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EIF4G1 mutations do not cause Parkinson's disease

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Abstract

EIF4G1 mutations were previously reported as a cause of PD. As a result of this finding considerable work has been performed to test this idea and to examine the functional role of eukaryotic translation initiation factor 4-gamma in the pathogenic process underlying PD. Here we show that the originally described mutation is likely a rare benign variant. We tested this variant in a very large series of subjects and show that it is more frequent in controls than cases. We argue here that this infers that *EIF4G1* mutations are not related to PD.

In 2011 the gene encoding eukaryotic translation initiation factor 4-gamma (*EIF4G1*) was suggested to contain mutations that cause autosomal dominant Parkinson's disease, often with dementia (Chartier-Harlin et al. 2011, 1). The authors performed genome-wide linkage analysis of a multi-incident northern French family with autosomal-dominant late-onset parkinsonism, the result of which indicated a disease segregating mutation at 3q26-q28. Following positional sequencing the authors identified a segregating mutation in *EIF4G1*, p.R1205H (rs112176450). On the basis of this mutation subsequent screening of a cohort of PD patients was performed. This revealed additional mutations in PD cases that were absent from controls, p.A502V, p.G686C, p.S1164R, and p.R1197W.

Following this report several groups have screened this gene, but to date no group has provided strongly supportive evidence for the involvement of *EIF4G1* mutations in PD (Siitonen et al. 2013, 1; Huttenlocher et al. 2014, 1; Blanckenberg et al. 2014, 1; Chen et al. 2013, 1; Fujioka et al. 2013, 144; Nishioka et al. 2014, 1; Lesage et al. 2012; Tucci et al.

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2012). While these reports have failed to provide support, the absence of evidence is not the evidence of absence, and thus the role of *EIF4G1* mutations in PD has remained unclear.

We designed the genotyping array NeuroX to include variants related to neurological disease, including risk variants identified by genome wide association studies and mutations implicated as disease causing. The NeuroX content includes several of the originally reported *EIF4G1* mutations, including the principle disease segregating p.R1205H mutation on which the nomination of *EIF4G1* as a PD gene rests. We have assayed 6,249 PD subjects and 6,032 controls using NeuroX (Nalls et al. 2014).

These data revealed an excess of p.R1205H heterozygotes in controls compared to cases, being present in 5 of 6,032 controls, and only in 1 of 6,249 cases. Cluster plots for the genotyping of this variant revealed apparently high quality genotyping (figure 1). Because this was the originally identified mutation, which led to the screening of other cases for *EIF4G1* mutations, we believe these data strongly suggest that this is not a gene for PD, and that this variant is a rare benign polymorphism.

We also had data available for two other variants that had previously been described as mutations, p.A502V (rs111290936) and p.R1197W (rs113388242). We identified one p.A502V heterozygote in 6,032 controls and five in 6,249 cases. We failed to identify any cases with the p.R1197W variant, but did find a single heterozygous control.

We confirmed each of these changes using Sanger sequencing in available DNA samples (figure 2).

These data argue convincingly that the mutation p.R1205H is not a cause of PD. Because this mutation was the underlying rationale for nominating *EIF4G1* mutations as a cause of PD we believe the consequence of this finding is that *EIF4G1* mutations are not a cause of PD. Given the investment in understanding the pathogenic role of the protein product of *EIF4G1* in the pathobiology of PD it is important to correct the belief that this is a PD associated gene (Dhungel et al. 2014). These data also highlight the utility of NeuroX in screening large sample series for mutations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- EIF4G1 mutations were previously reported as a cause of Parkinson's disease
- We show here that the originally reported mutation is present in controls more often than in cases
- These data argue that EIF4G1 mutations are not a cause of Parkinson's disease

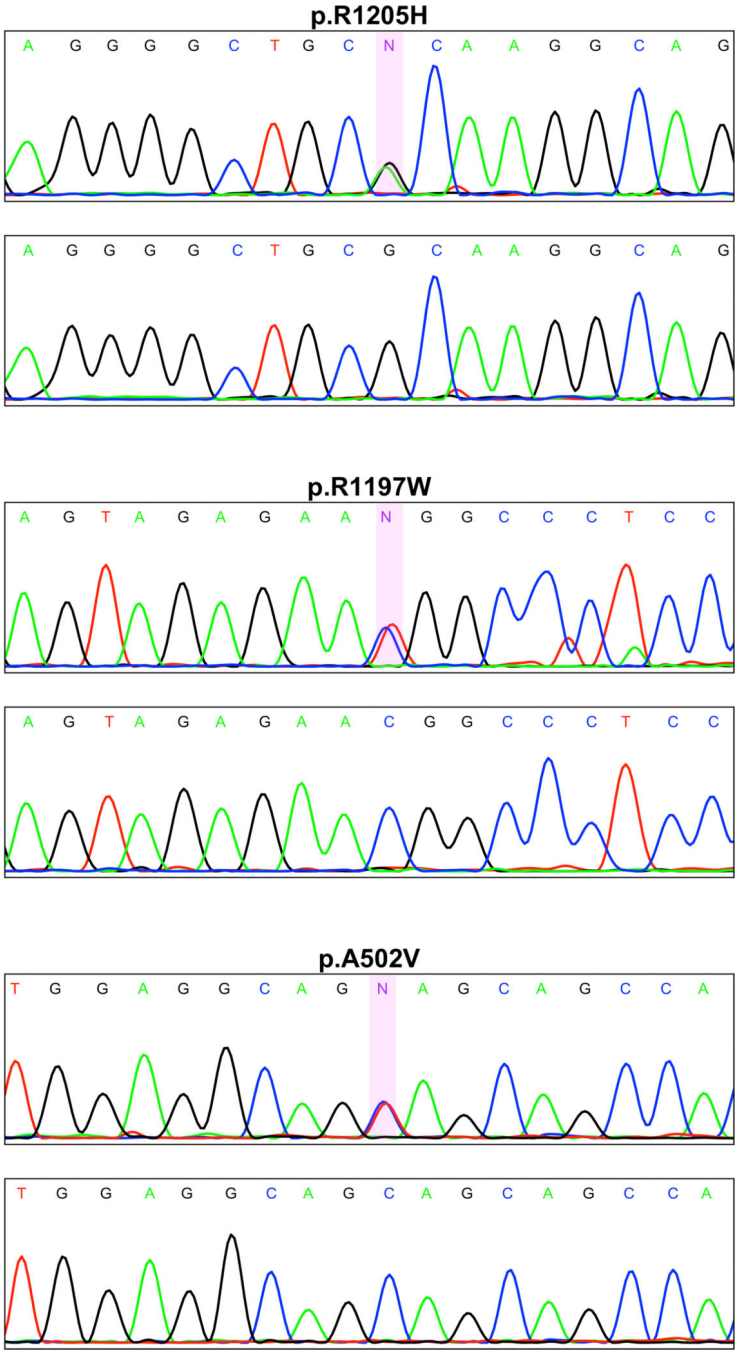

Figure 1.

Cluster plots from NeuroX for the 3 *EIF4G1* mutations. These plots were generated from log R Ratio and B Allele Frequency exported from Genome Studio (Illumina, Inc) and plotted in R.

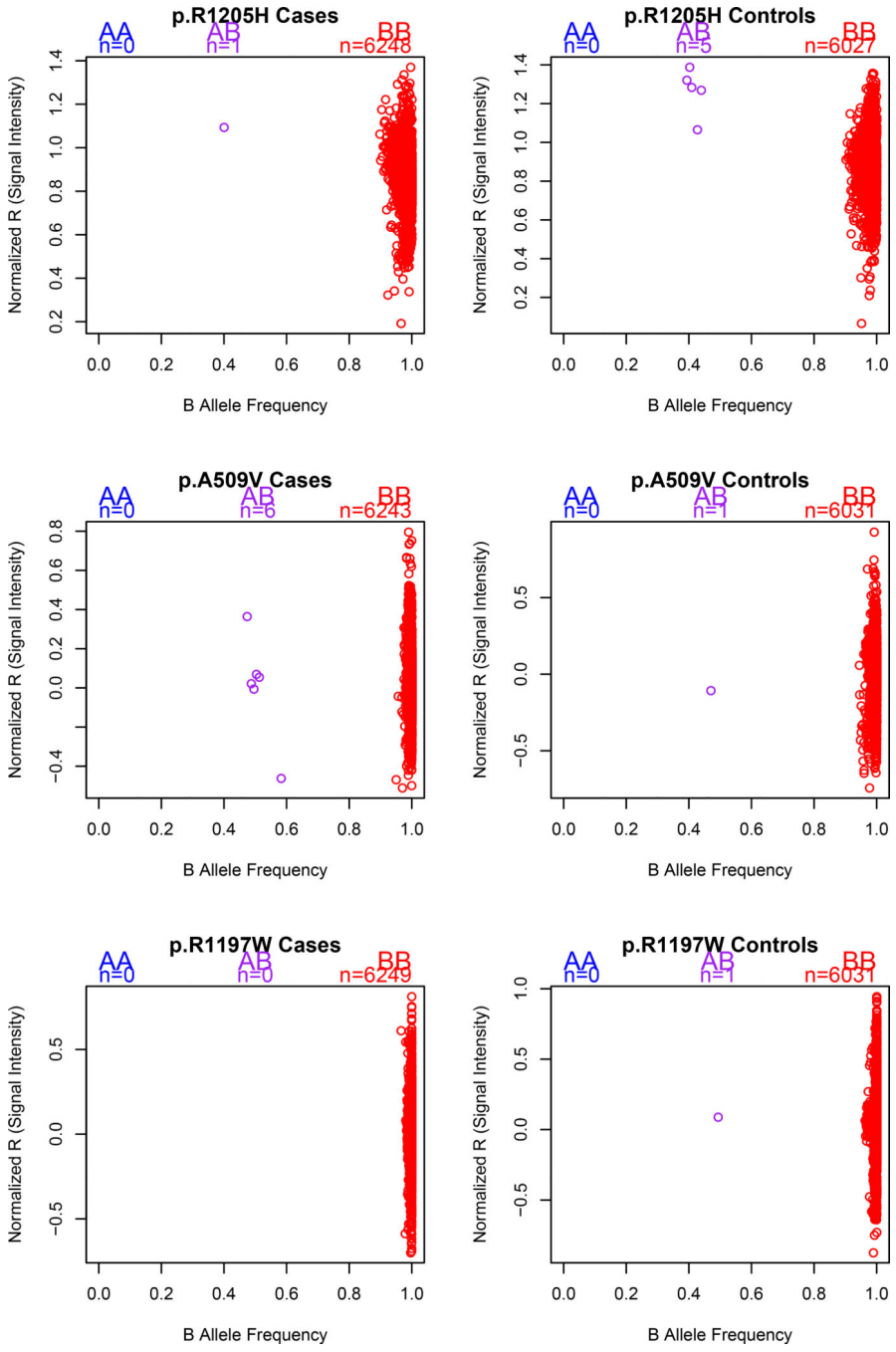

Figure 2.

Representative chromatograms from Sanger sequencing for each of the 3 mutations. For each mutation a heterozygous sample is shown above, with a homozygous wild type shown below. The variant of interest is highlighted in each case.

Table

Distribution of cases and controls with identified *EIF4G1* mutations.

	Cases (n=6249)			Controls (n=6032)		
	n	**Origin**	**Age at Onset**	**n**	**Origin**	**Age**
p.R1205H (rs112176450)	1	North American	60	5	North American North American North American European WUSTL_903	78 76 75 68 68
p.R1197W (rs113388242)	0	-	-	1	Greek*	46
p.A502V (rs111290936)	5	North American North American French North American** German	71 61 64 76 73	1	North American	77

* previously reported in (Lesage et al. 2012)

** PD by self-report