Purpose of review
We will review the recent advances in the genetics of Parkinson disease and other movement disorders such as dystonia, essential tremor and restless legs syndrome (RLS).

Recent findings
Mutations in VPS35 were identified as a novel cause of autosomal dominant Parkinson disease using exome sequencing. Next generation sequencing (NGS) was also used to identify PRRT2 mutations as a cause of paroxysmal kinesigenic dyskinesia (DYT10). Using a different technique, that is linkage analysis, mutations in EIF4G1 were implicated as a cause of Parkinson disease and mutations in SLC20A2 as a cause of familial idiopathic basal ganglia calcification. Furthermore, genome-wide association studies (GWAS) and meta-analyses have confirmed known risk genes and identified new risk loci in Parkinson disease, RLS and essential tremor. New models to study genetic forms of Parkinson disease, such as stem cell-derived neurons, have helped to elucidate disease-relevant molecular pathways, such as the molecular link between Gaucher disease and Parkinson disease.

Summary
New genes have been implicated in Parkinson disease and other movement disorders through the use of NGS. The identification of risk variants has been facilitated by GWAS and meta-analyses. Furthermore, new models are being developed to study the molecular mechanisms involved in the pathogenesis of these diseases.

Keywords
genetics, genome-wide association studies, glucocerebrosidase, Parkinson’s disease, VPS35

INTRODUCTION
Several genes are well validated as causes of a typical Parkinson disease phenotype. Although mutations in SNCA and LRRK2 cause autosomal dominant Parkinson disease, PARKIN, PINK1 and DJ1 mutations underlie autosomal recessive disease. However, known monogenic causes and genetic risk factors only partly explain the observed familial aggregation of Parkinson disease. Unsurprisingly, the application of new techniques such as next generation sequencing (NGS), genome-wide association studies (GWAS) and meta-analyses have allowed for the discovery of new genes and genetic risk factors for Parkinson disease and other movement disorders, such as dystonia, essential tremor and restless legs syndrome (RLS). In addition, clinicogenetic studies have been used to improve genotype–phenotype correlations and to reveal the earliest disease signs. Furthermore, there has been significant progress in the development of new disease models, particularly through the use of induced pluripotent stem (iPS) cell-derived neurons. Examples of these advances are given in this review.

MONOGENIC CAUSES OF PARKINSON DISEASE: UTILITY OF NOVEL TECHNIQUES
A novel approach to identify causative genes in single families is NGS, which allows for sequencing of the entire human genome in a single experiment.
Because disease-causing mutations usually change an encoded protein, NGS can be restricted to the coding part of the genome, the exome [1].

Two independent studies utilized exome sequencing in a Swiss and an Austrian kindred to identify the same p.D620N (c.1858G>A) mutation in the vacuolar protein sorting 35 homolog (VPS35) gene as the cause of autosomal dominant Parkinson disease in these families [2*,3**]. This mutation was subsequently found in several additional families but is a rare cause of Parkinson disease, with a frequency lower than 0.1% [2*,3**,4–6]. The p.D620N mutation cosegregates with a phenotype indistinguishable from idiopathic Parkinson disease (iPD) and has incomplete, age-associated penetrance. This mutation seems to have arisen by recurrent mutational events [2*,6], and screening of the entire VPS35 coding region has not revealed any other variants with unequivocal pathogenicity [2*,3**,5]. VPS35 is a component of the retromer complex and is involved in retrograde transport from the endosomes to the trans-Golgi network [3**]. The p.D620N mutation may lead to impaired recycling of membrane-associated proteins and dysfunctional endosomal–lysosomal trafficking [2*,3**]. Interestingly, retromer deficiency may also feature in the cause of Alzheimer disease, although there is no evidence so far that patients with the p.D620N mutation have prominent cognitive impairment [2*,6]. Further studies into VPS35 mutations are required to determine the pathological changes and molecular mechanisms involved, and to elucidate the link with Alzheimer disease.

Using a different approach, eukaryotic translation initiation factor 4-gamma (EIF4G1) was proposed as another new Parkinson disease gene [7**]. By genome-wide linkage analysis, a linkage region of 3q26–q28 was identified in a Northern French family with autosomal dominant parkinsonism. Sequencing of all coding exons in this critical region revealed only one novel variant that segregated with disease, the p.R1205H (c.3614G>A) mutation in the EIF4G1 gene. Further screening identified the p.R1205H mutation in additional families. The phenotype was consistent with late-onset Parkinson disease associated with a relatively long and mild course and preserved cognition. Screening of all 31 codons of the EIF4G1 gene revealed four missense variants not observed in controls: p.A502V, p.G686C, p.S1164R and p.R1197W. Functional analyses demonstrated that the p.R1205H and p.A502V mutations perturb binding of eIF3e and eIF4E, interactions which are normally required for the initiation of translation. Additionally, mutant cells were shown to be more vulnerable to oxidative stress. Despite being rare, EIF4G1 mutations potentially implicate a novel pathway in the pathogenesis of Parkinson disease involving a disturbance of mRNA translation initiation. However, it is worth noting that assessment of disease segregation was not possible for any of these variants apart from p.R1205H and so pathogenicity remains uncertain. Moreover, there has been no independent confirmation of mutations in this gene as yet and the authors acknowledged that the drawback of linkage in a multi-incident family is the possibility of missing other segregating variants [7**].

Linkage analysis and sequencing of candidate genes were also used to investigate the genetic cause of familial idiopathic basal ganglia calcification (IBGC). IBGC usually has an autosomal dominant pattern of inheritance and is characterized by symmetrical calcium deposits in the basal ganglia and other brain regions on neuroimaging and a clinical phenotype including parkinsonism with neuropsychiatric and cognitive symptoms. Mutations in the type III sodium-dependent phosphate transporter 2 (SLC20A2) gene were shown to cause IBGC linked to 8p21.1–8q11.23. Mutations in this gene were subsequently found in affected families from different ethnic groups [8**].

For another more complex form of Parkinson disease (parkinsonism-pyramidal syndrome with juvenile onset and spasticity), mutations in the F-box only protein 7 (FBXO7) gene were identified.
in 2008 after genome-wide linkage analysis and sequencing of candidate genes [9]. Since then, additional families with mutations in FBOX7 have been described (reviewed in [10]).

Of note, monogenic forms of Parkinson disease were initially assigned a ‘PARK’ designation using consecutive numbering, such as PARK1 for the first mapped and identified Parkinson disease gene SNCA. However, the current system has problems that are sources of confusion, perpetuate misinformation and misrepresent the system as a useful reference tool. These include erroneously assigned loci, duplicated loci, missing symbols and loci, unconfirmed loci, combining causative genes and risk factor genes in the same list, and discordance between phenotype and list assignment. For this reason, a substantial revision of the classification of inherited forms of parkinsonism is required [11].

**IDENTIFICATION OF GENETIC RISK FACTORS FOR PARKINSON DISEASE: ASSOCIATION STUDIES**

GWAS have been a major advance in genetic research, enabling the assessment of genetic risk factors associated with complex diseases via large-scale, population-based studies.

Several GWAS for Parkinson disease have been reported [12–19] and three meta-analyses have been performed [20,21*,22**]. All GWAS indicate a strong association to the SNCA gene and most studies also confirm an association with the MAPT gene (Table 1) [12–16,18,19]. Early in 2011, the International Parkinson’s Disease Genomics Consortium (IPDGC) performed a meta-analysis of datasets from five Parkinson disease GWAS across the United States and Europe in order to identify novel risk loci for Parkinson disease [22**]. The investigators identified 11 loci that surpassed the threshold for genome-wide significance. Six had been previously identified (MAPT, SNCA, HLA-DRB5, BST1, GAK and LRRK2), whereas five were novel (ACMSD, STK39, MCCCI/LAMP3, SYT11 and CCDC62/HIP1R). A second meta-analysis by the IPDGC in collaboration with the Wellcome Trust Case Control Consortium 2 revealed another five Parkinson disease risk loci (PARK16, STX1B, FGF20, STBD1 and GPNMB) [20]. The third and most comprehensive meta-analysis included data from seven million polymorphisms originating either from GWAS datasets or from smaller scale Parkinson disease association studies and was supplemented by unpublished data [21**]. Many previously reported risk loci were confirmed and evidence for a new risk variant in the ITGA8 gene was found [21**]. The risk factors identified by these studies provide clues to the underlying molecular mechanisms involved and offer potential targets for novel treatments.

In addition to the GWAS, candidate gene association studies have also improved our knowledge of genetic risk factors. Variants in LRRK2 can cause monogenic Parkinson disease (e.g. p.G2019S) [23] or act as risk factors (e.g. p.G2385R) [24]. A large multicenter study systematically investigated the association of 121 exonic variants in LRRK2 with Parkinson disease in more than 15,000 individuals of different ethnic backgrounds including white, Asian, and Arab–Berber probands [25*]. New independent risk associations were identified for white individuals (p.M1646T) and Asian individuals (p.A419 V), as well as a protective haplotype for all ethnic populations studied (p.N551K–p.R1398H–p.K1423K). This was a comprehensive study, focusing solely on the role of LRRK2 variants in Parkinson disease. The results supplemented information gained from GWAS and showed that different variants in the same gene can have independent effects on Parkinson disease risk [25*].

However, the applicability of genetic risk factors to personalized medicine is limited. Analysis of the results from the IPDGC meta-analysis show they are not useful for distinguishing between patients and controls [26**]. Additionally, given the relatively low frequency of Parkinson disease in the general population [27], the elevated risk (as much as 2.5 times) reported by the consortium does not have a great bearing on an individual patient’s care [26**]. It is essential that clinicians are well informed of the implications of GWAS given that they may be approached by patients who have undertaken a commercially available genetic profile.

**AGE-DEPENDENT PENETRANCE IN GENETIC PARKINSON DISEASE: AN OPPORTUNITY TO STUDY THE EARLY PHASES OF THIS DISEASE**

The uptake of NGS and GWAS has resulted in a rapid expansion of our understanding of the genetics of Parkinson disease. However, there has often been a delay in the reporting of detailed genotype–phenotype correlations. Recently, several studies were published that attempted to address this issue.

**LRRK2 mutations: increasing risk for Parkinson disease**

Mutations in LRRK2 are a well-established cause of autosomal dominant Parkinson disease, with the most common mutation being the p.G2019S substitution. LRRK2 mutations have incomplete age-associated penetrance, for example the penetrance
Table 1. Results of published genome-wide association studies in Parkinson disease

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (stage I/II/III)</td>
<td>2521/14139/1614</td>
<td>3978/4573/NA</td>
<td>619/1745/NA</td>
<td>1986/856/612</td>
<td>29624/15470/NA</td>
<td>5175/1984/NA</td>
<td>1984/5200/1864</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SNP</th>
<th>Ethnicity</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNCA (4q22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1931074</td>
<td>Japanese</td>
<td>1.37 (1.27–1.48)</td>
<td>7.35 x 10^-8</td>
</tr>
<tr>
<td>rs2736990</td>
<td>European</td>
<td>1.23</td>
<td>2.24 x 10^-15</td>
</tr>
<tr>
<td>SNP</td>
<td>European</td>
<td>1.30 (1.18–1.43)</td>
<td>3.4 x 10^-11</td>
</tr>
<tr>
<td>OR</td>
<td>American/European</td>
<td>1.29 (1.12–1.36)</td>
<td>2.3 x 10^-10</td>
</tr>
<tr>
<td>P value</td>
<td>US</td>
<td>1.23 (1.14–1.33)</td>
<td>1.36 x 10^-7</td>
</tr>
<tr>
<td>Controls (stage I/II/III)</td>
<td>1705/1039/NA</td>
<td>1.37 (1.22–1.53)</td>
<td>2.82 x 10^-8</td>
</tr>
<tr>
<td>MAPT/PLEKH1 (17q21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNP</td>
<td>Not significant</td>
<td>0.77</td>
<td>0.71 (0.62–0.79)</td>
</tr>
<tr>
<td>OR</td>
<td>Not significant</td>
<td>0.74 (0.66–0.84)</td>
<td>0.76 (0.71–0.82)</td>
</tr>
<tr>
<td>P value</td>
<td>Not significant</td>
<td>1.31 (1.19–1.44)</td>
<td>1.34</td>
</tr>
<tr>
<td>Controls (stage I/II/III)</td>
<td>1705/1039/NA</td>
<td>1.36</td>
<td>2.82</td>
</tr>
<tr>
<td>PARK16 (1q32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNP</td>
<td>rs947211</td>
<td>1.52</td>
<td>1.52</td>
</tr>
<tr>
<td>OR</td>
<td>rs823128</td>
<td>0.66</td>
<td>0.66</td>
</tr>
<tr>
<td>P value</td>
<td>rs823156</td>
<td>0.83 (0.77–0.89)</td>
<td>0.83</td>
</tr>
<tr>
<td>Controls (stage I/II/III)</td>
<td>1705/1039/NA</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>LRRK2 (12q12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNP</td>
<td>rs1994090</td>
<td>1.39 (1.24–1.56)</td>
<td>1.55</td>
</tr>
<tr>
<td>OR</td>
<td>rs1491923</td>
<td>1.14</td>
<td>0.03</td>
</tr>
<tr>
<td>P value</td>
<td>rs1491942</td>
<td>1.15 (1.01–1.30)</td>
<td>1.6</td>
</tr>
<tr>
<td>Controls (stage I/II/III)</td>
<td>1705/1039/NA</td>
<td>1.15</td>
<td>1.6</td>
</tr>
<tr>
<td>BST1/GAK (4p15-p16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNP</td>
<td>rs4538475</td>
<td>1.24</td>
<td>3.2</td>
</tr>
<tr>
<td>OR</td>
<td>Not significant</td>
<td>1.29 (1.29–1.30)</td>
<td>1.2</td>
</tr>
<tr>
<td>P value</td>
<td>Not significant</td>
<td>1.03 (1.34–1.34)</td>
<td>1.03</td>
</tr>
<tr>
<td>Controls (stage I/II/III)</td>
<td>1705/1039/NA</td>
<td>1.28</td>
<td>1.28</td>
</tr>
<tr>
<td>HLA-DRA (6p21.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNP</td>
<td>Not reported</td>
<td>1.26</td>
<td>1.26</td>
</tr>
<tr>
<td>OR</td>
<td>Not reported</td>
<td>1.07 (1.01–1.13)</td>
<td>1.07</td>
</tr>
<tr>
<td>P value</td>
<td>Not reported</td>
<td>1.9 x 10^-10</td>
<td>1.9 x 10^-10</td>
</tr>
<tr>
<td>Controls (stage I/II/III)</td>
<td>1705/1039/NA</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>FAM47E (4q21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNP</td>
<td>Not reported</td>
<td>0.839 (0.79–0.89)</td>
<td>0.839</td>
</tr>
<tr>
<td>OR</td>
<td>Not reported</td>
<td>7.6 x 10^-10</td>
<td>7.6 x 10^-10</td>
</tr>
<tr>
<td>P value</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Controls (stage I/II/III)</td>
<td>1705/1039/NA</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>SREBF1 (17p11.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SNP</td>
<td>Not reported</td>
<td>0.851 (0.80–0.90)</td>
<td>0.851</td>
</tr>
<tr>
<td>OR</td>
<td>Not reported</td>
<td>5.6 x 10^-8</td>
<td>5.6 x 10^-8</td>
</tr>
<tr>
<td>P</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
of the p.G2019S mutation is 28% at age 59 years, 51% at 69 years, and 74% at 79 years [28]. The age at onset seems to be at least partly influenced by variants in the MAPT gene [29].

The phenomenon of age-dependent penetrance provides an opportunity to study at-risk individuals, that is asymptomatic carriers of LRRK2 mutations, with the expectation that many will go on to develop Parkinson disease. These individuals may have the best prospects to benefit from neuroprotective agents developed in the future, based on the perception that substantial irreversible neuronal damage has not yet occurred in these individuals. In addition, studying these patients provides an opportunity to explore the earliest disease manifestations, and thus helps to better understand the pathophysiology and natural course of the disease.

A recent study compared the phenotype of probands with the p.G2019S mutation and their family members to patients with iPD and unrelated controls [30]. Although tremor was a more common presenting feature of LRRK2-Parkinson disease than iPD, the phenotypes were largely indistinguishable at the bedside. Nonmanifesting mutation carriers were also compared to related noncarriers, and a higher frequency of postural or action tremor was found in the nonmanifesting mutation carriers. However, the specificity of this sign as a predictor of future parkinsonism is likely to be low. Another study found evidence of olfactory dysfunction in nonmanifesting carriers of the p.G2019S mutation, supporting the notion that this is a premotor sign of Parkinson disease [31]. Additionally, sensitive gait analysis was used to demonstrate subtle gait abnormalities among asymptomatic carriers of the p.G2019S mutation [32].

Glucocerebrosidase mutations in Parkinson disease: risk variant or dominant causal gene?

Although monogenic forms of Parkinson disease are caused by rare mutations, genetic risk factors are usually common variants (Fig. 1). Mutations in the glucocerebrosidase (GBA) gene, causing Gaucher disease when both alleles are mutated, have an intermediate frequency in Parkinson disease patients (6.7% in a large European study) [33]. The phenotype associated with heterozygous GBA mutations in Parkinson disease may be indistinguishable from iPD in terms of severity, however, it seems that GBA-Parkinson disease patients may be at higher risk of developing cognitive impairment [34].

A French study found the penetrance of GBA mutations to be 7.6, 13.7, 21.4 and 29.7% at 50, 60,
The relatively high penetrance of Parkinson disease in GBA carriers suggested that GBA is in fact a dominant causal gene with reduced penetrance, rather than just a risk-confering gene. These findings should be taken into consideration when counseling relatives of patients with Gaucher disease or GBA-associated Parkinson disease.

**FUNCTIONAL MODELING OF PARKINSON DISEASE: INDUCED PLURIPOTENT STEM CELLS AS A NEW TOOL**

Functional studies of Parkinson disease-causing mutations have been hindered by lack of access to affected human dopaminergic neurons. The use of iPS cell-derived neurons (Fig. 2) provides a unique opportunity to overcome this difficulty.

Several studies have utilized iPS cell-derived neurons as cellular models in idiopathic and genetic Parkinson disease including SNCA, LRRK2 and PINK1 mutations. For example, increased production of SNCA was demonstrated in iPS cell-derived midbrain neurons from an SNCA triplenation carrier [36]. Dopaminergic neurons with mis-sense or nonsense mutations in PINK1 were shown to have reduced PINK1-mediated recruitment of Parkin to mitochondria [37]. Expression of wildtype PINK1 rescued the effect of mutant PINK1 on Parkin translocation, further confirming the relevance of PINK1/Parkin pathway in human neurons [37]. Dopaminergic neurons with the p.G2019S mutation...
In LRRK2 showed enhanced sensitivity to stress, a finding which could correlate with an early Parkinson disease phenotype [38]. In another study, a reduction in the number of neurites and neurite arborization as well as an accumulation of autophagic vacuoles was found in iPS-derived dopaminergic neurons from LRRK2 carriers and iPD patients [39].

These studies have effectively replicated molecular mechanisms known to be important in Parkinson disease. In addition, iPS cell-derived neurons have also been used to elucidate the molecular link between Gaucher disease and Parkinson disease [40**]. It was demonstrated that functional loss of Gaucher disease-linked glucocerebrosidase enzyme (GCase) in primary cultures or human iPS neurons impairs lysosomal protein degradation, causing accumulation of SNCA and resulting in neurotoxicity via aggregation-dependent mechanisms [40**]. It was also shown that SNCA inhibits the lysosomal activity of normal GCase in neurons and in the iPD brain. Based on these findings, a self-propagating and ‘bidirectional pathogenic loop’ model was proposed. In this model, impaired activity of GCase (e.g. due to a GBA mutation) results in lysosomal dysfunction followed by accumulation and aggregation of SNCA. The accumulated SNCA then blocks vesicle transport between the endoplasmic reticulum and golgi apparatus, which is the chief trafficking route for GCase to reach the lysosome. This leads to a reduction in GCase in the lysosome, amplifying the pathological process by causing further impairment of SNCA degradation, fuelling a feed-forward loop [41]. Presumably, at some point, SNCA reaches a critical level and becomes associated with disease. This model raises the possibility of a new therapeutic strategy for Parkinson disease, that is, raising GCase levels in sporadic Parkinson disease patients [41].

**ADVANCES IN OTHER MOVEMENT DISORDERS**

Key advances in the genetics of paroxysmal dyskinesia, essential tremor and RLS have recently been made through the use of NGS and GWAS. There is an emerging recognition of the important role of genetics in other movement disorders, such as Tourette syndrome, and this is covered in detail elsewhere [42**].

**PRRT2 mutations as a cause of paroxysmal kinesigenic dyskinesia and benign familial infantile seizures: two faces of the same coin**

Paroxysmal kinesigenic dyskinesia (PKD; DYT10) is an episodic dyskinesia of brief duration triggered by movement. Infantile convulsions and choreoathetosis (ICCA) syndrome is characterized by the co-inheritance of benign familial infantile seizures (BFIS) and PKD.

Using NGS, several studies independently identified mutations in the PRRT2 gene as the major cause of PKD and ICCA syndrome [43–45,46**]. Furthermore, PRRT2 mutations have now been identified in pure BFIS families [47,48]. An unprecedented number of studies have been published regarding PRRT2 mutations in a relatively short period of time. These reports have demonstrated that mutations in the same gene can cause two conditions (BFIS and PKD), which at first glance appear to be clinically distinct [49].

**Genome-wide association studies: further clues to the genetic contribution to essential tremor**

The first GWAS in essential tremor found an association of essential tremor risk with two single nucleotide polymorphisms (SNPs) (rs9652490 and rs11856808) located in an intron of the leucine-rich repeat and Ig domain containing 1 (LINGO1) gene [50]. Recently, a meta-analysis compared the results from 11 studies and supported a relationship between rs11856808 and the risk for essential tremor, whereas rs9652490 was only associated with familial essential tremor [51*]. It is important to note that LINGO1 rs9652490 may be in linkage disequilibrium with an as yet uncovered functional variant, which may be located in LINGO1 or in another gene [52]. Another GWAS found an association of essential tremor with variants in the glutamate transporter SLC1A2 [53].

**Restless legs syndrome: additional risk variants have been identified**

RLS is characterized by high familial aggregation suggesting a genetic component. Despite intensive efforts, no monogenic cause has been detected to date. However, major advances have been achieved through the identification of genetic risk factors by a GWAS (BTBD9, MEIS1, MAP2KS/ SKOR1) and candidate region analysis (PTPRD) [54,55]. These results were confirmed in several studies [56,57]. A recent GWAS has identified two additional RLS susceptibility loci within an intergenic region on chromosome 2p14 and a locus on 16q12.1 [58**]. Opportunities now exist to study the functionality of the RLS risk susceptibility loci and the molecular pathways involved [59]. An illustrative example includes a study reporting that the MEIS1 risk variant influences iron metabolism [60], adding to
a growing body of evidence that iron dysregulation contributes to the pathogenesis of many movement disorders [61].

**CONCLUSION**

The increasing application of new technologies such as NGS and GWAS has allowed for a clearer picture of the heritability of Parkinson disease and other movement disorders. The genetic factors involved can be placed on a curve of effect size versus allele frequency (Fig. 1) [62]. Detailed analysis of the specific phenotypes associated with genetic forms of Parkinson disease is imperative, given that establishment of endophenotypes within the Parkinson disease spectrum may enable a better understanding of the pathogenesis and aid the development of targeted therapeutic interventions [63]. Monogenic forms of Parkinson disease account for only a small proportion of Parkinson disease cases. However, the finding of new genetic factors is vital, given that research into the molecular mechanisms underlying these mutations may provide insights into the pathophysiology of PD. With the emergence of new disease models such as iPSC cell-derived neurons, we now greatly enhanced our capability to study these mechanisms.

**Acknowledgements**

We would like to thank Dr Philip Seibler for providing Fig. 2. K.R.K. is supported by the Dora Lush NHMRC postgraduate scholarship. K.L. has been supported by grants from German Research Foundation (DFG) and the Bachmann Strauss Dystonia & Parkinson foundation. C.K. is supported by grants from the Hermann and Lilly Schilling Foundation, the BMBF (01GI0201) and the EU (MEFOPA).

**Conflicts of interest**

C.K. editorial board member of the journals Neurology and Movement Disorders, is a member of the Scientific Advisory Board of the Bachmann Strauss Dystonia and Parkinson’s Disease Foundation, and serves as a consultant for Centogene.

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 516).


This study identified mutations in SLC2A2 as a cause of familial diastolic basal ganglia calcification linked to 8p21.1–q11.23.
23. A two-stage meta-analysis conducted by the International Parkinson Disease Genomic Consortium was the first meta-analysis of GWAS in Parkinson disease.
27. This detailed study focuses on the association of LRRK2 variants with Parkinson disease susceptibility in different ethnic groups.
29. Lancet 2011; 377:613–614. This is a comment of high interest to clinicians who aim to translate results from GWAS into clinical practice.
Movement disorders


35. Anheim M, Elbaz A, Lesage S, et al. Penetration of Parkinson disease in glucocerebrosidase gene mutation carriers. Neurology; 2012; 78:417–420. In this study, investigators estimated Parkinson disease penetrance in a familial study of GBA mutation carriers. The penetrance was higher than expected, especially for older age groups, suggesting that GBA should be considered as a dominant causal gene with reduced penetrance rather than a genetic risk factor.


This article describes morphological alterations in IPS cell-derived dopaminergic neurons generated from patients with idiopathic and LRRK2-related Parkinson disease.


This important study provides evidence for a new molecular model to explain the association of GBA mutations and Parkinson disease.


The authors performed a comprehensive, up-to-date review of the genetic contribution to the pathogenesis of Tourette syndrome.


One of several articles to identify mutations in the PRRT2 gene as a cause of paroxysmal kinesigenic dyskinesia and infantile convulsions and choreoathetosis syndrome.


There were conflicting results from follow-up studies of the landmark GWAS (Stefansson et al. [50]) which showed a significant association between LINGO1 polymorphisms and essential tremor risk in an Icelandic population. In response, Navarro and colleagues performed this meta-analysis of all published data involving the rs9652490 and rs11856808 polymorphisms in LINGO1.


This article identified two novel genetic risk factors for RLS, and confirmed the four previously identified risk variants. The findings demonstrate that there are numerous genetic variants that contribute to the risk of RLS.


