A multi-centre clinico-genetic analysis of the VPS35 gene in Parkinson disease indicates reduced penetrance for disease-associated variants

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SHORT REPORT

A multi-centre clinico-genetic analysis of the VPS35 gene in Parkinson disease indicates reduced penetrance for disease-associated variants

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ABSTRACT

Background Two recent studies identified a mutation (p.Asp620Asn) in the vacuolar protein sorting 35 gene as a cause for an autosomal dominant form of Parkinson disease. Although additional missense variants were described, their pathogenic role yet remains inconclusive.

Methods and results We performed the largest multi-center study to ascertain the frequency and pathogenicity of the reported vacuolar protein sorting 35 gene variants in more than 15,000 individuals worldwide. p.Asp620Asn was detected in 5 familial and 2 sporadic PD cases and not in healthy controls. p.Leu774Met in 6 cases and 1 control, p.Gly51Ser in 3 cases and 2 controls. Overall analyses did not reveal any significant increased risk for p.Leu774Met and p.Gly51Ser in our cohort.

Conclusions Our study apart from identifying the p.Asp620Asn variant in familial cases also identified it in idiopathic Parkinson disease cases, and thus provides genetic evidence for a role of p.Asp620Asn in Parkinson disease in different populations worldwide.

INTRODUCTION

There is increasing interest to try to identify uncommon and rare genetic variants that increase the risk of common diseases and that are difficult to identify using traditional genome-wide association studies (GWAS) approaches.1 Rare variants which are not mapped by GWAS can be identified by using next generation sequencing, that is, exome sequencing in large families with multiple affected individuals.2 Exome sequencing is now routinely used to identify rare mutations in familial forms of disease in diverse phenotypes.2 Two recent studies independently performed exome sequencing in large families of Caucasian descent, and identified a mutation in the vacuolar protein sorting 35 (VPS35) gene as a possible cause for an autosomal dominant form of Parkinson disease (PD).3,4 In addition, several non-synonymous base exchanges were identified, but their involvement in disease pathogenesis remains inconclusive. Furthermore, recently published studies provided conflicting results regarding the role of VPS35 in PD.5,4 Here, we performed a large multi-centre study to determine the frequency and pathogenicity of VPS35 variants in PD in diverse populations worldwide.

METHODS

Consortium Investigators from the Genetic Epidemiology of Parkinson disease Consortium were invited to participate in this study. A total of 23 sites representing 19 countries from four continents agreed to contribute DNA samples and clinical data for a total of 15,583 individuals (8870 cases and 6513 controls). Control individuals underwent neurological examination and were excluded from the study whenever there was clinical evidence for any extrapyramidal disorder.

Genotyping We selected seven non-synonymous variants exactly as they were proposed.3 In addition, we selected tag single nucleotide polymorphisms

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Additional supplementary tables are published online only. To view these files please visit the journal online (http://dx.doi.org/10.1136/jmedgenet-2012-101155).

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Genotype-phenotype correlations

(SNPs) (HapMap Rel 28 phase II+III, Aug10, National Centre for Biotechnology Information. B36 dbSNP b126; http://www.hapmap.org) that cover the common genetic variants in the VPS35 gene using an $r^2$ threshold of 0.8–1.0 to select tag SNPs for VPS35 gene. Using this strategy, we were able to capture 23 SNPs in a 40 kb region, including VPS35 (chr16:46 693 589–46 723 144 based on hg 19). Therefore, in total, 10 SNPs located in the VPS35 were genotyped (including seven rare non-synonymous and three common variants). Genotyping was performed by a central genotyping core. Genotyping was performed using a matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry on a MassArray system (Sequenom, San Diego, California, USA). Cleaned extension products were analysed by a mass spectrometer (Bruker Daltronics, Billerica, MA, USA) and peaks were identified using the MassArray Typer 4.0 software (Sequenom). Assays were designed by the AssayDesigner software 4.0 (Sequenom) with the default parameters for the iPLEX Gold chemistry and the Human Genotyping Tools ProxSNP and PreXTEND (Sequenom). All variants were genotyped in one multiplex assay. The average call rate of the variants was >97%. The local Ethics Committee approved the study. All participants gave signed informed consent.

Statistical analysis

Logistic regression was used to test the association between VPS35 and PD in our overall cohort. For common variants (minor allele frequency >5%), we synthesised the effect estimates using fixed and random effects models. Fixed effect models assume that the genetic effect is the same in populations from different sites and that observed differences are due to chance alone. For associations showing between-study heterogeneity, fixed effect estimates yield narrower CIs and smaller $p$ values as compared with random effects models, which incorporate between-study heterogeneity. Random effects models allow the genetic effects might be different due to genuine heterogeneity that may exist across different sites. Random effects calculations take into account the estimated between-study heterogeneity. Cochran's $Q$ test of homogeneity and the $I^2$ metric were used to evaluate the between-site heterogeneity. The $I^2$ metric ranges from 0% to 100% and measures the proportion of variability that is beyond chance. Typically, estimates of $I^2$ <25% are considered to reflect little or no heterogeneity, 25%–50% moderate heterogeneity, 50%–75% large heterogeneity and >75% very large heterogeneity. The overall main analysis considered all sites and populations irrespective of ancestry. For variants with minor allele frequency <1%, an exact test was used to compare the frequency differences between cases and controls combining data across all 21 sites.

RESULTS

Characteristics of sites and overall database

Overall, 23 sites contributed a total of 8870 cases and 6513 controls. Characteristics of all participating sites are shown in table 1. Most sites contributed participants of Caucasian ancestry (N=19); four sites included participants of Asian ancestry. The proportion of men and women ranged from 42% to 55% across different participating sites (table 1). The median age at onset of PD in our studied population was 61 years.

Rare variants

Overall, we observed p.Asp620Asn in seven cases, p.Leu774Met in six cases and one control, p.Gly51Ser in three cases and two controls. Details per site are shown in table 2. The controls subjects carrying p.Leu774Met (P-13) and p.Gly51Ser (P2 and P-16) at the time of study sampling were 81, 84 and 76 years, respectively. In Caucasian populations, the number of carriers in cases and controls for the three variants were 5 versus 0 (p.Asp620Asn), 4 versus 1 (p.Leu774Met) and 3 versus 1 (p.Gly51Ser), respectively. In Asian descent populations, the respective numbers were 2 versus 0 (p.Asp620Asn), 2 versus 0 (p.Leu774Met) and 0 versus 1 (p.Gly51Ser). Most interestingly, two out of seven patients carrying the p.Asp620Asn variant presented without any family history for PD. This represents the first evidence for reduced penetrance of the respective variant initially attributed to autosomal dominant familial PD. We did not observe any carriers for one variant (p.Arg524Trp) in our cohort. Two non-synonymous variants (p.Met57Ile, p.Thr82Arg) failed genotyping. By collapsing the rare variants across different sites, we did not observe statistically significant increased risk for p.Leu774Met and p.Gly51Ser in our cohort (see online supplementary table S1).

Overall data synthesis for common variants

Out of three tag SNPs, one SNP (rs5218745) failed genotyping. We did not observe significant association for any of common variants with PD either with either fixed effect or random effect models (see online supplementary table S2). The OR ranged from 0.96 to 0.99 and tight 95% CIs excluded modest association effects. We observed no substantial heterogeneity for the two genotyped SNPs, and also the Q test was non-statistically significant for common SNPs. Moreover, examining the Caucasian or Asian populations separately did not change our results (data not shown).

Clinical features

All PD patients who carried potential pathogenic variants (p.Asp620Asn, p.Gly51Ser, p.Leu774Met) were clinically diagnosed with PD (Online supplementary clinical analysis data). A few of these (0.2%) affected individuals also have a positive family history. Affected individuals exhibited classical symptoms of PD (resting tremor, bradykinesia, rigidity) (table 2). The clinical diagnosis of PD was made by movement disorder specialists who used UK brain bank criteria for PD. Non-motor symptoms were present in the majority of PD patients carrying a pathogenic variant (table 2). Interestingly, hallucinations and dementia were also observed in one asymptomatic carrier suggesting clinical heterogeneity associated with VPS35. The identified healthy carriers have not shown any sign of PD as yet (table 2).

DISCUSSION

We performed the first multi-centre study to define the role of the VPS35 gene (PARK17) in PD by assessing the frequency of the reported non-synonymous variants in familial and sporadic PD patients from different populations worldwide. Among 15 383 subjects genotyped, we found a pathogenic relevance for p.Asp620Asn in different populations. Most interestingly, out of seven subjects who carry p.Asp620Asn, two have a negative family history. Therefore, our results provide additional evidence that VPS35 is a rare cause of familial as well as the common sporadic form of PD. In total, about 0.4% of PD cases in diverse population were due to disease-associated variant in the VPS35 gene. Our result of supporting the role of common variants of the VPS35 gene in PD is consistent with recently published GWAS and also meta- analyses of GWAS of PD, as none of these highlighted the role of common variability in VPS35 gene as a risk factor for PD. The p.Asp620Asn
variant is located in the C-terminal region of the VPS35 protein pointing that subtle structural changes might influence the disease pathogenesis.3

The spectrum of proteins involved in PD aetiology has grown considerably. This includes proteins that are related to mitochondrial quality control (Parkin, PINK1 and DJ1), proteins involved in protein aggregation (SNCA) (Synuclein, MAPT) Microtubule associated protein T au), and proteins which are involved in sorting and degradation within endocytic and autophagy pathways ((VDAC) Voltage dependent anion channel, (GBA) Glucocerebrosidase gene, VPS35).16 17 So far, very little is known about the specific role of VPS35 in PD, except that it is hypothesised that it is involved in cargo recognition as part of a retrograde complex recycling membrane proteins from endosomes to the trans-Golgi network.34 Indeed, in vitro and in vivo studies strongly implicate the role of VPS35

### Table 1

<table>
<thead>
<tr>
<th>Site</th>
<th>Country</th>
<th>N</th>
<th>Case</th>
<th>Control</th>
<th>Male (%)</th>
<th>Female (%)</th>
<th>Mean AAO</th>
<th>Mean Age at study</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
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<tr>
<td>Annesi</td>
<td>Italy</td>
<td>394</td>
<td>197</td>
<td>197</td>
<td>204 (51.7%)</td>
<td>190 (48.2%)</td>
<td>61.5</td>
<td>63.7</td>
<td>UKPDBB</td>
</tr>
<tr>
<td>Brice</td>
<td>France</td>
<td>505</td>
<td>272</td>
<td>233</td>
<td>302 (59.8%)</td>
<td>203 (40.1%)</td>
<td>47.6</td>
<td>57.8</td>
<td>UKPDBB</td>
</tr>
<tr>
<td>Bozi</td>
<td>Greece</td>
<td>222</td>
<td>114</td>
<td>108</td>
<td>107 (48.1%)</td>
<td>115 (51.8%)</td>
<td>69.9</td>
<td>74.5</td>
<td>UKPDBB</td>
</tr>
<tr>
<td>Wsizolek</td>
<td>USA</td>
<td>1518</td>
<td>692</td>
<td>826</td>
<td>794 (52.3%)</td>
<td>724 (47.6%)</td>
<td>64.4</td>
<td>71.7</td>
<td>UKPDBB</td>
</tr>
<tr>
<td>Garnaux</td>
<td>Belgium</td>
<td>82</td>
<td>68</td>
<td>14</td>
<td>45 (54.8)</td>
<td>37 (45.1%)</td>
<td>62.1</td>
<td>69.6</td>
<td></td>
</tr>
<tr>
<td>Hjærgaardgi</td>
<td>Greece</td>
<td>714</td>
<td>357</td>
<td>357</td>
<td>379 (53.0%)</td>
<td>335 (46.9%)</td>
<td>63.4</td>
<td>62.7</td>
<td>UKPDBB</td>
</tr>
<tr>
<td>Jern</td>
<td>Korea</td>
<td>749</td>
<td>408</td>
<td>341</td>
<td>314 (41.9%)</td>
<td>435 (58.0%)</td>
<td>57.6</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Opala</td>
<td>Poland</td>
<td>629</td>
<td>352</td>
<td>277</td>
<td>340 (54.0%)</td>
<td>289 (45.7%)</td>
<td>50.2</td>
<td>68.1</td>
<td>UKPDBB</td>
</tr>
<tr>
<td>Lynch</td>
<td>Ireland</td>
<td>740</td>
<td>368</td>
<td>372</td>
<td>340 (45.9%)</td>
<td>400 (54.0%)</td>
<td>50.5</td>
<td>70.7</td>
<td>UKPDBB</td>
</tr>
<tr>
<td>Lin</td>
<td>Taiwan</td>
<td>320</td>
<td>160</td>
<td>160</td>
<td>160 (50%)</td>
<td>160 (50%)</td>
<td>62.0</td>
<td>70.8</td>
<td></td>
</tr>
<tr>
<td>Fachers</td>
<td>Italy</td>
<td>181</td>
<td>114</td>
<td>67</td>
<td>86 (47.5%)</td>
<td>95 (52.4%)</td>
<td>63.0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Maragane</td>
<td>USA</td>
<td>1024</td>
<td>801</td>
<td>223</td>
<td>600 (58.5%)</td>
<td>361 (35.3%)</td>
<td>59</td>
<td>74.7</td>
<td>Bower</td>
</tr>
<tr>
<td>Mellick</td>
<td>Australia</td>
<td>2024</td>
<td>1012</td>
<td>1012</td>
<td>1042 (51.4%)</td>
<td>981 (48.4%)</td>
<td>59</td>
<td>72.2</td>
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</tr>
<tr>
<td>Morrison</td>
<td>England</td>
<td>1120</td>
<td>766</td>
<td>354</td>
<td>606 (54.1%)</td>
<td>294 (38.8%)</td>
<td>61.5</td>
<td>69.6</td>
<td>UKPDBB</td>
</tr>
<tr>
<td>Mok</td>
<td>China</td>
<td>436</td>
<td>260</td>
<td>176</td>
<td>264 (60.5%)</td>
<td>170 (39.8%)</td>
<td>65.8</td>
<td>74.1</td>
<td></td>
</tr>
<tr>
<td>Asa˘ıy</td>
<td>Norway</td>
<td>1278</td>
<td>656</td>
<td>622</td>
<td>721 (56.4%)</td>
<td>557 (43.5%)</td>
<td>58.8</td>
<td>72.9</td>
<td>UKPDBB</td>
</tr>
<tr>
<td>Wirdefeldt</td>
<td>Sweden</td>
<td>299</td>
<td>83</td>
<td>216</td>
<td>147 (48.1%)</td>
<td>152 (50.8%)</td>
<td>65.8</td>
<td>71.4</td>
<td></td>
</tr>
<tr>
<td>Van Broeckhoven</td>
<td>Belgium</td>
<td>1010</td>
<td>501</td>
<td>509</td>
<td>500 (49.5%)</td>
<td>509 (50.3%)</td>
<td>60.5</td>
<td>66.3</td>
<td></td>
</tr>
<tr>
<td>Rogavea</td>
<td>Canada</td>
<td>560</td>
<td>387</td>
<td>173</td>
<td>303 (54.1%)</td>
<td>257 (45.8%)</td>
<td>49.7</td>
<td>64.2</td>
<td>UKPDBB</td>
</tr>
<tr>
<td>Tan</td>
<td>Singapore</td>
<td>391</td>
<td>194</td>
<td>197</td>
<td>244 (62.4%)</td>
<td>147 (37.5%)</td>
<td>59.7</td>
<td>54.0</td>
<td>UKPDBB</td>
</tr>
<tr>
<td>Hattori</td>
<td>Japan</td>
<td>121</td>
<td>121</td>
<td>0</td>
<td>62 (51.2%)</td>
<td>59 (48.7%)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Gasser/Shaarma</td>
<td>Germany</td>
<td>760</td>
<td>760</td>
<td>0</td>
<td>0 (50.3%)</td>
<td>0 (50.3%)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Toda</td>
<td>Japan</td>
<td>306</td>
<td>227</td>
<td>79</td>
<td>160 (52.6%)</td>
<td>160 (52.6%)</td>
<td>57.8</td>
<td>65.1</td>
<td>UKPDBB</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>15383</td>
<td>8870</td>
<td>6513</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AAO, Age at onset; NA: Not applicable.

### Table 2

<table>
<thead>
<tr>
<th>Id</th>
<th>Ethnicity</th>
<th>Rare variant</th>
<th>Age at onset</th>
<th>Clinical signs</th>
<th>Bradykinesia</th>
<th>Rigidity</th>
<th>Tremor</th>
<th>Postural instability</th>
<th>L-dopa responsive</th>
<th>Non-motor symptoms</th>
<th>Family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-1</td>
<td>Caucasian</td>
<td>p.Asp620Asn</td>
<td>59</td>
<td>Classical PD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>Negative</td>
<td>Dementia, visual hallucinations</td>
</tr>
<tr>
<td>P-2</td>
<td>Caucasian</td>
<td>p.Gly51Ser</td>
<td>NA</td>
<td>Control</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Negative</td>
<td>Negative</td>
<td>–</td>
</tr>
<tr>
<td>P-3</td>
<td>Caucasian</td>
<td>p.Gly51Ser</td>
<td>NAV</td>
<td>Classical PD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>Negative</td>
<td>–</td>
</tr>
<tr>
<td>P-4</td>
<td>Caucasian</td>
<td>p.Gly51Ser</td>
<td>55</td>
<td>Classical PD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>Negative</td>
<td>Dementia, visual hallucinations</td>
</tr>
<tr>
<td>P-5</td>
<td>Caucasian</td>
<td>p.Gly51Ser</td>
<td>49</td>
<td>Classical PD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>P-6</td>
<td>Caucasian</td>
<td>p.Asp620Asn</td>
<td>37</td>
<td>Classical PD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>Positive</td>
<td>–</td>
</tr>
<tr>
<td>P-7</td>
<td>Caucasian</td>
<td>p.Asp620Asn</td>
<td>59</td>
<td>Classical PD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>Positive</td>
<td>–</td>
</tr>
<tr>
<td>P-8</td>
<td>Caucasian</td>
<td>p.Asp620Asn</td>
<td>55</td>
<td>Classical PD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>Positive</td>
<td>–</td>
</tr>
<tr>
<td>P-9</td>
<td>Caucasian</td>
<td>p.Asp620Asn</td>
<td>66</td>
<td>Classical PD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>Positive</td>
<td>–</td>
</tr>
<tr>
<td>P-10</td>
<td>Caucasian</td>
<td>p.Leu774Met</td>
<td>41</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>Positive</td>
<td>–</td>
</tr>
<tr>
<td>P-11</td>
<td>Caucasian</td>
<td>p.Leu774Met</td>
<td>65</td>
<td>Classical PD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>Positive</td>
<td>–</td>
</tr>
<tr>
<td>P-12</td>
<td>Caucasian</td>
<td>p.Leu774Met</td>
<td>65</td>
<td>Classical PD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>Positive</td>
<td>Disturbance of gait and balance</td>
</tr>
<tr>
<td>P-13</td>
<td>Caucasian</td>
<td>p.Leu774Met</td>
<td>NA</td>
<td>Control</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>Negative</td>
<td>–</td>
</tr>
<tr>
<td>P-14</td>
<td>Caucasian</td>
<td>p.Leu774Met</td>
<td>44</td>
<td>Classical PD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Autonomic dysfunction</td>
<td>Positive</td>
<td>–</td>
</tr>
<tr>
<td>P-16</td>
<td>Asian</td>
<td>p.Gly51Ser</td>
<td>52</td>
<td>Classical PD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>Negative</td>
<td>–</td>
</tr>
<tr>
<td>P-17</td>
<td>Asian</td>
<td>p.Leu774Met</td>
<td>75</td>
<td>Classical PD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Negative</td>
<td>Negative</td>
<td>–</td>
</tr>
</tbody>
</table>

NA, not applicable; NA0, not available; PD, Parkinson disease; + positive; –negative.
gene in neurodegeneration. For example, reduced levels of VPS35 have been found in affected brain regions of Alzheimer disease (AD) patients\(^{19}\) and loss of VPS35 function has been shown to increase the levels of amyloid β and cause synaptic impairment in a mouse model of AD. Furthermore, variants in another member of the VPS family and substrate of retromer complex, SORL1, have been implicated in AD.\(^{19}\)

In this study, we have focused only on non-synonymous variants identified by Zimprich and colleagues.\(^{5}\) Of note, we confirmed the pathogenic relevance of the p.Asp620Asn variant which was identified by both studies for familial cases and in sporadic PD. Recently, published studies also identified p.Asp620Asn mutations in PD,\(^{6,20}\) thus providing support to the role of p.Asp620Asn in PD. In our study, clinically, the symptomatic carriers showed a broad spectrum of clinical phenotypes ranging from typical PD to (DLB) Dementia with Lewy body, so longitudinal evaluation of carriers at risk will provide unique information on the natural course of the disease caused by VPS35. Even though our data support the role of p.Asp620Asn variant in PD, given the fact that the frequency in diverse population is far below <1%, it is likely to be a rare cause of PD worldwide. Nevertheless, sequencing of families is encouraged for identifying additional missense variants which may provide mechanistic insight into the causes of PD.

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5. Genotype-phenotype correlations


Correction


A multi-centre clinico-genetic analysis of the VPS35 gene in Parkinson disease indicates reduced penetrance for disease-associated variants

Manu Sharma, John P A Ioannidis, Jan O Aasly, et al.

doi: 10.1136/jmedgenet-2012-101155

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