

Supplementary Material

Clinical heterogeneities among LRRK2 variants in Parkinson's disease: a meta-analysis

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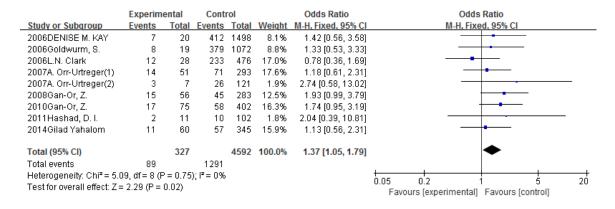
	Experim	ental	Conti	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2006L.N. Clark	26	28	384	476	1.9%	3.11 [0.73, 13.36]	
2009RN Alcalay	23	26	614	665	3.3%	0.64 [0.18, 2.19]	
2011Hashad, D. I.	9	11	92	102	2.0%	0.49 [0.09, 2.59]	<u></u> _
2017San Luciano, M.	283	530	396	759	92.9%	1.05 [0.84, 1.31]	+
Total (95% CI)		595		2002	100.0%	1.06 [0.86, 1.32]	*
Total events	341		1486				
Heterogeneity: Chi ² = 3	.60, df = 3	P = 0.3	1); $I^2 = 17$	°%			0.05 0.2 1 5 20
Test for overall effect: Z	= 0.57 (P =	0.57)					0.05 0.2 1 5 20 Favours [experimental] Favours [control]

1.1 Asymmetrical onset of G2019S

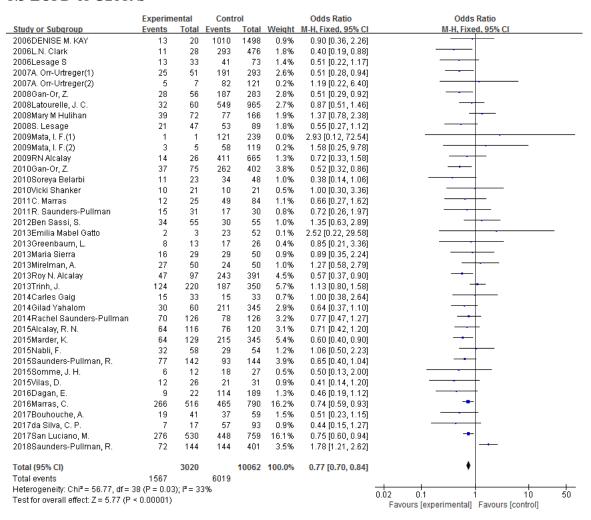
	Exp	eriment	al	(Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2006L.N. Clark	52.1	11.4	28	53.9	13.7	476	3.0%	-1.80 [-6.20, 2.60]	
2006Lesage S	45.2	9.4	33	43.2	15.3	73	2.8%	2.00 [-2.75, 6.75]	
2007A. Orr-Urtreger(1)	57.7	11.6	51	59.2	11.6	293	3.6%	-1.50 [-4.95, 1.95]	
2007Ishihara, L.	58.9	13	73	48.6	18.3	128	3.0%	10.30 [5.95, 14.65]	
2008Gan-Or, Z.	56.9	11.4	56	60.7	11.5	283	3.7%	-3.80 [-7.07, -0.53]	
2008S. Lesage	54.6	12.1	35	54.7	12.6	81	2.7%	-0.10 [-4.96, 4.76]	
2009Mata, I. F.(1)	68	0	1	59.1	11.6	239		Not estimable	
2009Mata, I. F.(2)	50.2	9.3	5	55.4	14	119	1.4%	-5.20 [-13.73, 3.33]	
2009RN Alcalay	42.9	5	26	41.7	6.7	665	4.5%	1.20 [-0.79, 3.19]	+
2010Soreya Belarbi	58.7	9.7	21	57.8	8.7	21	2.4%	0.90 [-4.67, 6.47]	
2011C. Marras	59	11	25	54	14	78	2.5%	5.00 [-0.31, 10.31]	
2011Hashad, D. I.	55.3	5.4	11	56.4	6.8	102	3.6%	-1.10 [-4.55, 2.35]	
2011R. Saunders-Pullman	64.7	9.8	31	63.4	7.8	30	3.0%	1.30 [-3.14, 5.74]	 -
2012Ben Sassi, S.	54.4	10.3	55	55.3	8.6	55	3.5%	-0.90 [-4.45, 2.65]	
2012Gilad Yahalom	58.1	11.2	33	60.9	13.4	316	3.2%	-2.80 [-6.90, 1.30]	
2013Emilia Mabel Gatto	66.67	4.04	3	58.78	12.45	52	2.3%	7.89 [2.20, 13.58]	
2013Greenbaum, L.	49.5	6.8	13	49.15	6.6	26	3.0%	0.35 [-4.13, 4.83]	
2013Maria Sierra	62.5	11.05	29	62.98	9.67	50	2.8%	-0.48 [-5.31, 4.35]	
2013Roy N. Alcalay	60	10	97	62	10.5	391	4.3%	-2.00 [-4.25, 0.25]	
2013Trinh, J.	57.1	11.6	220	55.3	14.4	350	4.4%	1.80 [-0.35, 3.95]	
2014Gilad Yahalom	58.2	10.1	60	61.9	12	345	4.0%	-3.70 [-6.55, -0.85]	
2015Alcalay, R. N.	57.2	10.8	116	58.2	10.8	120	4.0%	-1.00 [-3.76, 1.76]	
2015Marder, K.	58.4	11	129	61.6	10.4	345	4.4%	-3.20 [-5.39, -1.01]	
2015Saunders-Pullman, R.	57.4	11	142	58	10.9	144	4.2%	-0.60 [-3.14, 1.94]	
2016Marras, C.	55.65	11.6	506	58.69	12.5	773	4.8%	-3.04 [-4.38, -1.70]	
2016Pal, G. D.	47.5	2.4	4	41.2	5.3	72	4.1%	6.30 [3.65, 8.95]	
2017Bouhouche, A.	52.15	11.28	41	55.12	11.65	59	2.9%	-2.97 [-7.53, 1.59]	
2017da Silva, C. P.	46.76	9.14	17	55.02	12.36	93	2.7%	-8.26 [-13.28, -3.24]	
2017San Luciano, M.	55.7	11.3	530	58.7	12.5	759	4.8%	-3.00 [-4.31, -1.69]	
2018Saunders-Pullman, R.	60	9.3	144	61.5	10.7	401	4.6%	-1.50 [-3.35, 0.35]	
Total (95% CI)			2535			6939	100.0%	-0.46 [-1.64, 0.72]	•
Heterogeneity: Tau2 = 7.07; C	hi² = 123	.49. df=	= 28 (P	< 0.000	01): I² =	77%			
Test for overall effect: Z = 0.76			(>1 -				-10 -5 0 5 10
		.,							Favours [experimental] Favours [control]

1.2 Age at onset of G2019S

[†] These authors have contributed equally to this work and are co-first authors.



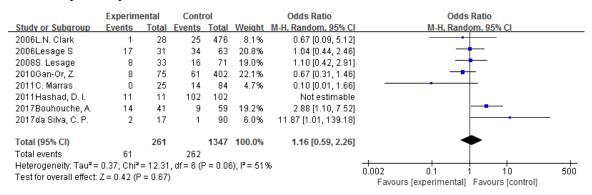
1.3 EOPD of G2019S



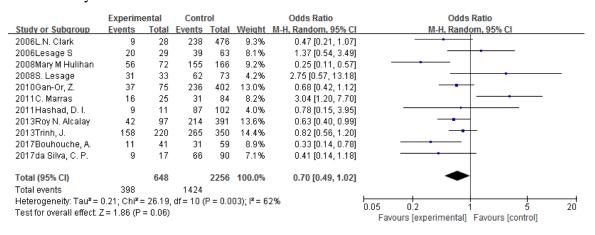
1.4 Gender-male of G2019S

	Experim	ental	Conti	rol		Odds Ratio	Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
2005Jose Miguel Bras	6	11	20	117	0.8%	5.82 [1.62, 20.95]			
2006DENISE M. KAY	11	20	344	1498	2.1%	4.10 [1.69, 9.98]			
2006Gaig, C.	6	13	85	286	2.1%	2.03 [0.66, 6.21]	_		
2006Goldwurm, S.	10	19	226	1073	2.0%	4.16 [1.67, 10.37]			
2006L.N. Clark	7	26	54	453	2.2%	2.72 [1.09, 6.78]			
2007A. Orr-Urtreger(1)	25	51	71	293	5.6%	3.01 [1.63, 5.54]		-	
2007A. Orr-Urtreger(2)	3	7	32	121	1.0%	2.09 [0.44, 9.83]			
2008Gan-Or, Z.	24	56	64	283	6.3%	2.57 [1.41, 4.67]			
2008Latourelle, J. C.	54	60	845	965	5.2%	1.28 [0.54, 3.04]	_	-	
2009Mata, I. F.(1)	0	1	4	239	0.0%	17.44 [0.62, 489.20]	_		
2009Mata, I. F.(2)	1	5	28	119	0.9%	0.81 [0.09, 7.57]			
2009RN Alcalay	5	26	99	665	3.2%	1.36 [0.50, 3.69]	_	-	
2010Gan-Or, Z.	34	75	85	402	7.7%	3.09 [1.85, 5.17]		-	
2012Gilad Yahalom	16	33	70	316	3.6%	3.31 [1.59, 6.88]		_ -	
2013Emilia Mabel Gatto	3	3	13	50	0.1%	19.44 [0.94, 401.55]		· · · · · · · · · · · · · · · · · · ·	
2013Roy N. Alcalay	34	97	69	391	9.3%	2.52 [1.54, 4.12]		-	
2014Gilad Yahalom	26	60	73	345	6.4%	2.85 [1.61, 5.05]			
2016Dagan, E.	8	21	32	177	2.2%	2.79 [1.07, 7.28]			
2017Bouhouche, A.	22	41	11	59	2.2%	5.05 [2.06, 12.40]			
2017da Silva, C. P.	9	17	15	93	1.1%	5.85 [1.95, 17.59]			
2017San Luciano, M.	151	530	116	759	35.8%	2.21 [1.68, 2.90]		-	
Total (95% CI)		1172		8704	100.0%	2.62 [2.25, 3.06]		•	
Total events	455		2356						
Heterogeneity: Chi ² = 18.7	4. df = 20 (P = 0.54	i); I² = 0%	6			 	 	_
Test for overall effect: Z = 1							0.001 0.1		000
	v		,				Favours [experimental]	Favours [control]	

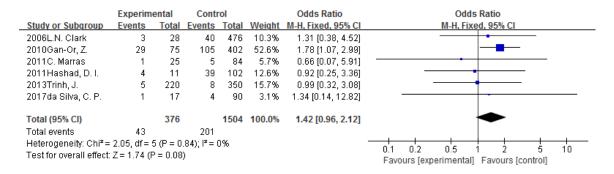
1.5 Family history of G2019S



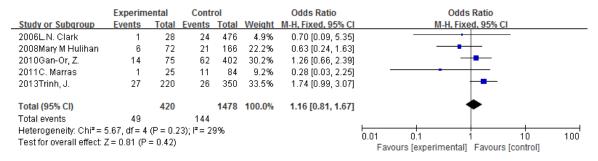
1.6 FS-bradykinesia of G2019S



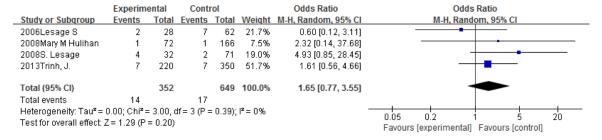
1.7 FS-resting tremor of G2019S



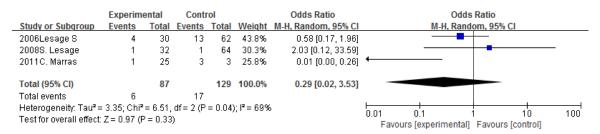
1.8 FS-rigidity of G2019S



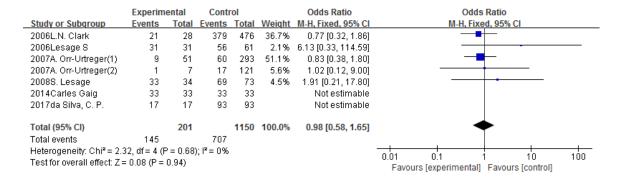
1.9 FS-Postural instability or Gait difficulty of G2019S



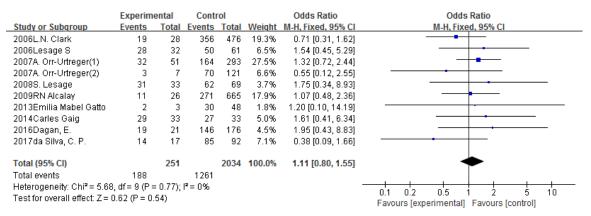
1.10 FS-Dystonia of G2019S



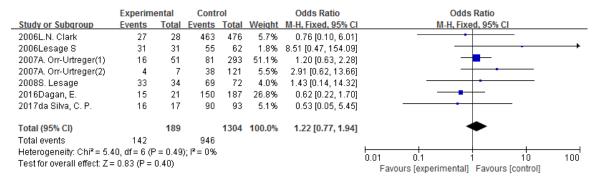
1.11 FS-Micrographia of G2019S



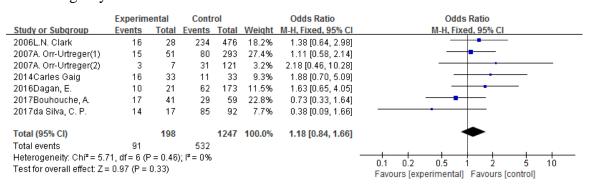
1.12 Bradykinesia of G2019S



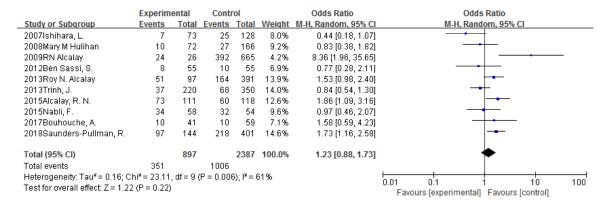
1.13 Resting tremor of G2019S



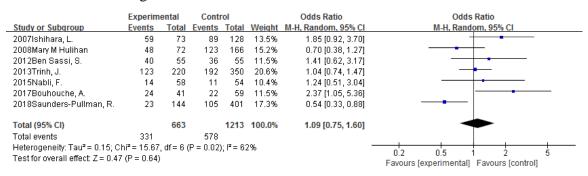
1.14 Rigidity of G2019S



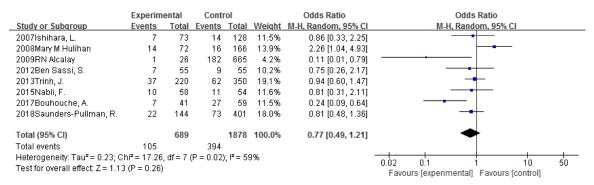
1.15 Postural instability or Gait difficulty of G2019S



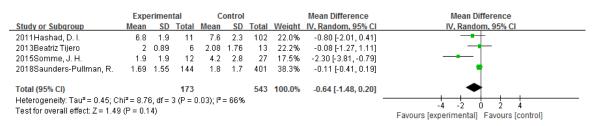
1.16 T-Akinetic-rigid/PIGD of G2019S



1.17 T-Mixed/Intermediate of G2019S



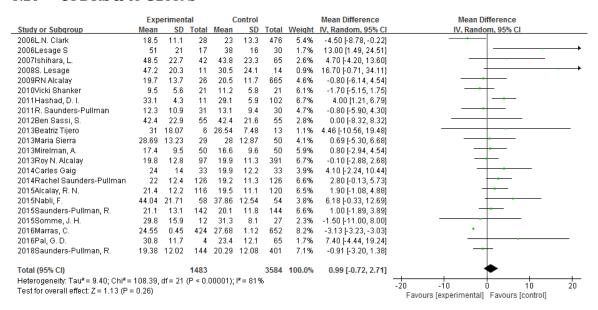
1.18 T-Tremor-dominant of G2019S



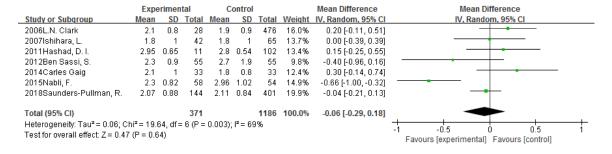
1.19 UPDRS I of G2019S

	Expe	rimen	tal	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2010Vicki Shanker	6.4	5.8	21	8.1	4.1	21	5.0%	-1.70 [-4.74, 1.34]	+
2011Hashad, D. I.	24.3	6.7	11	24.2	5.8	102	3.0%	0.10 [-4.02, 4.22]	
2013Beatriz Tijero	12.5	8.8	6	9.58	2.74	13	1.0%	2.92 [-4.28, 10.12]	
2013Trinh, J.	1.41	0.77	220	1.31	0.72	350	29.3%	0.10 [-0.03, 0.23]	•
2014Carles Gaig	10.3	7.5	33	8.3	4.9	33	5.0%	2.00 [-1.06, 5.06]	+-
2015Nabli, F.	11.17	6.71	58	12.02	5.4	54	8.0%	-0.85 [-3.10, 1.40]	
2015Somme, J. H.	12.5	8.4	12	13.6	6.6	27	1.8%	-1.10 [-6.47, 4.27]	
2016Marras, C.	10.18	0.75	449	11.09	0.19	684	29.5%	-0.91 [-0.98, -0.84]	•
2018Saunders-Pullman, R.	8.42	6.06	144	9.01	5.94	401	17.4%	-0.59 [-1.74, 0.56]	
Total (95% CI)			954			1685	100.0%	-0.38 [-1.13, 0.36]	
Heterogeneity: Tau ² = 0.49; CI Test for overall effect: Z = 1.01			= 8 (P	< 0.000	01); l²:	= 96%		-	-10 -5 0 5 10
restror overall effect. Z = 1.01	$\mu = 0.3$	17							Favours [experimental] Favours [control]

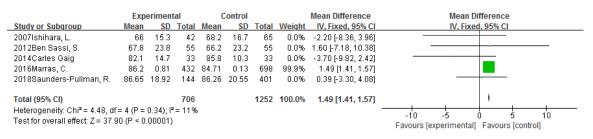
1.20 UPDRS II of G2019S



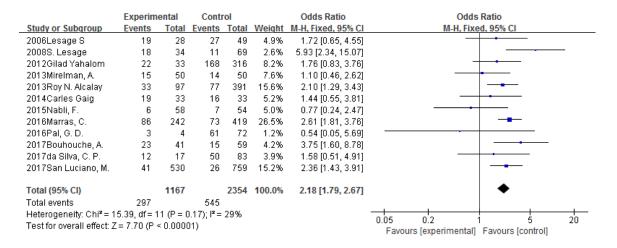
1.21 UPDRSIII of G2019S



1.22 H-Y of G2019S



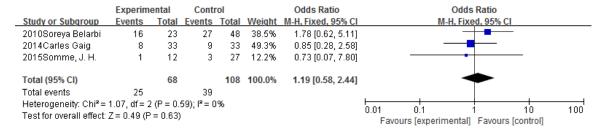
1.23 Schwab & England of G2019S



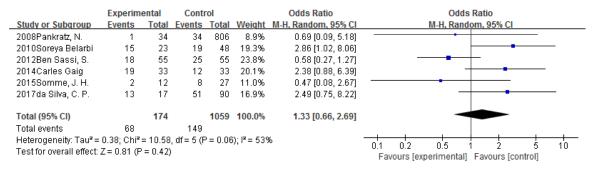
1.24 Dyskinesia of G2019S

	Experim	ental	Conti	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2008S. Lesage	18	34	19	69	16.4%	2.96 [1.26, 6.97]	_ -
2013Emilia Mabel Gatto	3	3	31	48	4.1%	3.89 [0.19, 79.71]	
2014Carles Gaig	18	33	17	33	15.3%	1.13 [0.43, 2.97]	- -
2015Nabli, F.	25	58	23	54	17.4%	1.02 [0.48, 2.16]	
2016Marras, C.	86	135	95	396	20.4%	5.56 [3.65, 8.46]	-
2017Bouhouche, A.	25	41	29	59	16.8%	1.62 [0.72, 3.63]	 •
2017da Silva, C. P.	15	17	51	59	9.6%	1.18 [0.23, 6.14]	-
Total (95% CI)		321		718	100.0%	2.02 [1.03, 3.97]	•
Total events	190		265				
Heterogeneity: Tau ² = 0.54	4; Chi² = 23	3.52, df=	= 6 (P = 0		+ + + + + + + + + + + + + + + + + + + +		
Test for overall effect: Z = 3	2.03 (P = 0	.04)		0.02 0.1 1 10 5 Favours [experimental] Favours [control]			

1.25 Motor fluctuations of G2019S



1.26 Anxiety of G2019S



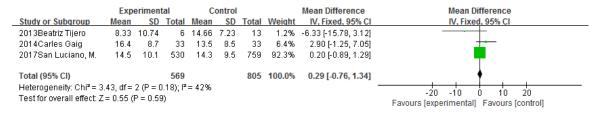
1.27 Depression of G2019S

	Expe	rimen	ıtal	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2012Ben Sassi, S.	16.8	5.9	55	20.2	10.1	55	1.2%	-3.40 [-6.49, -0.31]	
2013Mirelman, A.	4.2	3.5	50	3.2	3.2	50	6.6%	1.00 [-0.31, 2.31]	 -
2013Roy N. Alcalay	4.2	3.2	97	3.7	3.4	391	22.0%	0.50 [-0.22, 1.22]	 • -
2015Alcalay, R. N.	3.7	3.3	116	3.2	3.2	120	16.6%	0.50 [-0.33, 1.33]	+-
2017San Luciano, M.	5.4	4.2	530	5	4.1	759	53.6%	0.40 [-0.06, 0.86]	
Total (95% CI)			848			1375	100.0%	0.43 [0.09, 0.77]	◆
Heterogeneity: Chi² = 6	1.70, df = 4	1 (P =	0.15); I	-	-4 -2 0 2 4				
Test for overall effect: Z	(= 2.51 (F	9 = 0.0	01)		Favours [experimental] Favours [control]				

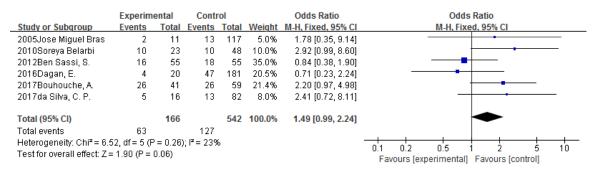
1.28 GDS15 of G2019S

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2009RN Alcalay	1	26	46	665	10.0%	0.54 [0.07, 4.06]	
2010Soreya Belarbi	6	23	3	48	4.3%	5.29 [1.19, 23.58]	
2013Emilia Mabel Gatto	3	3	12	48	0.7%	20.44 [0.99, 423.90]	· · · · · · · · · · · · · · · · · · ·
2014Carles Gaig	3	33	5	33	13.7%	0.56 [0.12, 2.56]	
2015Somme, J. H.	0	12	7	27	13.7%	0.11 [0.01, 2.08]	
2017Bouhouche, A.	25	41	28	59	26.9%	1.73 [0.77, 3.89]	+-
2017da Silva, C. P.	3	17	39	90	30.7%	0.28 [0.08, 1.04]	-
Total (95% CI)		155		970	100.0%	1.07 [0.67, 1.71]	+
Total events	41		140				
Heterogeneity: Chi² = 16.8	2, df = 6 (F	= 0.010	$(1)^2 = 64$	%			0.002 0.1 1 10 500
Test for overall effect: Z = (0.28 (P = 0	78)					0.002

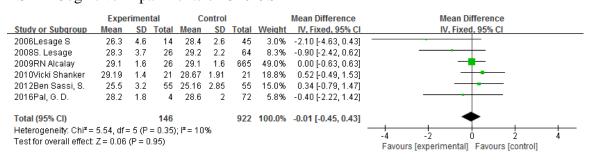
1.29 Hallucination of G2019S



1.30 SCOPA-AUT of G2019S



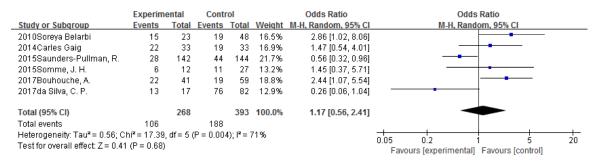
1.31 Cognitive impairments of G2019S



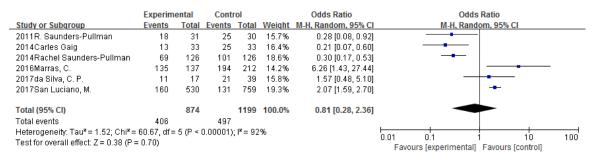
1.32 MMSE of G2019S

	Expe	erimen	tal	Co	ontro	I		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2012Ben Sassi, S.	21.8	4.3	20	21.8	3.7	17	1.2%	0.00 [-2.58, 2.58]	
2013Roy N. Alcalay	25.2	2.9	97	24.7	3.9	391	16.8%	0.50 [-0.19, 1.19]	 •
2014Rachel Saunders-Pullman	25.4	3	126	25.2	3.8	126	11.4%	0.20 [-0.65, 1.05]	
2015Alcalay, R. N.	25.4	2.7	116	25	3.4	120	13.3%	0.40 [-0.38, 1.18]	
2017San Luciano, M.	24.1	4.3	530	24.5	4.4	759	35.0%	-0.40 [-0.88, 0.08]	
2018Saunders-Pullman, R.	25.14	2.85	144	24.71	3.9	401	22.4%	0.43 [-0.17, 1.03]	 •
Total (95% CI)			1033			1814	100.0%	0.12 [-0.17, 0.40]	*
Heterogeneity: Chi² = 7.18, df = 5	(P = 0.21)); ² = 3	30%					-	-2 -1 0 1 2
Test for overall effect: Z = 0.80 (P =	= 0.42)								Favours [experimental] Favours [control]

1.33 MoCA of G2019S



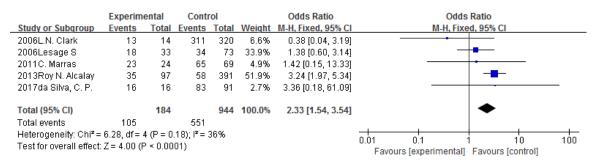
1.34 Sleep disturbances of G2019S



1.35 Olfactory disturbances of G2019S

	Expe	tal	Control				Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
2011R. Saunders-Pullman	24.8	7.08	31	18.8	8.05	30	15.9%	6.00 [2.19, 9.81]	_ -		
2014Carles Gaig	23.5	6.8	33	18.4	6	33	24.1%	5.10 [2.01, 8.19]			
2014Rachel Saunders-Pullman	22.8	8.7	126	18.6	7.1	126	60.0%	4.20 [2.24, 6.16]			
Total (95% CI)			190			189	100.0%	4.70 [3.18, 6.22]	←		
Heterogeneity: Chi² = 0.76, df = 2 (Test for overall effect: Z = 6.07 (P <		-10 -5 0 5 10 Favours [experimental] Favours [control]									

1.36 UPSIT scores of G2019S



1.37 Good response to 1-dopa of G2019S

	Expe	erimental	ı	(Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2006Lesage S	697	322	30	601	356	48	4.0%	96.00 [-57.03, 249.03]	
2008S. Lesage	580	335	31	491	245	58	5.3%	89.00 [-44.72, 222.72]	
2009RN Alcalay	556	624	26	471	492	665	1.6%	85.00 [-157.75, 327.75]	
2011C. Marras	631	410	25	585	423	73	2.7%	46.00 [-141.74, 233.74]	
2012Ben Sassi, S.	558.1	321.7	55	517.7	229.5	55	8.7%	40.40 [-64.04, 144.84]	
2013Mirelman, A.	300.1	251.9	50	191.8	262.8	50	9.3%	108.30 [7.40, 209.20]	
2013Roy N. Alcalay	443	444	97	348	373	391	10.3%	95.00 [-0.78, 190.78]	
2014Carles Gaig	793.7	482.1	33	823	516.4	33	1.6%	-29.30 [-270.34, 211.74]	
2015Alcalay, R. N.	389	402	116	220	288	120	11.8%	169.00 [79.52, 258.48]	_ -
2015Somme, J. H.	1,066.3	388	12	857	325	27	1.5%	209.30 [-42.14, 460.74]	
2016Marras, C.	539.31	578.5	516	366.13	373	527	26.9%	173.18 [113.97, 232.39]	_ -
2018Saunders-Pullman, R.	407.39	410.23	144	337.1	367.58	401	16.3%	70.29 [-5.76, 146.34]	
Total (95% CI)			1135			2448	100.0%	115.20 [84.47, 145.93]	•
Heterogeneity: Chi² = 11.28, d	f= 11 (P =	0.42); l²:	= 2%						300 400 0 400 300
Test for overall effect: Z = 7.35	(P < 0.00	001)							-200 -100 0 100 200 Favours [experimental] Favours [control]

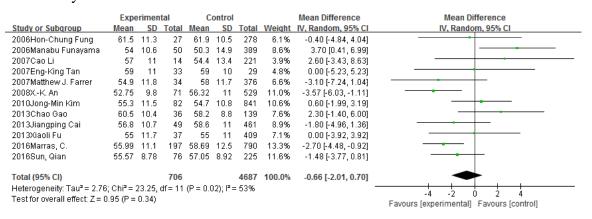
1.38 LEDD of G2019S

	Experim	ental	Conti	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2011R. Saunders-Pullman	11	31	11	29	6.6%	0.90 [0.31, 2.57]	
2014Rachel Saunders-Pullman	65	126	44	126	19.1%	1.99 [1.20, 3.29]	_ -
2016Marras, C.	407	498	584	783	74.3%	1.52 [1.15, 2.01]	
Total (95% CI)		655		938	100.0%	1.57 [1.24, 1.99]	•
Total events	483		639				
Heterogeneity: Chi² = 1.95, df = 2	(P = 0.38);	l² = 0%					0.01 0.1 1 10 100
Test for overall effect: Z = 3.73 (P = 0.0002)							Favours [experimental] Favours [control]

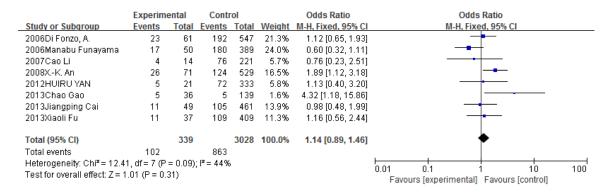
1.39 Smoke of G2019S



1.40 Asymmetrical onset of G2385R



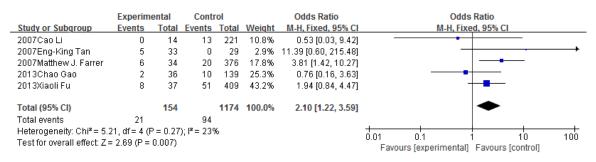
1.41 Age at onset of G2385R



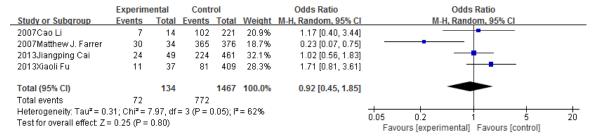
1.42 EOPD of G2385R

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2006Di Fonzo, A.	34	61	328	547	8.4%	0.84 [0.49, 1.43]	
2007Cao Li	5	14	128	221	4.5%	0.40 [0.13, 1.24]	
2007Eng-King Tan	16	33	17	29	5.1%	0.66 [0.24, 1.82]	
2007Matthew J. Farrer	18	34	214	376	7.1%	0.85 [0.42, 1.72]	
2008Daniel Kam Yin Chan	3	3	21	31	0.9%	3.42 [0.16, 72.45]	· · · · · · · · · · · · · · · · · · ·
2008XK. An	40	71	314	529	8.7%	0.88 [0.54, 1.46]	-
2010Jong-Min Kim	35	82	373	841	9.0%	0.93 [0.59, 1.48]	-
2012HUIRU YAN	10	21	192	333	5.8%	0.67 [0.28, 1.62]	
2013Chao Gao	21	36	15	139	6.0%	11.57 [4.94, 27.13]	
2013Jiangping Cai	28	49	275	461	7.9%	0.90 [0.50, 1.64]	
2013Xiaoli Fu	21	37	201	409	7.3%	1.36 [0.69, 2.68]	 -
2016Cao, M.	16	25	28	43	5.0%	0.95 [0.34, 2.67]	
2016Marras, C.	122	199	465	790	10.1%	1.11 [0.81, 1.52]	+
2016Sun, Qian	37	76	125	225	8.5%	0.76 [0.45, 1.28]	
2017Hong, J. H.	7	23	136	276	5.6%	0.45 [0.18, 1.13]	
Total (95% CI)		764		5250	100.0%	0.98 [0.73, 1.34]	+
Total events	413		2832				
Heterogeneity: Tau² = 0.21; 0	hi² = 42.45	6, df = 1	4 (P = 0.0)	001); P	= 67%		0.01 0.1 1 10 100
Test for overall effect: Z = 0.1	0 (P = 0.92)					
	•						Favours [experimental] Favours [control]

1.43 Gender-male of G2385R



1.44 Family history of G2385R



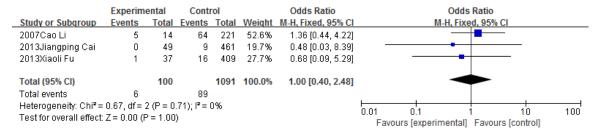
1.45 FS-Bradykinesia of G2385R

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2007Cao Li	8	14	134	221	9.8%	0.87 [0.29, 2.58]	
2008XK. An	37	71	263	529	42.6%	1.10 [0.67, 1.81]	-
2013Jiangping Cai	34	49	299	461	25.1%	1.23 [0.65, 2.32]	
2013Xiaoli Fu	21	37	220	409	22.5%	1.13 [0.57, 2.22]	_
Total (95% CI)		171		1620	100.0%	1.12 [0.81, 1.54]	*
Total events	100		916				
Heterogeneity: Chi ² =	0.30, df=	3(P = 0)	.96); I²=	0%			1 10 100
Test for overall effect	Z = 0.66 (P = 0.51)				0.01 0.1 1 10 100 Favours [experimental] Favours [control]

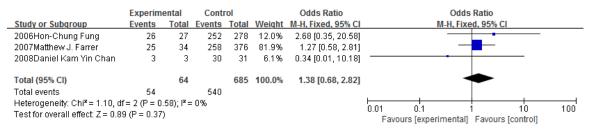
1.46 FS-Resting tremor of G2385R

	Experim	ental	Conti	rol		Odds Ratio	Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
2007Cao Li	7	14	83	221	16.9%	1.66 [0.56, 4.91]	_	-	
2013Jiangping Cai	18	49	168	461	69.6%	1.01 [0.55, 1.87]	\dashv	-	
2013Xiaoli Fu	3	37	26	409	13.5%	1.30 [0.37, 4.52]		-	
Total (95% CI)		100		1091	100.0%	1.16 [0.71, 1.89]	•	•	
Total events	28		277						
Heterogeneity: Chi ^z =	0.65, df = 3	2(P = 0)	$.72); I^2 = I$	0%			L	1 10	400
Test for overall effect:	Z = 0.60 (F	P = 0.55)				0.01 0.1 Favours [experimental]	1 10 Favours [control]	100

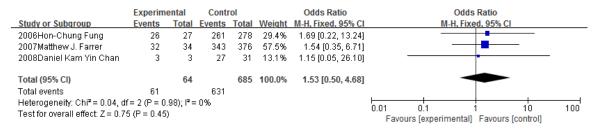
1.47 FS-Rigidity of G2385R



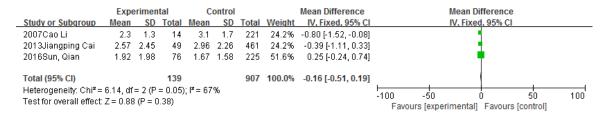
1.48 FS-Postural instability or Gait difficulty of G2385R



1.49 Resting tremor of G2385R



1.50 Rigidity of G2385R



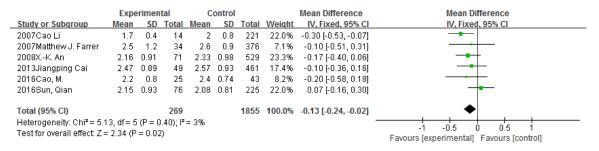
1.51 UPDRS I of G2385R

	Expe	erimen	tal	С	ontrol			Mean Difference		M	ean Difference	9	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV,	Random, 95%	CI	
2007Cao Li	13.1	5.9	14	16.8	6.2	221	21.8%	-3.70 [-6.90, -0.50]			-		
2013Jiangping Cai	16.8	8.8	49	17.2	8.26	461	23.7%	-0.40 [-2.98, 2.18]			+		
2016Marras, C.	14.74	0.19	192	11.09	0.19	684	28.0%	3.65 [3.62, 3.68]			•		
2016Sun, Qian	11.16	5.71	76	11.32	4.35	225	26.5%	-0.16 [-1.56, 1.24]			†		
Total (95% CI)			331				100.0%	0.08 [-3.12, 3.27]			†		
Heterogeneity: Tau² = Test for overall effect:				= 3 (P ·	< 0.001	001); l²	= 95%		-100 Favo	-50 urs [experim	0 ental] Favour:	50 s [control]	100

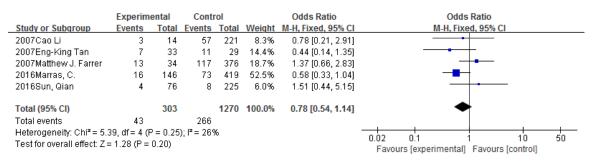
1.52 UPDRS II of G2385R

	Exp	eriment	tal	(Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2007Cao Li	19.6	5.1	14	20.5	7.3	221	14.6%	-0.90 [-3.74, 1.94]	
2007Eng-King Tan	26	11	33	27	11	29	12.9%	-1.00 [-6.49, 4.49]	
2007Matthew J. Farrer	19.3	7.4	34	19.9	9.1	376	14.7%	-0.60 [-3.25, 2.05]	
2013Jiangping Cai	21.4	8.78	49	22.1	8.35	461	14.7%	-0.70 [-3.27, 1.87]	
2016Marras, C.	35.82	0.4	192	27.68	1.12	652	15.3%	8.14 [8.04, 8.24]	•
2016Sun, Qian	24.55	12.08	76	26.52	12.64	225	14.4%	-1.97 [-5.15, 1.21]	
2017Hong, J. H.	19.8	11.2	23	23.6	8.7	276	13.5%	-3.80 [-8.49, 0.89]	
Total (95% CI)			421			2240	100.0%	-0.00 [-4.99, 4.99]	
Heterogeneity: Tau² = 43				6 (P <	0.00001	l); l² = 9	17%	-	-10 -5 0 5 10
Test for overall effect: Z:	= 0.00 (P	² = 1.00)							Favours [experimental] Favours [control]

1.53 UPDRSIII of G2385R



1.54 H-Y of G2385R



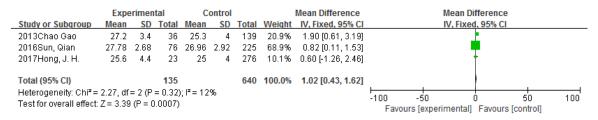
1.55 Dyskinesia of G2385R

	Experim	ental	Conti	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2007Matthew J. Farrer	12	34	122	376	33.7%	1.14 [0.54, 2.37]	-
2008Daniel Kam Yin Chan	0	3	3	31	1.7%	1.16 [0.05, 27.54]	-
2016Marras, C.	61	130	95	396	64.1%	2.80 [1.85, 4.24]	=
2016Sun, Qian	27	27	50	225	0.5%	191.14 [11.46, 3188.64]	
Total (95% CI)		194		1028	100.0%	3.17 [2.30, 4.38]	•
Total events	100		270				
Heterogeneity: Chi ² = 16.38,	df = 3 (P = 1)	0.0009)	; I² = 82%	5			1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Test for overall effect: $Z = 7.0$	5 (P < 0.00	001)					0.001 0.1 1 10 1000 Favours [experimental] Favours [control]

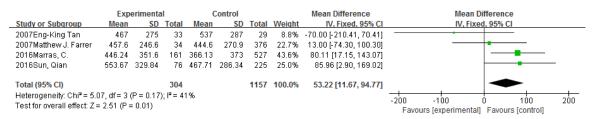
1.56 Motor fluctuations of G2385R

	Experim	ental	Contr	ol		Odds Ratio	Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixe	ed, 95% CI	
2008Daniel Kam Yin Chan	1	3	12	31	5.2%	0.79 [0.06, 9.71]	-		
2016Sun, Qian	27	76	58	225	69.8%	1.59 [0.91, 2.77]	-		
2017Hong, J. H.	5	23	56	276	24.9%	1.09 [0.39, 3.07]			
Total (95% CI)		102		532	100.0%	1.42 [0.88, 2.29]		•	
Total events	33		126						
Heterogeneity: $Chi^2 = 0.61$, df Test for overall effect: $Z = 1.44$,		: 0%				0.01 0.1	1 10	100
restroi overali ellett. Z = 1.44	+ (r = 0.10)	,					Favours [experimental]	Favours [control]	

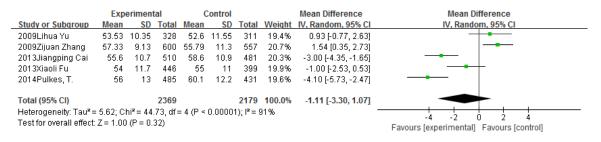
1.57 Depression of G2385R



1.58 MMSE of G2385R



1.59 LEDD of G2385R



1.60 Age at onset of R1628P

	Experim	ental	Conti	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2009Lihua Yu	6	17	132	311	21.1%	0.74 [0.27, 2.05]	
2009Zijuan Zhang	5	43	145	557	22.6%	0.37 [0.14, 0.97]	-
2013Jiangping Cai	10	29	106	481	26.3%	1.86 [0.84, 4.13]	
2013Xiaoli Fu	15	47	109	399	30.1%	1.25 [0.65, 2.39]	
Total (95% CI)		136		1748	100.0%	0.95 [0.49, 1.83]	
Total events	36		492				
Heterogeneity: Tau ² =	= 0.27; Chi ^a	= 7.39	df = 3 (P	= 0.06); I ² = 59%	, -	0.2 0.5 1 2 5
Test for overall effect:	Z = 0.17 (I	P = 0.87)				Favours [experimental] Favours [control]

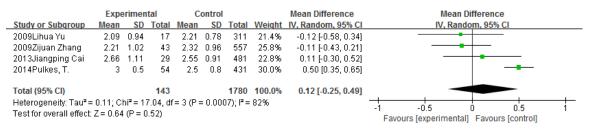
1.61 EOPD of R1628P

	Experim	ental	Cont	rol		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	
2009Lihua Yu	9	17	169	311	24.9%	0.95 [0.36, 2.51]		
2013Jiangping Cai	18	29	285	481	37.1%	1.13 [0.52, 2.43]	-	
2013Xiaoli Fu	33	47	201	399	38.1%	2.32 [1.21, 4.47]		
Total (95% CI)		93		1191	100.0%	1.54 [0.99, 2.38]	•	
Total events	60		655					
Heterogeneity: Chi²=	3.10, df=	2(P = 0)	.21); ==	35%				400
Test for overall effect:	Z = 1.91 (P = 0.06)				0.01 0.1 1 10 Favours [experimental] Favours [control]	100

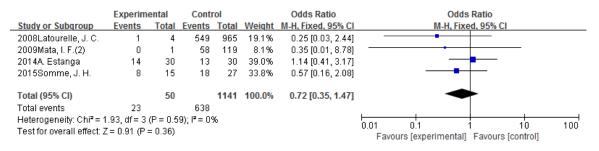
1.62 Gender-male of R1628P

	Experim	ental	Conti	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
2009Lihua Yu	9	17	162	311	11.9%	1.03 [0.39, 2.75]	
2009Zijuan Zhang	18	43	282	557	35.4%	0.70 [0.37, 1.32]	
2013Jiangping Cai	19	29	314	481	18.5%	1.01 [0.46, 2.22]	
2013Xiaoli Fu	24	47	220	399	34.2%	0.85 [0.46, 1.55]	
Total (95% CI)		136		1748	100.0%	0.85 [0.60, 1.21]	•
Total events	70		978				
Heterogeneity: Chi ² =	0.70, df = 3	3(P = 0)	.87); l ^z = l	0%			
Test for overall effect:	Z = 0.91 (F	P = 0.36)				0.01

1.63 FS-Resting tremor of R1628P



1.64 H-Y of R1628P



1.65 Gender-male of R1441G

	Exp	erimen	tal	(Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2013Beatriz Tijero	28.17	8.56	6	26.54	7.48	13	19.4%	1.63 [-6.34, 9.60]	
2014A. Estanga	18.86	10.61	30	21.17	12.56	30	35.6%	-2.31 [-8.19, 3.57]	
2015Somme, J. H.	28.5	8.4	15	31.3	8.1	27	45.0%	-2.80 [-8.03, 2.43]	
Total (95% CI)			51			70	100.0%	-1.77 [-5.28, 1.75]	-
Heterogeneity: Chi²=	0.88, df	= 2 (P =	0.64);	$ ^2 = 0\%$				-	-10 -5 0 5 10
Test for overall effect	Z = 0.99	P = 0	32)						Favours [experimental] Favours [control]

1.66 UPDRSIII of R1441G

Supplementary Figure 1. Forest plots of the association between specific variants in *LRRK2* and PD clinical features. 1.1-1.39 reflected the pooled results of G2019S-related clinical features.1.40-1.59 reflected the pooled results of G2385R-related clinical features. 1.60-1.64 represented the pooled results of R1628P-related clinical features. 1.65-1.66 represented the pooled results of R1441G-related clinical features.