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REVIEW ARTICLE

Linking autism spectrum disorders and parkinsonism: clinical and genetic association

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Abstract

Background: Autism spectrum disorders (ASD) comprise many complex and clinically distinct neurodevelopmental conditions, with increasing evidence linking them to parkinsonism. **Methods**: We searched Medline and Embase from inception to 21 March 2022 and reviewed the bibliographies of relevant articles. Studies were screened and reviewed comprehensively by two independent authors. **Results**: Of 863 references from our search, we included eight clinical studies, nine genetic studies, and five case reports. Regardless of age group, Parkinson's disease (PD) and parkinsonian syndromes were more frequently observed in patients with ASD, though the evidence for increased rates of parkinsonism is less clear for children and adolescents. Parkinsonian features and hypokinetic behavior were common in Rett syndrome, with prevalence estimates ranging from 40% to 80%. Frequently observed parkinsonian features include bradykinesia, rigidity, hypomimia, and gait freezing. PD gene *PARK2* copy number variations appear more frequently in ASD cases than controls. Evidence suggests that *RIT2* and *CD157/BST1* are implicated in ASD and PD, while the evidence for other PD-related genes (*DRD2*, *GPCR37*, the *SLC* gene family, and *SMPD1*) is less clear. Rare mutations, such as *ATP13A2*, *CLN3*, and *WDR45*, could result in autistic behavior and concomitant parkinsonism. **Conclusion**: The prevalence of parkinsonism in ASD is substantially greater than in the general population or matched controls. Various PD-associated gene loci, especially *PARK2*, could confer susceptibility to ASD as well. Important future directions include conducting prospective cohort studies to understand how parkinsonian symptoms may progress, genetic studies to reveal relevant gene loci, and pathophysiologic studies to identify potential therapeutic targets.

Introduction

Autism spectrum disorders (ASDs) comprise a multitude of complex and clinically distinct neurodevelopmental conditions. These conditions are typically diagnosed in childhood and persist for life in most patients. They are characterized by difficulties with communication and social interactions, and patients also frequently demonstrate repetitive movements and behaviors. ASDs are increasingly common, and recent estimates in 2018 in the United States suggest one in 44 children to be affected by an ASD.[1]

With the steadily rising prevalence estimates of ASD, the number of adults with ASD will increase concordantly. Recent literature has already indicated the increased vulnerability, relative to the general population, to medical and mental conditions experienced by adults with ASD.[2,3] With more patients on the autistic spectrum progressing in adulthood and even older adulthood (i.e., greater than 65 years of age), the associated risk of ASD patients getting age-dependent neurodegenerative disorders has attracted increasing attention.

A recent study suggested that middle-aged and older autistic adults with no intellectual disabilities reported a higher prevalence of parkinsonism (bradykinesia, poor balance, etc.) compared with the general population,[3] supporting other reports of parkinsonism in patients with ASD.[4–6] The rates of parkinsonism remain unexpectedly high among ASD patients, even after excluding those (both currently and previously) on atypical antipsychotics.[6]

There is also suggestion of genetic overlap between Parkinson's disease (PD) and ASD, where certain genes associated with PD were found to be implicated in ASD.[7] It would be interesting to determine if pathogenic gene mutations responsible for PD are also found in patients with ASD. There is also biological plausibility as both conditions may share similar pathophysiologic mechanisms. Both animal and human studies have demonstrated dopaminergic dysregulation in ASD, which is central to the pathogenesis of PD,[8–10] Moreover, these studies have identified dopamine receptors to be potential drug targets, though more research must be done to confirm this hypothesis.[8]

Despite reports linking ASD with parkinsonian-like features, there has not been a systematic review of the clinical, genetic, and pathophysiologic data on the association between the two conditions. To address current gaps in knowledge, we conducted a systematic review to comprehensively consider the current evidence linking parkinsonism with ASD. In this article, the term "PD" refers the specific diagnosis of PD, while "parkinsonism" and "parkinsonian" features refer to the extrapyramidal signs that may be present in hypokinetic (such as in PD) and hyperkinetic (such as in Huntington's disease) disorders.

Methods

Search strategy

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[11] this systematic review summarizes the current evidence on the associations between ASD and parkinsonism. We registered this study on PROSPERO at CRD42022320765 and searched Medline and Embase on 21 March 2022 for relevant articles. In Medline, we utilized the following search strategy: (*Parkinson*.ti,ab. OR exp "Parkinsonian Disorders"/) AND (Autis*.ti,ab. OR exp "Autism Spectrum Disorder"/)*. Furthermore, the bibliographies of related reviews and meta-analyses were screened to ensure a comprehensive search.

Study selection

Two reviewers (ASM and DWJW) screened the title and abstract of each reference in an independent manner, before retrieving the full texts for further review. Any disputes were referred to a third author for resolution (FST). We included primary research articles reporting parkinsonian features in ASD and genetic associations, as well as case studies highlighting patients presenting with ASD and parkinsonism. Reviews, meta-analyses, editorials, commentaries, conference abstracts, non-human studies (animal and in vitro studies), and articles not published in English were excluded.

Data extraction

Two blinded reviewers (ASM and DWJW) extracted the following data items for clinical studies: first author and year of publication, study design, population studied, sample size, method of ASD diagnosis and parkinsonism assessment (based on the cardinal features of rigidity, bradykinesia, resting tremor, and postural instability), as well as baseline patient demographics (e.g., age and sex). For gene studies, we further extracted the nationality and ancestry of included patients, method of gene sequencing and analysis, as well as the genes studied. For case studies, we retrieved information for the following fields: patient demographics (age, gender, and ethnicity), final diagnosis, family history, associated genetic mutations, features of ASD as well as parkinsonism, other reported problems, and attempted treatments. Unless otherwise stated, the data reported were presented as mean ± standard deviation for continuous outcomes, and percentage (events/sample size).

Quality assessment

For clinical studies, we employed the Joanna Briggs Institute (JBI)'s Critical Appraisal Tools for quality assessment. The cross-sectional studies were evaluated using the Checklist for Prevalence Studies (maximum score of 9), case–control studies using the Checklist for Case–Control Studies (maximum score of 10), case series using the Checklist for Case Series (maximum score of 10), and lastly case reports using the Checklist for Case Reports (maximum score of 8). The quality ratings were reported as scores out of the maximum score attainable for each study design. Two reviewers (ASM and DWJW) assessed the quality of each study independently, and any unresolved conflicts were directed to a third reviewer (FST). All appropriate studies were included, irrespective of quality ratings, as this is an under-researched topic.

Results

Summary of included articles

Following the search, 863 references with 29 duplicates were exported to Zotero. We removed the duplicates and

screened the remaining 834 references. The full texts of 31 articles were retrieved, but we were unable to obtain the full texts of another eight references, as they were either conference abstracts or were not published in English. After a review of the full texts, 22 articles were included in the final review. The PRISMA flow diagram can be found in Supplementary Figure S1. Of the included studies, eight were clinical studies involving 6894 patients,[2–6,12–14] nine were genetic studies of 6975 subjects,[15–23] and five were case reports of patients presenting with both ASD and parkinsonism features.[24–28] A summary of the key ideas presented in this review can be found in Fig. 1.

Of the clinical studies, five were descriptive cross-sectional studies[4,6,12–14] and three were case–control studies.[2,3,5] Three studies scored the maximum score for the quality assessment,[2–4] while four cross-sectional studies scored 8 out of 9 points due to their small sample sizes (<100 participants),[6,12–14] and one case–control study scored 8 out of 10 points as confounding factors were not identified and controlled for.[5]

Among the genetic studies, five studied single genes,[16–19,21] two studied the whole genome,[22,23] one studied the whole exome, one used a mix of whole-exome sequencing (WES), next-generation sequencing (NGS) panel, and targeted single-gene testing.[20] Five studies employed a case–control study design,[16,18,21–23] while the remaining employed either a cross-sectional[17,19] or a case series study design.[15,20]

Five genetic studies involved only Asian populations,[15,18,20–22] except for three which included only Caucasian populations[16,17,23] and one study which recruited a mix of Asian and Caucasian patients.[19] Most studies scored the maximum number of points, except for three studies which had a small sample size,[19] lack of case–control matching,[16,22] or identification and adjustments for confounders.[16] All case reports scored the maximum number of points for quality assessment.

Clinical Studies

Autism and related conditions

This systematic review included clinical studies characterizing features of parkinsonism in ASD, as well as potential risk factors. We present the study characteristics, as well as their quality ratings, in Table 1 and their key findings in Table 2. Parkinsonism is more prevalent in adult patients with ASD when compared with non-ASD controls, irrespective of age group.[2,3] Among younger adults (mean age 29.0 ± 12.2 years), PD were significantly more common at 0.93% (14/1507), compared with 0.03% (5/15,070) in controls, with an odds ratio (OR) of 32.73 (95% CI 7.76–137.96, $P < 0.001$).[2] Similarly, older adults (ages ≥65 years) with ASD were also more prone to developing PD (adjusted OR [aOR] 6.1, 95% CI 5.3–7.0).[3] Females, however, had higher odds of PD (aOR 8.2, 95% CI 6.2–10.7) relative to males (aOR 5.4, 95% CI 4.6–6.4).[3]

Parkinsonian features in ASD adults were common.[4,6] Starkstein et al[6] similarly found a high frequency of parkinsonism in adults with autism (32% [12/37] of the whole sample), and after excluding those taking atypical

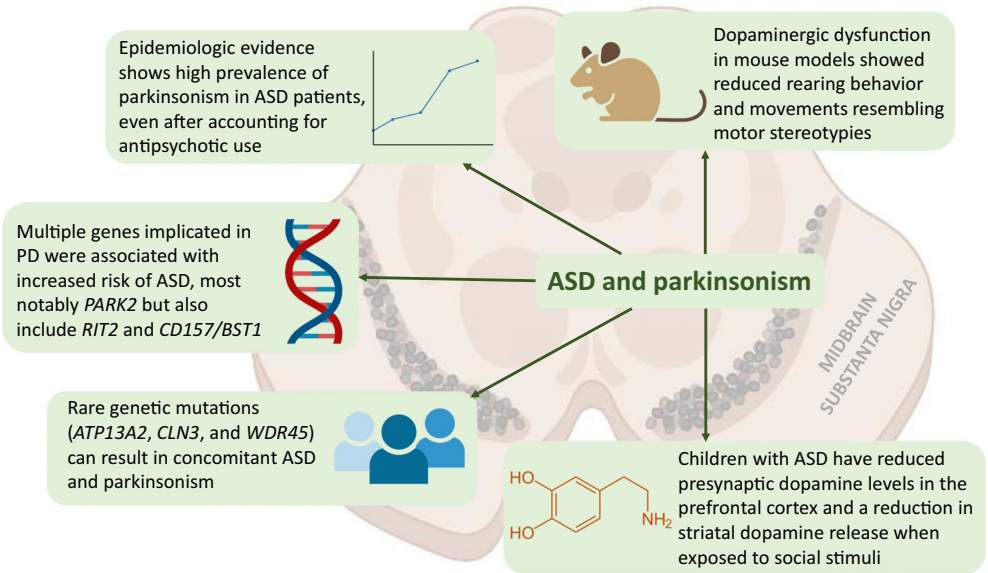

Figure 1. Central illustration.

Table 1. Clinical studies on parkinsonism in autism spectrum disorders.

Study	Design	Population	Sample size	Criteria for ASD diagnosis	Method of parkinsonism assessment	Age, years	Female, N (%)	Quality[a]
Croen et al, 2015[b]	Case–control	Adults with ASD	1507/15,070	ICD-9 codes in the electronic medical record system of Kaiser Permanente in Northern California		29 + 12.2/ 29.4 + 12.1	405 (26.9%)/4050 (26.9%)	10/10
FitzGerald et al, 1990	Cross-sectional	Rett syndrome	32	Motor-behavioral assessment scale and assessment of ≥2 videotapes	Assessment of ≥1 videotape over 2-year follow-up	Range 30 months to 28 years	32 (100%)	8/9
Geurts et al, 2022	Cross-sectional	ASD adults without suspected intellectual disability	Netherlands sample: 296 US sample: 209	DSM-4 or DSM-5	Parkinsonism Screening Questionnaire (parkinsonism defined as ≥7)	Netherlands sample: 58.4 + 5.9 US sample: 59.35 + 7.15	Netherlands sample: 113 (38%) US sample: 109 (52%)	9/9
Hand et al, 2020[b]	Case–control	Older adults (ages ≥65 years) with ASD	4685/46,850	ICD-10 codes from Medicare Standard Analytic Files		65–69 years 2,442 (52.1%)/ 24,420 (52.1%) 70–74 years 1190 (25.4%)/11,900 (25.4%) ≥75 years 1053 (22.5%)/10,530 (22.5%)	1510 (32.2%)/15,100 (32.2%)	10/10
Humphreys and Barrowman, 2016	Cross-sectional	Rett syndrome	51	Standardized historical questionnaire and neurologic examination	Rett Syndrome Rigidity Distribution score[c]	Range 2 years 5 months to 54 years	51 (100%)	8/9
Mostert-Kerckhoffs et al, 2020[b]	Case–control	Children and adolescents with ASD	6–12 years: 22/22 13–26 years: 23/26	ADI-R and ADOS	UPDRS and mechanical assessment	6–12 years: 10.4 + 1.7/ 10.3 + 1.8 13–26 years: 18.7 + 4.6/ 20.2 + 4.1	6–12 years: 5 (22.7%)/5 (22.7%) 13–26 years: 6 (26.1%)/6 (23.1%)	8/10
Starkstein et al, 2015[d]	Cross-sectional	Adults with autism	Study 1: 19 Study 2: 37	DSM-5, ADI-R, and ADOS	UPDRS and MDS-UPDRS	Study 1: 57 + 6.7 Study 2: 51.2 + 8.5	Study 1: 0 Study 2: 5 (13.5%)	8/9
Young et al, 2020	Cross-sectional	Rett syndrome	14	Revised diagnostic criteria by Neul et al	Videotapes assessed by ≥2 independent assessors	9.2 + 5.4	14 (100%)	8/9

ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorders; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; MDS, Movement Disorder Society; UPDRS, Unified Parkinson's Disease Rating Scale; US, United States.

[a]The quality of cross-sectional studies was assessed using the Joanna Briggs Institute's Checklist for Prevalence Studies (rated out of 9 points), and case–control studies using the Checklist for Case–Control Studies (rated out of 10 points).

[b]Relevant variables (i.e., sample size, age, and proportion of females) were reported as *cases/controls* for these case–control studies.

[c]The Rett Syndrome Rigidity Distribution score is an investigator-developed survey evaluating the extent of rigidity in Rett syndrome.

[d]The authors first conducted a hypothesis-generating pilot study of 19 adults with ASD, followed by a second study of 37 individuals with ASD to confirm their findings.

Table 2. Key findings of clinical studies.

Study	Key findings
Croen et al, 2015	• Parkinson's disease and related conditions were more common in ASD cases than controls—0.93% (14/1507) versus 0.03% (5/15,070), OR 32.73 (95% CI 7.76–137.96), $P < 0.001$.
FitzGerald et al, 1990	• Parkinsonism features were very common in RTT—hypomimia in 62.5% (20/32), rigidity in 43.8% (14/32), and bradykinesia in 40.6% (13/32). • Most experienced hyperkinetic disorders as well—bruxism in 100% (32/32), oculogyric crises in 62.5% (20/32), and dystonia in 59.4% (19/32).
Geurts et al, 2022	• A total of 23.6% (119/505) of ASD patients screened positive for parkinsonism (PSQ ≥7)—16.9% (50/296) in the Netherlands sample, and 33% (69/209) in the US sample. • In the Netherlands sample, screen-positive patients had lower rates of cognitive failures than screen-negative patients (70.4 ± 15.7 vs. 83.8 ± 14.5, $P < 0.001$) but more medical (87.8% [43/49] vs. 63.1% [147/233], $P = 0.002$) and mental health diagnoses (62.2% [28/45] vs. 38.2% [87/228], $P = 0.003$). • In the US sample, screen-positive group had greater proportion of females than the screen-negative group (65.2% [45/69] vs. 45.7% [64/140], $P = 0.008$). • Antipsychotic use did not differ significantly between the screen-positive and screen-negative in both samples ($P = 0.98$ for the Netherlands sample; $P = 0.05$ for the US sample).
Hand et al, 2020	• Higher odds of PD in ASD cases than controls (aOR 6.1, 95% CI 5.3–7.0) • According to subgroup analysis by sex, female ASD patients had higher odds of PD compared to controls (aOR 8.2, 95% CI 6.2–10.7) than male ASD patients (aOR 5.4, 95% CI 4.6–6.4) .
Humphreys and Barrowman, 2016	• Rigidity seen in 84.3% (43/51) of RTT patients. • Higher RTTRD[a] scores observed in patients of older age groups—3.00 ± 2.16 for ages 6–10 years; 6.70 ± 3.47 for ages 11–19 years; and 7.67 ± 3.80 for ages >20 years. • Lower homovanillic acid levels in cerebrospinal fluid correlated with higher RTTRD scores (R −0.83, $P = 0.005$).
Mostert-Kerckhoffs et al, 2020	• Increased rates of parkinsonism in ASD versus controls in both children (54.5% [12/22] vs. 4.5% [1/22], $P < 0.001$) and adolescents (73.9% [17/23] vs. 11.5% [3/26], $P < 0.001$).[b] • Relative to controls, bradykinesia significantly more common in both age groups (children—50.0% [11/22] vs. 4.5% [1/22], $P < 0.001$; adolescents—65.2% [15/23] vs. 7.7% [2/26], $P < 0.001$). • Rigidity was more commonly seen in adolescent ASD patients than controls (30.4% [7/23] vs. 0, $P < 0.001$) but not in children ($P = 0.325$). • Tremors were equally frequent in ASD cases and controls for both age groups ($P = 0.144$ for children; $P = 0.439$ for adolescents).
Starkstein et al, 2015	• A total of 32% (12/37) of ASD adults in the sample met the diagnostic criteria for parkinsonism. • Excluding patients currently taking atypical antipsychotics, 20% (4/20) had parkinsonism.
Young et al, 2020	• Gait freezing highly prevalent in RTT patients—78.6% (11/14) on overground, and 85.7% (12/14) on treadmill. • A total of 21.4% had parkinsonian shuffling, and 35.7% had an initiation freeze.

aOR, adjusted odds ratio; ASD, autism spectrum disorders; CI, confidence intervals; OR, odds ratio; RTT, Rett syndrome; RTTRD, Rett Syndrome Rigidity Distribution score; US, United States.

[a]The Rett Syndrome Rigidity Distribution score is an investigator-developed survey evaluating the extent of rigidity in Rett syndrome.

[b]ASD patients of ages 6–12 years were considered children, while those of ages 13–26 years were considered adolescents.

antipsychotics, 20% (4/20) had significant parkinsonism. In another study of 505 ASD adults without intellectual disability, 23.6% (119/505) scored above the cutoff score (≥7 points, defined as the "screen-positive group") for the Parkinsonism Screening Questionnaire (PSQ), which is suggestive of clinically significant parkinsonism.[4] In the United States sample, the proportion of females in the screen-positive group was significantly higher than that in the screen-negative group (65.2% [45/69] vs. 45.7% [64/140], $P = 0.008$).[4] In the Netherlands sample, screen-positive patients also reported lower rates of cognitive failures than screen-negative patients (70.4 ± 15.7 vs. 83.8 ± 14.5, $P < 0.001$), but more medical (87.8% [43/49] vs. 63.1% [147/233], $P = 0.002$) and mental health diagnoses (62.2% [28/45] vs. 38.2% [87/228], $P = 0.003$). Importantly, antipsychotic use did not differ between the screen-positive and screen-negative groups for both samples ($P = 0.98$ for the Netherlands sample; $P = 0.05$ for the US sample).[4]

In children and adolescents, though, the evidence for increased rates of parkinsonism is less clear. Compared with matched controls, bradykinesia was significantly

more common in both children and adolescents with ASD (children [ages 6–12 years]—50.0% [11/22] vs. 4.5% [1/22], $P < 0.001$; adolescents [ages 13–26 years]—65.2% [15/23] vs. 7.7% [2/26], $P < 0.001$).[5] However, rigidity was significantly more frequent in adolescents with ASD (30.4% [7/23] vs. 0, $P < 0.001$) but not in children ($P = 0.325$). In addition, the prevalence of tremors was not significantly increased in both age groups ($P = 0.144$ for children; $P = 0.439$ for adolescents).[5]

Rett syndrome (RTT)

Despite being classified within the autism spectrum, RTT is clinically distinct and is associated with movement disorders of greater severity. Indeed, parkinsonism features were very prevalent in patients with RTT, with many patients reporting rigidity (43.8–84.3%), hypomimia (62.5%), bradykinesia (40.6%), and freezing (85.7%).[12–14] A cross-sectional study by FitzGerald et al[12] observed hypomimia in 62.5% (20/32), rigidity in 43.8% (14/32), and bradykinesia in 40.6% (13/32).

Furthermore, Humphreys and Barrowman[13] reported rigidity in 84.3% (43/51) of patients, which was evaluated by an investigator-developed survey, the RTT rigidity distribution (RTTRD) score (higher scores indicate greater severity). The rigidity was more severe in older age groups (3.00 ± 2.16 for ages 6–10 years; 6.70 ± 3.47 for ages 11–19 years; and 7.67 ± 3.80 for ages >20 years) and higher RTTRD scores were correlated with lower levels of homovanillic acid in the cerebrospinal fluid (R -0.83, $P = 0.005$).[13]

Freezing was observed in 85.7% of RTT patients, with gait shuffling observed in 21.4% and initiation freeze in 35.7%.[14] In addition, RTT patients often experience hyperkinetic movement disorders as well (such as bruxism in 100% [32/32], oculogyric crises in 62.5% [20/32], and dystonia in 59.4% [19/32]), combined with the hypokinetic parkinsonian features described above.[12]

Genetic studies

The genetic studies included in this review examined a variety of genes, such as *PARK2*, *RIT2*, *CD157/BST1*, *DRD2*, *SLC*, *GPCR37*, and *SMPD1*. We present a detailed summary of these articles in Table 3. *PARK2* was investigated in three studies, and associated mutations were more commonly observed in ASD patients. In a study of 342 Portuguese individuals with ASD, the prevalence of *PARK2* deletions was 1.5% (5/342), which was relatively high for a single gene variant in ASD.[17] In addition, 53 patients had copy number variations (CNVs) in *PARK2* between introns 4 and 6, of which 24 also had CNVs spanning intron 9.[17] Another study of 335 Han Chinese ASD patients found six patients who had CNVs in the *PARK2* exonic regions, ranging over exons 2 to 7.[22] Lastly, another genetic study of patients of European ancestry (with comparison to healthy controls) found *PARK2* CNVs to be exclusive to ASD cases.[23]

Single-nucleotide polymorphisms (SNPs) in *RIT2* appear to confer susceptibility to both PD and ASD.[18] When compared to matched controls, the genotype and allele frequencies of rs12456492 differed significantly for PD ($P = 0.001$ and $P = 0.007$, respectively), as well as for ASD with borderline significance ($P = 0.05$ and $P = 0.06$, respectively).[18] Polymorphisms in *CD157/BST1*, another gene associated with PD, were associated with ASD as well. Three SNPs—rs4301112 (OR 6.4, 95% CI 1.9–22, $P = 0.0007$), rs28532698 (OR 6.2, 95% CI 1.8–21, $P = 0.0012$), and rs10001565 (OR 5.5, 95% CI 1.6–19, $P = 0.0038$)—demonstrated significantly higher allele frequencies in ASD cases than unaffected controls.[21]

The evidence supporting the involvement of other genes in ASD and PD, however, is less convincing. While the prevalence of the *Taq I* allele of *DRD2* was significantly higher in ASD than in controls (54.5% vs. 24.5%, $P = 0.0005$), there were no significant differences for PD (17.6% vs. 24.5%, $P = 0.42$).[16] Fujita-Jimbo et al[19] reported two male patients—one Japanese and one Caucasian—with mutations in *GPCR37*, which is a PD-associated gene. *SLC* has also been implicated in ASD and PD. Mir et al[20] reported *SLC9A9* mutations in a patient with autism, and *SLC6A3* mutations in another with infantile parkinsonism-dystonia 1. Lastly, a pathogenic mutation in *SMPD1*—variants of which were recently associated with PD—was found in a patient presenting with autism and epilepsy.[15] Further large-scale studies will be needed to understand the role of these genes in ASD and PD.

Multiple case reports also presented various rare genetic mutations that have resulted in parkinsonism and autistic behavior. This review included five such case reports, two of which presented patients with RTT (caused by mutations in *MECP2*). The two patients described here demonstrated bradykinesia with rigidity and were unresponsive to levodopa therapy. The remaining three cases each had mutations in *ATP13A2*, *CLN3*, and *WDR45*, respectively. Levodopa therapy appeared to have variable efficacy in these individuals. Further details are presented in Table 4.

Discussion

In this systematic review, we evaluate the clinical and genetic association between ASD and parkinsonian features. We found that persons with ASD have a higher prevalence of parkinsonism, including PD for older adults. We also highlighted various genes, most notably

Table 3. Genetic studies on genes potentially involved in parkinsonism and autism spectrum disorders.

Study	Study design	Genetic testing employed	Population	Sample size	Key genes studied	Age, years	Female, N (%)	Findings	Quality[a]
Chang et al, 2019	Case series	Whole-exome sequencing	Taiwanese patients with ASD	5	*SMPD1*	Range 6–21 years	0	Pathogenic mutation in *SMPD1* in a patient with autism and epilepsy	10/10
Comings et al, 1991[b]	Case–control	Single gene testing	Non-Hispanic white ASD and separately PD	50 (33 ASD and 17 PD)/ 314	*DRD2*	Not reported	Not reported	Prevalence of A1 allele significantly higher in autism-PDD patients than controls (54.5% vs. 24.5%, $P = 0.0005$) but not significant in PD (17.6% vs. 24.5%, $P = 0.42$)	7/10
Conceicao et al, 2017	Cross-sectional	Single gene testing	Portuguese ASD patients	342	*PARK2*	Range 3–9 years	0	Five patients have *PARK2* deletions, 53 patients with neurodevelopmental disorders have *PARK2* CNVs in region between introns 4 and 6, and 24 spanned intron 9	9/9
Emamalizadeh et al, 2017[b]	Case–control	Single gene testing	Unrelated Iranian subjects with ASD and separately PD	PD: 520/520 ASD: 470/470	*RIT2*	PD: 59.5 + 12.5/ 58.12 + 12.22 ASD: 7.9 + 2.7/ 8.2 + 2.5	PD:242 (46.5%)/252 (48.5%) ASD:184 (39.1%)/191 (40.6%)	Genotype and allele frequencies of rs12456492 differed significantly for PD ($P = 0.001$ and $P = 0.007$, respectively), as well as for ASD with borderline significance ($P = 0.05$ and $P = 0.06$, respectively)	10/10
Fujita-Jimbo et al, 2012	Cross-sectional	Single gene testing	Unrelated Japanese and Caucasian ASD patients	Japanese: 72 Caucasian: 200	*GPCR37*	Japanese: Range 2 –32 Caucasian: Not reported	Japanese:15 (20.8%) Caucasian:28 (14%)	Mutations in *GPCR37* found in one Japanese patient and in one Caucasian patient	8/9
Mir et al, 2022	Case series	A mix of whole-exome sequencing, NGS panel, or single gene testing	Pediatric Saudi Arabian patients	25	*SLC*	Range 1.5–14	10 (40%)	*SLC9A9* mutations found in a patient with autism, and *SLC6A3* mutations found in another with infantile parkinsonism-dystonia 1	10/10
Yokoyama et al, 2015[b]	Case–control	Single gene testing	Japanese ASD patients	147/150	*CD157/BST1*	15.6 + 0.6/ 23.8 + 0.3	34 (23.1%)/35 (23.3%)	rs4301112 (OR 6.4, 95% CI 1.9–22, $P = 0.0007$), rs28532698 (OR 6.2, 95% CI 1.8–21, $P = 0.0012$), and rs10001565 (OR 5.5, 95% CI 1.6–19, $P = 0.0038$) demonstrated significantly higher allele frequencies in ASD cases than unaffected controls	10/10

(*Continued*)

Table 3 Continued.

Study	Study design	Genetic testing employed	Population	Sample size	Key genes studied	Age, years	Female, N (%)	Findings	Quality[a]
Yin et al, 2016[b]	Case–control	Whole-genome sequencing	Han Chinese ASD patients	335/1093	*PARK2*	9.39 + 4.04/ 68.07 + 10.12	36 (10.7%)/ 568 (52%)	Six patients had *PARK2* CNVs over exons 2–7	9/10
Glessner et al, 2009[b]	Case–control	Whole-genome sequencing	ASD patients of European ancestry	859/2519	*PARK2*	Range 2–21 years (mean or median not reported)/ 8.7 + 5.46	156 (18.2%)/ 1197 (47.5%)	*PARK2* CNVs were exclusive to ASD cases	10/10

ASD, autism spectrum disorders; CI, confidence interval; CNV, copy number variation; OR, odds ratio; PD, Parkinson's disease.
[a]The quality of case–control studies was assessed using the Checklist for Case–Control Studies (rated out of 10 points), cross-sectional studies using the Joanna Briggs Institute's Checklist for Prevalence Studies (rated out of 9 points), and case series using the Checklist for Case Series (rated out of 10 points).
[b]Relevant variables (i.e., sample size, age, and proportion of females) were reported as *cases/controls* for these case–control studies.

PARK2, that are associated with ASD and PD, including individuals carrying certain rare genetic variants presenting with autistic behavior and parkinsonism.

While the motor disturbances in ASD remain to be better characterized, most reports suggest that motor deficits are common in patients with ASD. A meta-analysis led by Fournier et al[29] indicated a presence of impairments across various motor domains, such as in motor planning, upper extremity function, as well as gait and balance. Some reports also likened the gait observed in patients with ASD to the gait in patients with other movement disorders, such as PD[30,31] and cerebellar ataxia.[32]

A series of recent studies corroborated these findings. They found that a significant proportion of individuals with ASD demonstrated clinically apparent motor difficulties, but only a small portion of them received a specific diagnosis.[33–35] About 80–90% of pediatric patients with ASD presented with motor impairment as assessed by a well-established parent report measure. However, there is gross under-recognition of these symptoms and only a fraction (ranging from 1.5% to 15%) received a motor-specific diagnosis.

The link between ASD and parkinsonism has garnered substantial interest, particularly because of the presence of motor abnormalities in individuals with autism. Gait abnormalities in ASD have been previously studied, both qualitatively and quantitatively, but whether the pattern is more suggestive of cerebellar dysfunction, or striatal dysfunction, remains to be clarified.[10] It is also unclear if motor dysfunction in ASD is a risk factor or predisposes to the development of parkinsonism.

Sex differences may play an important role in the presentation of parkinsonism in ASD patients. The study by Geurts et al[4] found a substantial difference in the proportion of subjects with ASD screening positive for parkinsonism between the United States and the Netherlands samples. Of note, the US sample included more females and found parkinsonism to be more prevalent in females than males. This suggestion is in line with the findings of a previous study by Rydzewska et al,[36] which concluded female ASD patients were at greater risk of developing health conditions compared with their male counterparts. Rydzewska et al[36] did not evaluate parkinsonism in their study, which will limit the applicability of their results to support sex differences in the parkinsonism rates among ASD patients.

Age could be another important factor affecting the presentation of parkinsonism in ASD patients. The study by Mostert-Kerckhoffs et al[5] demonstrated that, relative to healthy age-matched controls, rigidity was significantly more prevalent in adolescents but not in children with ASD. This may be attributed to thalamocortical

Table 4. Case reports of patients with features of parkinsonism and autism spectrum disorders.

Study	Age, gender, and ethnicity	Diagnosis	Family history	Associated genetic mutations	Features of ASD	Features of Parkinsonism	Treatments attempted
Balint et al, 2020	18-year-old Pakistani male	Pallido-pyramidal syndrome	Consanguineous couple	*ATP13A2* (NM_022089.4: c.2218C>T mutation)	Difficulty with social interaction, as well as stereotypies, gaze avoidance, and reclusive behavior	Young-onset dystonia-parkinsonism with slow finger tapping	Levodopa with good response but development of dyskinesia
Roze et al, 2007	49-year-old French female	Rett syndrome	None	*MECP2* (heterozygous frameshift mutation c.1163del35 in exon 4)	Stereotypies and was unable to speak, but could make good eye contact with her family	Generalized bradykinesia and rigidity with dystonic posturing of the distal limbs, unsteady broad-based gait, and difficulties with gait initiation	Levodopa failed to improve dystonia and parkinsonism, and trihexyphenidyl discontinued due to daytime sedation
Valadares et al, 2011	12-year-old Brazilian female	Juvenile neuronal ceroid lipofuscinosis	Consanguineous couple	*CLN3* (1.02 kb deletion involving exons 7 and 8)	Autistic behavior with tics but understands and cooperates	Parkinsonism, ataxia, and can only walk with support since 10 years	None
Venkateswaran et al, 2014	15-year-old European female	Rett syndrome	None	*MECP2* (missense mutation: c.419C>T; p.Ala140Val)	Socialized parallel to peer group and thrived with routine	Bradykinesia and rigidity with hypomimia	Levodopa/carbidopa did not improve symptoms; quetiapine partially controlled psychiatric symptoms
Verhoeven et al, 2014	42-year-old female (unknown ethnicity)	Beta-propeller protein-associated neurodegeneration	Father died from Parkinsonian dementia at 73 years	*WDR45* (c.1030del leading to frameshift)	Poor language and social communication skills considered to fall on the autism spectrum	Bradykinesia and broad-based gait with freezing tendency	Levodopa/carbidopa with partial response

dysconnectivity, which was more pronounced in adolescents than in children and adults.[37] The hypothesis that there are age-specific effects on the abnormalities in brain connectivity is supported by other studies as well.[38,39]

Among the various genes evaluated in this systematic review, the association of *PARK2*—mutations in which is the common cause of recessive forms of PD[40]—with ASD is of particular interest. *PARK2* encodes the Parkin protein, which is a cytosolic ubiquitin E3 ligase, and plays an important role (along with PINK1) to regulate mitophagy. Defects in this pathway are hypothesized to result in greater vulnerability of the dopaminergic neurons to neurotoxins, resulting in their degeneration and hence PD.[41] The relationship between *PARK2* mutations and autistic symptoms still needs to be evaluated, though abnormalities in this gene were thought to cause developmental anomalies[42,43] and even deficits in facial recognition.[44]

Dopaminergic pathways could be implicated in the pathogenesis of ASD since dopamine is among the main neurotransmitters responsible for social behavior as well as movement control. Mutations in the dopamine transporter affecting dopaminergic transmission within the brain have been shown to result in autism-like behavioral patterns.[45,46] In addition, drug-induced alterations in the nigrostriatal circuit also resulted in stereotypical ASD-like behavior in mouse models.[47] Abnormalities with dopamine metabolism in the brain could contribute to the behavioral pattern observed in patients with ASD.

Dopaminergic projections from the midbrain extend into multiple brain regions such as the basal ganglia, cortex, and amygdala. The dopaminergic dysfunction in these pathways would likely contribute to the pathogenesis of ASD. In children with ASD, there were reduced presynaptic dopamine levels in the prefrontal cortex[48] and a reduction in phasic striatal dopamine release when exposed to social stimuli.[49,50] Brain imaging studies have consistently demonstrated abnormalities in dopaminergic structures and their connectivity. Firstly, enlargement of the caudate nucleus (a major target of the dopaminergic system) was found in individuals with ASD,[51] even in those who were medication-naïve.[52] Secondly, an MRI study found substantial and localized reductions in the gray matter of the frontostriatal networks, which implies abnormal connectivity between dopaminergic and cortical structures.[53]

Mouse models of ASD have also been employed to study the derangements in dopamine metabolism. A mouse model carrying the Val559 mutation in *SLC6A3* demonstrated an increase in the basal striatal dopamine levels with reduced rearing behavior.[54] A separate model with the T356M mutation in *DAT* demonstrated a decrease in the clearance and synthesis of dopamine with an increase in striatal dopamine metabolism.[45] These mice were more active and exhibited behavior that resembled motor stereotypies.[45] Evidently, ASD-relevant changes can arise from alterations in dopaminergic neurotransmission.

There are inherent challenges to evaluating parkinsonism in ASD subjects. First, atypical antipsychotics—which are commonly associated with extrapyramidal side effects—are frequently used in the management of ASD and were previously thought to explain the parkinsonism observed in persons with ASD. However, current evidence suggests that the prevalence of parkinsonism was higher than expected, even when accounting for antipsychotic use. Starkstein et al[6] found a substantial portion of ASD subjects to demonstrate clinical parkinsonism despite excluding patients on atypical antipsychotics. In addition, Geurts et al[4] failed to find a significant difference in the use of atypical antipsychotics between patients with and without parkinsonism. The frequent use of atypical antipsychotics nonetheless presents a great challenge in the evaluation of parkinsonism in persons with ASD.

Another challenge is with the ascertainment of parkinsonism in these individuals, especially those with hyperkinetic disorders. Signs of parkinsonism may be missed in individuals with ASD, either due to lack of awareness or mischaracterization as stereotypies related to the ASD itself. This is also because most individuals with ASD (except those with profound movement disorders) do not follow up with movement disorders specialists, making an accurate assessment of parkinsonism even more difficult.

Most ASD patients also have communication problems, which will complicate the history-taking process, especially in nonverbal subjects. As such, the progression of parkinsonian signs is also difficult to ascertain. The medical care providers may also change with time, leading to discontinuity of care and thereby difficulties with constructing an accurate timeline of parkinsonian symptoms.[55] History taking, therefore, should involve caregivers and family members, as well as primary care providers, and be complemented by a comprehensive review of past medical records.[55] Severity of parkinsonian symptoms should also be quantified using validated scales, to better detect symptomatic progression.

Future prospective studies with a longer follow-up of patients with and without ASD will be useful, as this allows for a better assessment of the progression of parkinsonism and the patients' response to levodopa and pharmacotherapeutic options. This would address the current limitation of inadequate follow-up. Functional imaging studies (such as diffusion tensor imaging, positron emission tomography, and dopamine transporter scan) to evaluate the dopaminergic function would provide quantification of the dopaminergic reserve and its changes over time.

The identification of suitable biomarkers to diagnose, monitor, and prognosticate idiopathic PD in ASD is another area of great importance. α-synuclein is currently the best-studied biomarker for PD, and its concentrations in the cerebrospinal fluid (CSF) or blood have been used in the investigative workup for and diagnosis of PD.[56] Other promising biomarkers include lysosomal enzymes, neurofilament light chain (NfL), and even the classic biomarkers for Alzheimer's disease.[56]

CSF NfL levels can differentiate idiopathic PD from atypical parkinsonian syndromes.[57–59] The identification of a reliable biomarker would greatly facilitate the monitoring of the severity of parkinsonism in ASD patients, which is currently limited to the histories taken from the patients and their caregivers.

Conclusion

The prevalence of ASD has been steadily rising over the past decades, especially among those who have progressed to adulthood. Our systematic review highlights evidence to suggest that parkinsonian symptoms appeared to be more prevalent in ASD cases as compared to matched controls regardless of age group. Variants in PD gene *PARK2* may also confer susceptibility to ASD, in addition to other PD-related gene loci such as *RIT2*, CD157/*BST1*, *GPCR37*, and the *SLC* gene family. Rare genetic mutations (such as *ATP13A2*, *CLN3*, and *WDR45*) could also result in autistic behavior and concomitant parkinsonism. Further prospective cohort studies will be useful to evaluate the progression of parkinsonian features in ASD patients. Genetic screening and clinical genetic correlations in ASD families with parkinsonism will also provide additional clues. Pathophysiologic studies in transgenic animal models and human organoid models derived from ASD patients with and without parkinsonism can identify novel clues that may uncover potential therapeutic targets. The additional risk of parkinsonism observed in ASD patients, as well as genetic associations and common pathogenetic mechanisms underlying the two conditions, are key areas to be further investigated.

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Conflicts of Interest

The authors do not have any competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Author Contributions

AS Mai, DWJ Wan, FS Tseng, QXJ Foo, DQ Wang, and Prof E-K Tan contributed to (1) the conception and design of this project; (2) acquisition, analysis, and interpretation of data; and (3) drafting and revising it critically for important intellectual content. All authors gave their final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for Publication

All authors consent to the publication of this article and related materials.

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Not applicable.

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. PRISMA flow diagram.

