%) of the GG patients who take amantadine experience excess saliva/drooling, and 251/589 (42.6%) of the non-GG patients experience this symptom. On the other hand, with a p-value of 0.15, no significant dependence is found in the general PD cohort of 8555. Furthermore, as with the previous Parkinson's effects, 462/1394 (33.1%) of GG patients experience excess drooling, and 2521/7161 (35.2%) AA/AG patients experience excess drooling. A two-sample z-test of proportions demonstrated by

$Z(251,2521,589,7161) = 3.505$, p-value = 0.003 < a = 0.05 (worsening in excessive saliva/drooling among rs356182 AA/AG genotypes when taking amantadine)

verifies an increase (worsening) in the amantadine cohort of non-GG patients regarding excess saliva/drooling. Next, a statistically significant dependence is found between the rs356182 genotype and chewing/swallowing issues that affect daily activity in a cohort of 709 Parkinson's patients who take amantadine. In comparison to the 6/120 (5.0%) of the GG patients in the cohort who have trouble eating, 65/589 (11.0%) of the AA/AG patients suffer similar challenges. Supporting the rest of the data, the p-value for this dependence in an extensive PD cohort of 8554 equals 0.88, a non-significant result. In this group, 99/1394 (7.1%) of GG Parkinson's patients have trouble chewing/swallowing, while 520/7160 (7.3%) of AA/AG Parkinson's patients have the same issues. Again, statistical evidence seen with

$Z(65,520,589,7160) = 2.84$, p-value = 0.002 < a = 0.05 (worsening in chewing/swallowing issues among rs356182 AA/AG genotypes when taking amantadine)

confirms an increase (worsening) for the AA/AG group with amantadine administration. The equations

$Z(6,155,120,1402) = -2.81$, p-value = 0.003 < a = 0.05 (improvement in bowel incontinence among rs356182 GG genotype when taking amantadine),

$Z(8,151,120,1402) = -1.69$, p-value = 0.045 < a = 0.05 (improvement in unexplained weight changes among rs356182 GG genotype when taking amantadine),

$Z(44,652,120,1402) = -2.14$, p-value = 0.016 < a = 0.05 (improvement in feelings of dizziness/light-headedness among rs356182 GG genotype when taking amantadine), and

$Z(187,1649,599,7203) = 4.25$, p-value = 0.00001 < a = 0.05 (worsening in excessive sweating among rs356182 AA/AG genotypes when taking amantadine)

offer parallel results for bowel incontinence, unexplained weight changes, dizziness/light-headedness, and excessive sweating, respectively.

In conclusion, numerous common Parkinson's symptoms (specifically, those that are significantly different between the two genotypes in the medication cohort) show improvement upon amantadine administration in patients with the GG genotype at *SNCA* rs356182 but not those with the AG/AA genotype (Table 1).

Table 1: *Amantadine vs. SNCA rs356182.* Display of whether administration of amantadine improves the specified symptom for PD patients with the GG genotype (column 1) or AG or AA genotype (column 2) at *SNCA* rs356182. √ indicates better or non-worsening results, and X indicates worse or non-improving results.

Symptom	Genotype	
	GG	AG/AA
ON/OFF periods	√	X
Tremors	√	X
Excess saliva/drooling	√	X
Trouble chewing/swallowing	√	X
Bowel incontinence	√	X
Unexplained weight changes	√	X
Dizziness/light-headedness	√	X
Excessive sweating	√	X

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Association with Rasagiline:

Next, we look at this same gene locus regarding the medicine rasagiline (of the brand Azilect).[9] Rasagiline is a MAO-B (monoamine oxidase-B) inhibitor, an effective molecule for Parkinson's because MAO-B assists in dopamine decomposition, so rasagiline can decrease further dopamine loss.[10] Most of the statistically significant dependences between the rs356182 genotypes and Parkinson's symptoms in rasagiline-taking Parkinson's cohorts involve the AA genotype. The reliance of daily activity-affecting tremors on rs356182 being AA produces a significant p-value of 0.04 among patients taking Azilect. In the cohort of 1638 Parkinson's patients taking this medicine, 204/560 (36.4%) of those with the AA genotype experience worse than mild tremors, while 336/1078 (31.2%) of those with the AG/GG genotype experience such tremors. No such significance occurs in an 8553-person cohort of general Parkinson's patients. In this cohort, 1140/3030 (37.6%) of patients with the AA genotype live with tremors that affect daily activity, while 2004/5523 (36.3%) of patients with the other two genotypes experience these tremors. As an example, these percentages can be seen in the following Figure (2):

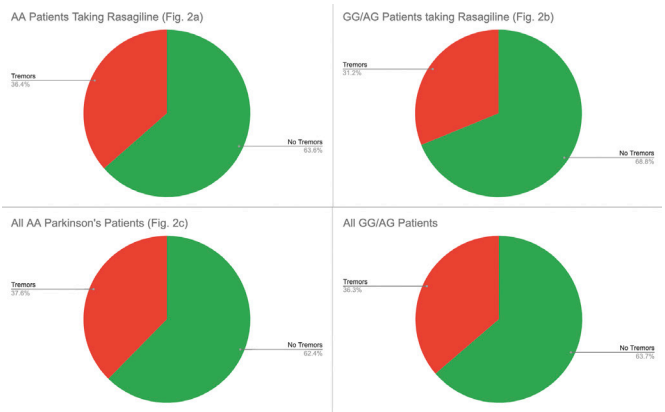

Figure 2: (a) Percentage of PD patients that take rasagiline with the AA genotype at SNCA rs356182 who experience tremors vs. those who do not experience tremors. (b) Percentage of PD patients that take rasagiline with the GG or AG genotype at *SNCA* rs356182 who experience tremors vs. those who do not experience tremors. (c) Percentage of all PD patients with the AA genotype at *SNCA* rs356182 who experience tremors vs. those who do not experience tremors. (d) Percentage of all PD patients with the GG or AG genotype at *SNCA* rs356182 who experience tremors vs. those who do not experience tremors.

While both percentages see a decrease in the rasagiline cohort, only the non-AA group sees a statistically significant improvement upon rasagiline administration by

$Z(336,2004,1078,5523) = -3.30$, p-value = 0.0005 < a = 0.05 (improvement in daily activity-affecting tremors among rs356182 AG/GG genotypes when taking rasagiline).

The relationship between rs356182 being AA vs. AG/GG and the experiencing of excessive saliva/drooling in the past month yields a statistically significant association in both the Parkinson's rasagiline cohort, with a p-value of 0.01 and the general Parkinson's cohort, with a p-value of 0.09 (at a = 0.10), but clearly less so in the latter. In the rasagiline group, 170/566 (30%) of AA patients experience excessive saliva, while 264/1093 (24.2%) non-AA patients suffer similarly. In the more extensive Parkinson's cohort, 914/3046 (30.0%) of the AA patients suffer from this drooling, while 1571/5561 (28.3%) of the AG/GG patients experience the same. This result, also represented by

$Z(264,1571,1093,5561) = -2.87$, p-value = 0.0021 < a = 0.05 (improvement in excess saliva/drooling among rs356182 AG/GG genotypes when taking rasagiline)

backs up the decreased effectiveness of rasagiline for excess saliva/drooling in rs356182 AA patients because, again, only the non-AA group sees significant improvement. For yet another common symptom of Parkinson's, frequent falls, a significant association with rs356182 is observed in the rasagiline cohort with a p-value of 0.04. Among those taking rasagiline, 95/566 (16.8%) of the patients with the AA genotype suffer from falls, while 141/1091 (12.9%) of patients in this group without the AA genotype experience this symptom. The PD cohort produced a p-value of 0.12: 602/3046 (19.8%) of the patients with the AA genotype fell recently, while 1021/5559 (18.4%) of the patients with the AG/GG genotype fell recently. As with the tremors, an improvement was seen in the rasagiline cohort for both the AG/GG and AA genotypes; however, a more significant improvement, represented by the p-value calculations,

$Z(95,602,566,3046) = -1.72$, p-value = 0.042 < a = 0.05 (improvement in falling among rs356182AA genotype when taking rasagiline)

$Z(141,1021,1091,5559) = -4.77$, p-value < 0.00001 < a = 0.05 (improvement in falling among rs356182 AG/GG genotypes when taking rasagiline)

among the non-AA groups suggests potentially greater effectiveness for falling for non-AA patients. The symptom of seeing/hearing things offers parallel results, with an evident decrease (improvement) following rasagiline administration for those without the AA genotype and vice versa for those with the AA genotype. Another symptom that we study, vomiting and feelings of nausea, actually produces unexpected results. The rasagiline cohort yields a p-value of 0.04 regarding the association between the rs356182 genotype and experiencing the symptom. In this group, 93/569 (16.3%) of the AA patients feel such nausea, while 225/1093 (20.6%) of the non-AA patients experience this discomfort. In the general Parkinson's group, no association is found between genotype and nausea, with a p-value of 0.80, but 668/3046 (21.9%) of the AA patients experience nausea and vomiting. In comparison, 1234/5560 (22.2%) of the GG/AG experience this symptom. Interestingly, nausea is a common side effect of rasagiline.[9] However, the AA genotype patients show a significant decrease by

$Z(93,668,569,3046) = -3.24$, p-value = 0.0006 < a = 0.05 (improvement in nausea/vomiting among rs356182 AA genotype when taking rasagiline)

in nausea/vomiting in the rasagiline cohort, compared to the general PD cohort. More research would need to be done to understand this result: AA genotypes seem less affected by a common side effect of rasagiline, even though rasagiline seems more ineffective for this group in numerous other aspects.

The associations between rs356182 and the discussed Parkinson's symptoms for patients taking rasagiline vary across symptoms. Generally, rasagiline shows more effectiveness for GG/AG genotypes, but exceptions are found (Table 2).

Table 2: *Rasagiline vs. SNCA* rs356182. Display of whether administration of rasagiline improves the specified symptom for PD patients with the AA genotype (column 1) or GG or AG genotype (column 2) at *SNCA* rs356182. √ indicates better or non-worsening results, and X indicates worse or non-improving results.

Symptom	Genotype	
	AA	AG/GG
Tremors	X	√
Excess saliva/drooling	X	√
Falls	X	√
Seeing/hearing things	X	√
Nausea/vomiting	√	X

This result indicates that an optimal medication should consider a patient's genotype and symptoms.

LRRK2 rs76904798:

This next section covers the rs76904798 locus on the *LRRK2* gene. In the first part, we look at the CC genotype at this locus's relationship with the carbidopa-based medication Lodosyn. In the second part, the CC genotype is studied with regard to the medication Stalevo.

Association with Lodosyn:

The most prominent results regarding *LRRK2* rs76904798 emerge in carbidopa-based cohorts, specifically of the Lodosyn and Stalevo brands. As described earlier, carbidopa inhibits L-DOPA decomposition, and Stalevo specifically consists of a mixture of carbidopa, levodopa, and entacapone. Entacapone additionally opposes COMT (catechol-O-methyltransferase) enzymes, which like MAO-B, break down dopamine.[11] Lodosyn mainly consists of carbidopa.[12] In Parkinson's patients who take Lodosyn, a statistically significant result (only at $a = 0.10$, as p-value = 0.07) suggests that experiencing daily activity-impairing tremors depends on the genotype of *LRRK2* rs76904798 - whether it be CC or CT/TT. 36/83 (43.4%) of the CC patients in the Lodosyn cohort experience worse than mild tremors compared to 8/34 (23.5%) of the CT/TT patients in the same cohort. No dependence occurs in the general Parkinson's cohort, but 2229/6098 (36.6%) of CC patients in this group experience such tremors, and 900/2398 (37.5%) of CT/TT patients in the general experience such tremors. These percentages can be seen in the example Figure (3) that follows.

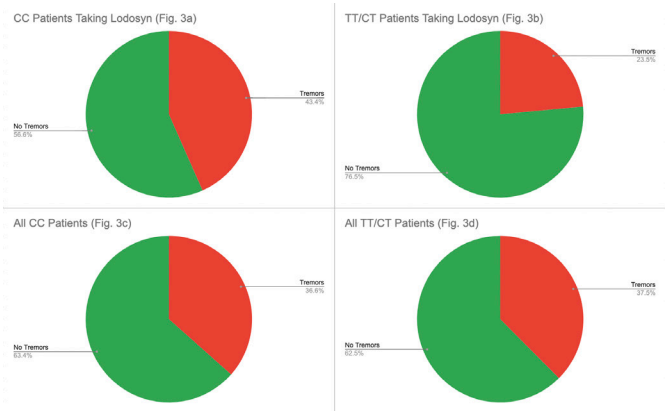

Figure 3: (a) Percentage of PD patients that take Lodosyn with the CC genotype at *LRRK2* rs76904798 who experience tremors vs. those who do not experience tremors. (b) Percentage of PD patients that take Lodosyn with the TT or CT genotype at *LRRK2* rs76904798 who experience tremors vs. those who do not experience tremors. (c) Percentage of all PD patients with the CC genotype at *LRRK2* rs76904798 who experience tremors vs. those who do not experience tremors. (d) Percentage of all PD patients with the TT or CT genotype at *LRRK2* rs76904798 who experience tremors vs. those who do not experience tremors.

While only at a significance level of 0.10, these two-sample z-tests of

$Z(36,2229,83,6098) = 1.25$, p-value = 0.10 (worsening in daily activity-affecting tremors among rs76904798 CC genotype when taking Lodosyn)

$Z(8,900,34,2398) = -1.91$, p-value = 0.0283 $< a = 0.05$ (improvement in daily activity-affecting tremors among rs76904798 CT/TT genotypes when taking Lodosyn)

suggest a trend of worsening tremors among those taking Lodosyn for CC patients and a significant improvement among those taking Lodosyn for CT/TT patients. Trouble performing hobbies also depends on rs76904798 being CC vs. CT/TT in the cohort of PD patients taking Lodosyn. 36/83 (43.4%) of CC patients taking Lodosyn have trouble performing their hobbies, while 7/34 (20.6%) patients without the CC genotype take Lodosyn and experience challenges with their hobbies. These issues do not depend on the rs76904798 genotype in the general PD cohort, where 1724/6098 (28.3%) of CC patients have issues engaging in their hobbies, and 669/2398 (27.9%) of CT/TT patients experience similar issues. Furthermore, a statistically significant worsening in hobby performance is found in the Lodosyn cohort compared to the general PD cohort for CC patients by

$Z(36,1724,83,6098)=2.76$, p-value = 0.0029 $< a = 0.05$ (worsening in issues performing hobbies among rs76904798 CC genotype when taking Lodosyn)

and no such correlation is found among the CT/TT patients, supporting decreased effectiveness for movement-related issues with Lodosyn for CC Parkinson's patients. Next, recent experience of vomiting/nausea also depends on the genotype of rs76904798 in the cohort of PD patients taking Lodosyn but not in the cohort of general PD patients. In the former

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group, 36/83 (43.4%) of CC patients experience this nausea, while 8/34 (23.5%) of CT/TT patients feel the same. In the latter general group, 1344/6132 (21.9%) of CC patients have vomiting/nausea, and 548/2417 (22.7%) of non-CC patients experience these issues. The increase in the percentage (worsening) of CC patients who suffer these gastrointestinal issues between the general and Lodosyn cohorts is significant, as seen with

$Z(36,1344,83,6132) = 3.93$, p-value = 0.00004 < a = 0.05,

again supporting decreased Lodosyn benefits for the CC group. Data from patients who feel a loss of interest due to Parkinson's agrees with the decreased effectiveness of Lodosyn for CC patients by

$Z(45,2306,83,6132) = 3.02$, p-value = 0.0013 < a = 0.05 (worsening in loss of interest among rs76904798 CC genotype when taking Lodosyn).

Talking and moving about in sleeping comprises another Parkinson's symptom that depends on rs76904798's status of CC vs. CT/TT in Parkinson's patients taking Lodosyn. 28/83 (33.7%) of CC patients taking Lodosyn have recently talked/moved about in their sleep, while 21/34 (61.8%) of CT/TT patients in the medicine cohort perform such actions. The sleep movement does not depend on the rs76904798 genotype among general Parkinson's patients - a cohort in which 1965/6132 (32.0%) of CC patients talk/move about in their sleep while 778/2416 (32.2%) of CT/TT patients do the same. These preliminary results are interesting because they suggest decreased effectiveness for dealing with sleep issues among the CT/TT patients with the administration of Lodosyn, unlike the results seen with tremors, challenges with hobbies, and nausea. The two-sample z test of proportions

$Z(21,778,34,2416) = 3.52$, p-value = 0.0002 < a = 0.05 (worsening in talking/moving about in sleep among rs76904798 CT/TT genotype when taking Lodosyn)

provides statistical evidence that, in fact, the Lodosyn cohort for CT/TT patients has a higher proportion of those who experience talking/moving about in sleep than the general PD cohort. Given that hallucinations and confusion are side effects of Lodosyn, this result could be similar to what was seen between nausea and rasagiline. Studying patients who experience swelling of the legs yields similarly unexpected results with

$Z(10,1150,83,6132) = -1.86$, p-value = 0.0316 < a =0.05 (improvement in swelling of the legs among rs76904798 CC genotype when taking Lodosyn),

with more improvement for CC patients. Though Lodosyn seems less effective for PD patients with the CC genotype at rs76904798, statistical evidence shows that certain side effects may also be less harmful on this genotype.

Ultimately, the overall results between the *LRRK2* rs76904798 genotype and the impact of Lodosyn on various PD symptoms suggest that Lodosyn usually provides more beneficial effects for Parkinson's patients with the CT/TT genotype at rs76904798. This is consistent with the fact that the T allele is more common in Parkinson's patients. However, suppose sleep issues or swelling are prevalent in a patient. In that case, Lodosyn may not be beneficial for those with the CT/TT genotype, as a significant proportion of PD patients with these two genotypes experience these symptoms with the administration of Lodosyn (Table 3).

Table 3: Lodosyn vs. *LRRK2* rs76904798. Display whether administration of Lodosyn improves the specified symptom for PD patients with the CC genotype (column 1) or CT or TT genotype (column 2) at LRRK2 rs76904798. √ Indicates better or non-worsening results, and X indicates worse or non-improving results.

Symptom	Genotype	
	CC	CT/TT
Tremors	X	√
Challenged hobbies	X	√
Nausea/vomiting	X	√
Loss of interest	X	√
Talking/moving about in sleep	√	X
Swelling of the legs	√	X

Association with Stalevo:

Specific PD symptoms also depend on the genotype of rs76904798 in a cohort of PD patients taking Stalevo. At a significance level of 0.10, there is statistically significant evidence that experiencing recent bowel incontinence depends on rs76904798 being CC vs. CT/TT among PD patients taking Stalevo. In this Stalevo cohort, 9/125 (7.2%) of patients with the CC genotype experience bowel incontinence, while 10/59 (16.9%) patients with the CT/TT genotype experience the same. This symptom does not depend on the rs76904798 genotype in the general PD cohort, which has 732/6132 (11.9%) of the CC patients experiencing bowel incontinence and 272/2416 (11.3%) of the CT/TT patients experiencing recent bowel incontinence, suggesting a decreased effectiveness with regards to bowel incontinence in non-CC patients. A visual example of these percentages is modeled in the following figure (4).

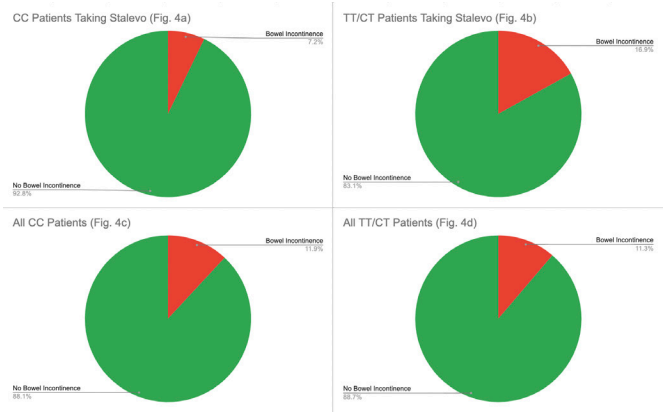

Figure 4: (a) Percentage of PD patients that take Stalevo with the CC genotype at LRRK2 rs76904798 who experience bowel incontinence vs. those who do not experience bowel incontinence. (b) Percentage of PD patients that take Stalevo with the TT or CT genotype at LRRK2 rs76904798 who experience bowel incontinence vs. those who do not experience bowel incontinence. (c) Percentage of all PD patients with the CC genotype at LRRK2 rs76904798 who experience bowel incontinence vs. those who do not experience bowel incontinence. (d) Percentage of all PD patients with the TT or CT genotype at LRRK2 rs76904798 who experience bowel incontinence vs. those who do not experience bowel incontinence.

In fact, a significant improvement in bowel incontinence is found by

$Z(9{,}732{,}125{,}6132) = -2.02$, p-value = 0.0218 < a = 0.05 (improvement in bowel incontinence among rs76904798 CC genotype when taking Stalevo)

only for CC patients taking Stalevo. Feeling unexplained pains in the past month also depends on the rs76904798 genotype in PD patients taking Stalevo. 46/125 (36.8%) of the CC patients taking Stalevo recently felt unexplained pains, while 31/59 (52.5%) of the CT/TT patients experienced similar sensations. In the general PD cohort, 2373/6132 (38.7%) of the CC patients feel these pains, and 888/2416 (36.8%) of the CT/TT patients have such pains. Comparing the proportions for the CT/TT patients in the two cohorts by the equation

$Z(31{,}888{,}59{,}2416) = 2.40$, p-value = 0.0082 < a = 0.05 (worsening of unexplained pains among rs76904798 CT/TT genotype when taking Stalevo)

provides evidence that there is an increase in unexplained pains among those CT/TT patients taking Stalevo, agreeing with the better effectiveness of Stalevo for CC patients. Certain patients with Parkinson's also have trouble remembering facts or events. For example, with a longer progression of the disease, Parkinson's disease dementia may arise.[13] This deteriorating memory is significantly associated with the status of CC vs. CT/TT in the cohort of Stalevo-taking PD patients. 58/125 (46.4%) of the CC patients taking Stalevo report impaired memory. In comparison, 36/59 (61.0%) of the non-CC patients report the same. In the general PD cohort, no association is found between the genotype at rs76904798 and forgetfulness, as 3049/6132 (49.7%) of CC patients have trouble remembering things, and 1187/2416 (49.1%) of the CT/TT patients have issues with remembering. This result, when plugged into

$Z(36{,}1187{,}59{,}2416) = 1.85$, p-value = 0.0323 < a = 0.05 (worsening of trouble remembering things in the past month among rs76904798 CT/TT genotypes when taking Stalevo)

also significantly demonstrates that the proportion of CT/TT patients with trouble remembering things increases in the cohort taking Stalevo compared to the general PD cohort. The last symptom that will be considered regarding rs76904798 involves double vision. Only at a = 0.10 there is statistically significant evidence that the experiencing (or not) of double vision depends on rs76904798 being CC vs. CT/TT among Parkinson's patients taking Stalevo. 32/125 (25.6%) of CC patients taking Stalevo experience double vision, while 8/59 (13.6%) of CT/TT patients taking Stalevo experience the same. In the general Parkinson's cohort, 995/6132 (16.2%) of CC patients have double vision, while 362/2416 (15.0%) of CT/TT patients have similar symptoms. In this case, much like what we saw between sleep issues, rs76904798, and Lodosyn, the symptom of double vision actually significantly worsens with Stalevo administration among the CC patients, as seen with

$Z(32{,}995{,}125{,}6132) = 2.38$, p-value = 0.0086 < a = 0.05 (worsening of double vision among rs76904798 CC genotype when taking Stalevo),

suggesting the importance of observing symptoms and not only genotype when determining drug effectiveness for each patient.

As with the previous genotype-medication relationships, for numerous symptoms, Stalevo appears more effective for the CC genotype at rs76904798 with few exceptions (Table 4).

Table 4: *Stalevo vs. LRRK2* rs76904798. Display of whether administration of Stalevo improves the specified symptom for PD patients with the CC genotype (column 1) or CT or TT genotype (column 2) at *LRRK2* rs76904798. √ Indicates better or non-worsening results, and X indicates worse or non-improving results.

Symptom	Genotype	
	CC	CT/TT
Bowel incontinence	√	X
Unexplained pains	√	X
Trouble remembering	√	X
Double vision	X	√

LRRK2 rs34637584:

The rs34637584 locus on *LRRK2* is the final one studied. In this case, we find that PD patients with the GG genotype at rs34637584 exhibit more severe symptoms regardless of medication. Specifically, 24 symptoms in the study support the correlation between GG genotype and increased severity. However, research has shown that the A allele is actually the one associated with Parkinson's disease.[14] Further examination into the data set, in which all AA people in the study have Parkinson's, confirms the same. While the A allele is a known risk factor for Parkinson's, more information would be needed to determine why the symptoms seem more prevalent in patients who do carry the GG genotype and to find new approaches to treatment that leverage this knowledge.

■ Conclusion

In determining our conclusions, we must first state the study's limitations. One data set is used throughout the study. Numerous data sets with even more people should be used for more conclusive results. Furthermore, in checking if the difference in the percentage of a certain genotype with a specific symptom is statistically significant between the general PD cohort and the cohort taking the medication, a two-sample z-test of proportions is used. Technically, this test requires two independent

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populations. In our study, the medicine cohort is a subset of the general Parkinson's cohort. However, since the proportion of the medicine cohort that also exists in the general cohort is relatively small, we assume independent populations.

With these limitations in mind, we would now like to summarize our findings. For Parkinson's patients taking amantadine (Symmetrel), we find that patients with the GG genotype at *SNCA* rs356182 see better results for numerous symptoms when taking the medication, in contrast to those with the AA or AG genotype. Next, for Parkinson's patients taking rasagiline (Azilect), it appears that those with the GG or AG genotype at this locus experience better results for multiple symptoms when taking the medication. On the other hand, Parkinson's patients with the CC genotype at LRRK2 rs76904798 appear to have poorer results from taking Lodosyn than their counterparts with the CT/TT genotypes. However, the CC group has better results with Stalevo. Through these findings, we see the importance of customizing medication based on a patient's genotype. For some genotypes, it appears that even counterproductive effects emerge after taking certain medications. At the same time, symptoms should also be thoroughly considered in medication prescriptions because the genotype-responsiveness relationships are symptom specific.

Furthermore, due to the cost and challenge of genetic testing, such customizations may be impractical, so external methods of identifying genotypes should be sought. Regarding the last gene locus, given the statistical significance of the A allele in Parkinson's, the locus may be a good candidate for gene editing. Using tools such as CRISPR gene-editing technology, it would be worth considering if an alteration of the A allele could help prevent some Parkinson's or if an alteration of the G allele could reduce specific Parkinson's symptoms.

In summary, this research has demonstrated the importance of considering genotypes for understanding the causes and onset of Parkinson's disease and choosing the most optimal medication. Despite the common features of Parkinson's disease that make a single diagnosis possible, the reasons behind dopamine deficiency and the different ways that symptoms emerge emphasize that we should be seeking thousands of cures in seeking a cure for Parkinson's.[15]

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