Neurobiology of Aging 73 (2019) 230.e1–230.e4

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Relationship between variants of 17 newly loci and Parkinson's disease in a Chinese population

Xiang Chen [a,1], Yousheng Xiao [b,1], Wenyuan Guo [a,1], Miaomiao Zhou [a], Shuxuan Huang [a], Mingshu Mo [a], Zhe Li [a], Guihua Li [a], Hanqun Liu [a], Guoyou Peng [a], Zhuohua Wu [a], Yijuan Wu [a], Chaohao Yang [a], Zhong Pei [c], Chaojun Chen [d,*], Pingyi Xu [a,**]

[a] Department of Neurology, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China
[b] Department of Neurology, The First Affiliated Hospital of Guangxi Medical University, Guangxi, China
[c] Department of Neurology, National Key Clinical Department and Key Discipline of Neurology, The First Affiliated Hospital of SunYat-sen University, Guangzhou, China
[d] Department of Neurology, Guangzhou Chinese Medical Integrated Hospital (Huadu), Guangzhou, China

ARTICLE INFO

Article history:
Received 23 April 2018
Received in revised form 26 July 2018
Accepted 15 August 2018
Available online 24 August 2018

Keywords:
Parkinson's disease
Gene variants
Association

ABSTRACT

Genetic factors play significant roles in the causes of Parkinson's disease (PD). Recently, a meta-analysis of genome-wide association study (GWAS) has identified 17 loci associated with PD. The objective of our study was to investigate the association of 17 single-nucleotide polymorphisms with the risk of PD in Chinese population. We performed a case-control association study, and 1189 subjects comprising 652 PD patients and 537 controls were genotyped by using a Mass ARRAY System or a TaqMan assay. We found that rs601999 (OR (95% CI) = 3.378 (2.273–5.051), $p < 0.001$), rs11343 (OR (95% CI) = 0.426 (0.210–0.862), $p = 0.018$), rs353116 (OR (95% CI) = 0.738 (0.577–0.943), $p = 0.015$), and rs2280104 (OR (95% CI) = 1.371 (1.078–1.743), $p = 0.010$) were significantly associated with PD in Chinese population. However, no significant association was found in the remaining 13 single-nucleotide polymorphisms between both groups.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder. It is characterized by a variety of motor and nonmotor symptoms. The neuropathological features of PD are caused by progressive loss of dopaminergic neurons in the substantia nigra and aggregation of α-synuclein–positive Lewy bodies (LBs) in the surviving neurons. The exact pathogenesis of PD remains poorly understood, but mounting evidence has revealed that genetic factors may play significant roles in the causes of PD (Deng et al., 2017; Rocha et al., 2018).

Genome-wide association studies (GWAS) have provided tangible gains in understanding the genetic architecture of PD. More than 24 loci involved in PD have been identified by GWAS (Nalls et al., 2014). Recently, Diana Chang et al. have identified 17 novel PD loci using a comprehensive meta-analysis of GWAS (Chang et al., 2017). To validate the role of these new loci in susceptibility to PD in other ethnicities, we conducted a case-control association study of these 17 variants in our Chinese Han population.

2. Materials and methods

Our study included a total of 652 patients with PD (male/female: 391/261, age: 61.17 ± 9.12 years) and 537 unrelated healthy control subjects (male/female: 342/195; age: 63.57 ± 12.9 years). The diagnosis of PD was made according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria. The genotypes of these 17 SNPs were determined using a Mass ARRAY System or a TaqMan assay (Beijing Genomics Institute). The power calculations were performed using Quanto (Gauderman, 2002). All other statistical analyses in this study were performed using SPSS 21.0 for Windows. Odds ratios (OR) and 95% confidence intervals (95% CI) were used to assess the strength of polymorphisms and PD

* Corresponding author at: Department of Neurology, Guangzhou Chinese Medical Integrated Hospital (Huadu), No. 87 Yingbin Road, Guangzhou, 510800, China. Tel.: +86 020-86888575-2109; fax: +86 020-86888997.
** Corresponding author at: Department of Neurology, The First Affiliated Hospital of Guangzhou Medical University, No. 151 Yanjiang Road, Guangzhou, 510120, China. Tel.: +86 13826161149; fax: +86 02083062726.
E-mail addresses: ccjbs@126.com (C. Chen), pingyixu@sina.com (P. Xu).
[1] These authors contributed equally to this work.

0197-4580/$ – see front matter © 2018 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.neurobiolaging.2018.08.017

Table 1
Genotypic analysis of 17 loci

SNP (Candidate gene)	HWE	Genotype/Allele	Association test	PD	Control	P	OR (95% CI)	P[a]	OR (95% CI)[a]
rs4653767 (*TPKB*)	0.511	Genotype	Genotypic (CC/CT/TT)	34/248/354	30/200/285				
			Dominant ((CC+CT)/TT)	282/354	230/285	0.913	0.987 (0.781−1.247)	0.886	0.983 (0.777−1.243)
			Recessive (CC/(CT+TT))	34/602	30/485	0.724	0.913 (0.551−1.513)	0.687	1.108 (0.673−1.826)
		Allele	C/T	318/956	262/770	0.814	0.978 (0.809−1.181)	0.788	0.975 (0.806−1.178)
rs34043159 (*IL1R2*)	0.403	Genotype	Genotypic (CC/CT/TT)	159/310/163	123/272/137				
			Dominant ((CC+CT)/TT)	469/163	395/137	0.988	0.998 (0.767−1.299)	0.988	0.998 (0.766−1.300)
			Recessive (CC/(CT+TT))	159/473	123/409	0.419	0.894 (0.683−1.205)	0.439	0/899 (0.685−1.178)
		Allele	C/T	628/636	518/546	0.631	1.041 (0.884−1.225)	0.633	1.041 (0.883−1.225)
rs353116 (*SCN3A***)**	0.378	Genotype	Genotypic (AA/GA/GG)	238/303/105	162/271/97				
			Dominant ((GG+GA)/AA)	408/238	368/162	**0.024**	0.755 (0.591−0.964)	**0.015**	0.738 (0.577−0.943)
			Recessive (GG/(GA+AA))	105/541	97/433	0.354	0.886 (0.640−1.174)	0.294	0.849 (0.626−1.153)
		Allele	G/A	513/779	595/465	**0.042**	0.843 (0.715−0.994)	**0.027**	0.829 (0.703−0.979)
rs4073221 (*SATB1*)	0.064	Genotype	Genotype (TT/GT/GG)	516/106/14	417/97/11				
			Dominant ((GG+GT)/TT)	120/516	108/417	0.467	0.898 (0.672−1.200)	0.530	1.098 (0.820−1.470)
			Recessive (GG/(GT+TT))	14/622	11/514	1.000	1.052 (0.473−2.337)	0.776	0.890 (0.398−1.987)
		Allele	G/T	134/1138	119/931	0.539	0.921 (0.709−1.196)	0.637	0.939 (0.722−1.221)
rs12497850 (*NCKIPS, CDC71*)	0.136	Genotype	Genotypic (GG/GT/TT)	0/53/597	2/36/493				
			Dominant ((GG+GT)/TT)	53/597	38/493	0.523	1.152 (0.747−1.777)	0.677	1.098 (0.976−1.698)
			Recessive (GG/(GT+TT))	0/650	2/529	0.202	-	0.117	-
		Allele	G/T	53/1247	40/1022	0.7	1.086 (0.714−1.651)	0.871	1.035 (0.680−1.577)
rs143918452 (*ALAS1*, *TLR9*, *DNAH1*, *BAP1*, *PHF7*, *NISCH*, *STAB1*, *ITIH3*, *ITIH4*)	0.808	Genotype	Genotypic (GG/GA/AA)	623/20/0	513/11/0				
			Dominant ((AA+AG)/GG)	20/623	11/513	0.361	1.497 (0.711−3.155)	0.330	1.451 (0.686−3.070)
			Recessive (AA/(AG+GG))	0/643	0/524	-	-	-	-
		Allele	A/G	20/1266	11/1037	0.364	1.489 (0.710−3.122)	0.333	1.444 (0.686−3.039)
rs78738012 (*ANK2*, *CAMK2D*)	0.983	Genotype	Genotypic (TT/TC/CC)	637/3/0	530/1/0				
			Dominant ((CC+CT)/TT)	3/637	1/530	0.631	2.496 (0.259−24.067)	0.455	2.381 (0.245−3.861)
			Recessive (CC/(CT+TT))	0/640	0/531	-	-	-	-
		Allele	C/T	3/1277	1/1061	0.631	2.493 (0.259−23.997)	0.455	2.377 (0.245−23.064)
rs2694528 (*ELOVL7*)	0.127	Genotype	Genotypic (AA/AC/CC)	555/79/2	478/47/3				
			Dominant ((CC+CA)/AA)	81/555	50/478	0.079	1.395 (0.961−2.024)	0.055	1.444 (0.992−2.102)
			Recessive (CC/(CA+AA))	2/634	3/525	0.664	0.552 (0.092−3.311)	0.545	0.574 (0.095−3.460)
		Allele	C/A	83/1189	53/1003	0.123	1.321 (0.927−1.884)	0.088	1.364 (0.955−1.947)
rs9468199 (*ZNF184*)	0.835	Genotype	Genotypic (GG/GA/AA)	408/195/27	337/169/20				
			Dominant ((AA+AG)/GG)	222/408	189/337	0.806	0.970 (0.762−1.236)	0.793	0.968 (0.759−1.235)
			Recessive (AA/(AG+GG))	27/603	20/506	0.679	1.133 (0.628−2.044)	0.694	1.126 (0.622−2.041)
		Allele	A/G	249/1011	209/843	0.950	0.993 (0.809−1.220)	0.932	0.991 (0.806−1.218)
rs2740594 (*CTSB*)	0.983	Genotype	Genotypic (GG/GA/AA)	0/6/641	0/1/533				
			Dominant ((GG+GA)/AA)	6/641	1/533	0.136	4.989 (0.599−41.570)	0.158	0.216 (0.026−1.811)
			Recessive (GG/(GA+AA))	0/647	0/534	-	-	-	-
		Allele	G/A	6/1288	1/1067	0.136	4.970 (0.587−41.350)	0.159	0.217 (0.026−1.815)
rs2280104 (*BIN3, SORBS3, PDLIM2, C8orf58***)**	0.681	Genotype	Genotypic (CC/TC/TT)	395/230/22	362/157/15				
			Dominant ((TT+TC)/CC)	252/395	172/362	**0.017**	1.343 (1.056−1.708)	**0.010**	1.371 (1.078−1.743)
			Recessive (TT/(TC+CC))	22/625	15/51	0.617	1.218 (0.625−2.372)	0.633	1.177 (0.603−2.298)
		Allele	T/C	274/1020	187/881	**0.025**	1.266 (1.029−1.555)	**0.025**	1.268 (1.031−1.561)
rs13294100 (*SH3GL2*)	0.472	Genotype	Genotypic (TT/GT/GG)	159/323/150	144/255/128				
			Dominant ((GG+GT)/TT)	473/159	383/144	0.403	1.118 (0.860−1.454)	0.448	1.107 (0.851−1.441)
			Recessive (GG/(GT+TT))	150/482	128/399	0.826	0.970 (0.740−1.272)	0.838	0.972 (0.741−1.276)
		Allele	G/T	623/641	511/543	0.699	1.033 (0.877−1.216)	0.728	1.030 (0.873−1.214)
rs10906923 (*FAM171A1*)	0.064	Genotype	Genotypic (CC/AC/AA)	202/307/130	180/240/111				
			Dominant ((AA+AC)/CC)	437/202	351/180	0.406	1.109 (0.868−1.418)	0.494	1.089 (0.852−1.395)
			Recessive (AA/(AC+CC))	130/509	111/420	0.814	0.966 (0.727−1.284)	0.733	0.951 (0.715−1.266)
		Allele	A/C	567/711	462/600	0.675	1.036 (0.879−1.220)	0.795	1.022 (0.867−1.205)

(*continued on next page*)

Table 1 (*continued*)

SNP (Candidate gene)	HWE	Genotype/Allele	Association test	PD	Control	P	OR (95% CI)	P[a]	OR (95% CI)[a]
rs8005172 (*GALC*)	0.256	Genotype	Genotypic (TT/TC/CC)	278/289/80	216/252/59				
			Dominant ((TT+TC)/CC)	567/80	468/59	0.586	0.894 (0.625–1.278)	0.562	0.899 (0.628–1.288)
			Recessive (TT/(TC+CC))	278/369	216/311	0.514	1.085 (0.859–1.370)	0.444	1.096 (0.867–1.385)
		Allele	C/T	449/845	370/684	0.837	0.982 (0.828–1.165)	0.777	0.976 (0.822–1.157)
rs11343 (*COQ7*)	0.182	Genotype	Genotypic (GG/TG/TT)	633/12/0	507/23/1				
			Dominant ((TT+TG)/GG)	12/633	24/507	**0.010**	0.4 (0.198–0.809)	**0.018**	0.426 (0.210–0.862)
			Recessive (TT/(TG+GG))	0/645	1/530	-	0.452	1.000	-
		Allele	T/G	12/1278	25/1037	**0.007**	0.389 (0.195–0.779)	**0.013**	0.416 (0.208–0.834)
rs4784227 (*TOX3*)	0.505	Genotype	Genotypic (CC/TC/TT)	357/236/43	305/197/27				
			Dominant ((TT+TC)/CC)	279/357	224/305	0.635	1.064 (0.843–1.344)	0.565	1.071 (0.847–1.353)
			Recessive (TT/(TC+CC))	43/593	27/502	0.266	1.348 (0.821–2.212)	0.216	1.370 (0.832–2.252)
		Allele	T/C	322/950	251/807	0.375	1.090 (0.901–1.318)	0.341	1.097 (0.907–1.327)
rs601999 (*ATP6V0A1, PSMC3IP, TUBG2*)	0.603	Genotype	Genotypic (CC/TC/TT)	522/127/0	498/34/1				
			Dominant ((TT+TC)/CC)	127/522	35/498	**<0.001**	3.462 (2.335–5.132)	**<0.001**	3.378 (2.273–5.051)
			Recessive (TT/(TC+CC))	0/649	1/532	0.451	-	1.000	-
		Allele	T/C	127/1171	36/1030	**<0.001**	3.106 (2.123–4.525)	**<0.001**	2.997 (2.046–4.389)

The four positive loci identified in this paper were marked in bold font.
Key: SNP, single-nucleotide polymorphism; HWE, Hardy-Weinberg equilibrium of control group; PD, Parkinson's disease; OR, odds ratio; CI, confidence intervals.
[a] Adjust age and sex by logistic regression.

susceptibility. A two-tailed $p < 0.05$ was considered significant for all analyses.

3. Results

There were no significant differences in gender or age distribution between patients and controls (supplementary file). All control genotype frequencies in all of the studied polymorphisms were in Hardy-Weinberg equilibrium. All genotyping reactions showed a high genotyping quality, with the exception of the SNP rs353116, rs4073221, and rs3740594. For this reason, we tested the three SNPs with a TaqMan assay. In genotypic analysis, the dominant models of rs2280104, rs601999, rs353116, and rs11343 were found to be significantly closely associated with PD and the powers of these four loci were more than 0.8 (table 1 and supplementary file). However, no significant association in recessive models was found among any of the SNPs between the two groups. In allelic analysis, the T allele of rs2280104 and rs601999, the A allele of rs353116, and G allele of rs11343 showed a higher risk of PD (table 1).

4. Discussion

GWAS is a powerful method for the detection of genetic factors in polygenic diseases, such as PD, but it can produce spurious association findings (Gomez-Garre et al., 2014). For this reason, replication of associations in other ethnic groups is essential to confirming the results. The present study was conducted to confirm the association of 17 novel loci that had recently been identified by Chang et al. through a comprehensive meta-analysis of GWAS with PD in our Chinese Han population.

Lysosomal defects contributing to protein aggregates and cell death are increasingly regarded as a major pathogenic event in PD (Dehay et al., 2013). The candidate gene of rs601999 *ATP6V0A1* (ATPase H+ transporting V0 subunit a1) encoding protein ATP6V0A1, a subunit of the vacuolar (H+)-ATPase, localizes to both the presynaptic membrane and synaptic vesicles present at nerve terminals. It is implicated in fusion between phagosomes and lysosomes during phagocytosis in the brain (Toei et al., 2010).

Numerous gene and toxin studies have implicated mitochondrial dysfunction in PD pathogenesis (Subramaniam and Chesselet, 2013). COQ7, which is encoded by *COQ7*, has been reported to play an essential role in COQ synthesis, maintenance of mitochondrial integrity, and neurogenesis in mice (Nakai et al., 2001). Reduction of the activity of COQ7 slowing down aging in *Caenorhabditis elegans* and in mice indicates its involvement in development of neurodegenerative diseases (Wang et al., 2009).

SCN3A, the candidate gene of rs353116, encodes the pore-forming Nav1.3 α subunit, which is responsible for the initiation and propagation of action potentials in excitable cells such as neurons (Hains et al., 2005). Dysregulation of sodium channel Nav1.3 expression may contribute to epilepsy syndromes and chronic neuropathic pain (Lamar et al., 2017). The Na^+/Ca^{2+} exchange defects induced Ca^{2+} toxicity by sodium channel Nav1.3 dysfunction may be a factor of degeneration of PD.

Bin3, the candidate gene of rs2280104, encodes a member of the BAR superfamily of curved membrane and GTPase-binding proteins. These proteins are implicated in signal transduction and vesicular trafficking (Ramalingam et al., 2008). However, further investigations are needed to explore the roles of these genes played in pathophysiologic pathways of PD.

In conclusion, we have confirmed that rs601999, rs11343, rs353116, and rs2280104 were associated with PD in Chinese population. However, we fail to replicate the association of other 13 SNPs with sporadic PD in this study. As the difference of MAF (minor allele frequency) between our population and 1000

Genomics in PubMed (supplementary file), the ethnic difference and environmental factors may account for the discrepancy between our study and Chang's study. To the best of our knowledge, this study is the first to replicate the novel GWAS meta-analysis by which Chang et al. identified 17 loci in a cohort of Chinese population. As the limitation of sample size, more studies in Chinese or other populations with larger samples may help to evaluate the relationship between these new loci and PD.

Disclosure statement

The authors declare no conflict of interests.

Acknowledgements

This work was supported by research grants from National Key R&D Program of China (2016YFC1306600, 2017YFC1310300), the National Natural Science Foundation of China (81471292, U1603281, U1503222, 81430021, 81870992, 88180126, 81870856), the Science Foundation of Guangdong of China (2015A030311021, 2018A030313649), a technology project of Guangzhou (201504281820463), and the collaborative innovation Planning Project of Guangzhou Science Bureau (No. 2017-10-1035).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neurobiolaging.2018.08.017.

References

Chang, D., Nalls, M.A., Hallgrimsdottir, I.B., Hunkapiller, J., van der Brug, M., Cai, F., International Parkinson's Disease Genomics Consortium, 23andMe Research Team, Kerchner, G.A., Ayalon, G., Bingol, B., Sheng, M., Hinds, D., Behrens, T.W., Singleton, A.B., Bhangale, T.R., Graham, R.R., 2017. A meta-analysis of genome-wide association studies identifies 17 new Parkinson's disease risk loci. Nat. Genet. 49, 1511–1516.

Dehay, B., Martinez-Vicente, M., Caldwell, G.A., Caldwell, K.A., Yue, Z., Cookson, M.R., Klein, C., Vila, M., Bezard, E., 2013. Lysosomal impairment in Parkinson's disease. Mov. Disord. 28, 725–732.

Deng, H., Wang, P., Jankovic, J., 2017. The genetics of Parkinson disease. Ageing Res. Rev. 42, 72–85.

Gauderman, W.J., 2002. Sample size requirements for association studies of gene-gene interaction. Am. J. Epidemiol. 155, 478–484.

Gomez-Garre, P., Huertas-Fernandez, I., Caceres-Redondo, M.T., Alonso-Canovas, A., Bernal-Bernal, I., Blanco-Ollero, A., Bonilla-Toribio, M., Burguera, J.A., Carballo, M., Carrillo, F., Jose Catalan-Alonso, M., Escamilla-Sevilla, F., Espinosa-Rosso, R., Carmen Fernandez-Moreno, M., Garcia-Caldentey, J., Garcia-Moreno, J.M., Giacometti-Silveira, S., Gutierrez-Garcia, J., Jesus-Maestre, S., Lopez-Valdes, E., Martinez-Castrillo, J.C., Medialdea-Natera, M.P., Mendez-Lucena, C., Minguez-Castellanos, A., Angel Moya, M., Ochoa-Sepulveda, J.J., Ojea, T., Rodriguez, N., Rubio-Agusti, I., Sillero-Sanchez, M., Del Val, J., Vargas-Gonzalez, L., Mir, P., 2014. Lack of validation of variants associated with cervical dystonia risk: a GWAS replication study. Mov Disord. 29, 1825–1828.

Hains, B.C., Saab, C.Y., Waxman, S.G., 2005. Changes in electrophysiological properties and sodium channel Nav1.3 expression in thalamic neurons after spinal cord injury. Brain 128 (Pt 10), 2359–2371.

Lamar, T., Vanoye, C.G., Calhoun, J., Wong, J.C., Dutton, S.B.B., Jorge, B.S., Velinov, M., Escayg, A., Kearney, J.A., 2017. SCN3A deficiency associated with increased seizure susceptibility. Neurobiol. Dis. 102, 38–48.

Nakai, D., Yuasa, S., Takahashi, M., Shimizu, T., Asaumi, S., Isono, K., Takao, T., Suzuki, Y., Kuroyanagi, H., Hirokawa, K., Koseki, H., Shirsawa, T., 2001. Mouse homologue of coq7/clk-1, longevity gene in Caenorhabditis elegans, is essential for coenzyme Q synthesis, maintenance of mitochondrial integrity, and neurogenesis. Biochem. Biophys. Res. Commun. 289, 463–471.

Nalls, M.A., Pankratz, N., Lill, C.M., Do, C.B., Hernandez, D.G., Saad, M., DeStefano, A.L., Kara, E., Bras, J., Sharma, M., Schulte, C., Keller, M.F., Arepalli, S., Letson, C., Edsall, C., Stefansson, H., Liu, X., Pliner, H., Lee, J.H., Cheng, R., International Parkinson's Disease Genomics, C., Parkinson's Study Group Parkinson's Research: The Organized, G.I., 23andMe, GenePd, NeuroGenetics Research, C., Hussman Institute of Human, G., Ashkenazi Jewish Dataset, I., Cohorts for, H., Aging Research in Genetic, E., North American Brain Expression, C., United Kingdom Brain Expression, C., Greek Parkinson's Disease, C., Alzheimer Genetic Analysis, G., Ikram, M.A., Ioannidis, J.P., Hadjigeorgiou, G.M., Bis, J.C., Martinez, M., Perlmutter, J.S., Goate, A., Marder, K., Fiske, B., Sutherland, M., Xiromerisiou, G., Myers, R.H., Clark, L.N., Stefansson, K., Hardy, J.A., Heutink, P., Chen, H., Wood, N.W., Houlden, H., Payami, H., Brice, A., Scott, W.K., Gasser, T., Bertram, L., Eriksson, N., Foroud, T., Singleton, A.B., 2014. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat. Genet. 46, 989–993.

Ramalingam, A., Duhadaway, J.B., Sutanto-Ward, E., Wang, Y., Dinchuk, J., Huang, M., Donover, P.S., Boulden, J., McNally, L.M., Soler, A.P., Muller, A.J., Duncan, M.K., Prendergast, G.C., 2008. Bin3 deletion causes cataracts and increased susceptibility to lymphoma during aging. Cancer Res. 68, 1683–1690.

Rocha, E.M., De Miranda, B., Sanders, L.H., 2018. Alpha-synuclein: Pathology, mitochondrial dysfunction and neuroinflammation in Parkinson's disease. Neurobiol. Dis. 109 (Pt B), 249–257.

Subramaniam, S.R., Chesselet, M.F., 2013. Mitochondrial dysfunction and oxidative stress in Parkinson's disease. Prog. Neurobiol. 106-107, 17–32.

Toei, M., Saum, R., Forgac, M., 2010. Regulation and isoform function of the V-ATPases. Biochemistry 49, 4715–4723.

Wang, Y., Branicky, R., Stepanyan, Z., Carroll, M., Guimond, M.P., Hihi, A., Hayes, S., McBride, K., Hekimi, S., 2009. The anti-neurodegeneration drug clioquinol inhibits the aging-associated protein CLK-1. J. Biol. Chem. 284, 314–323.