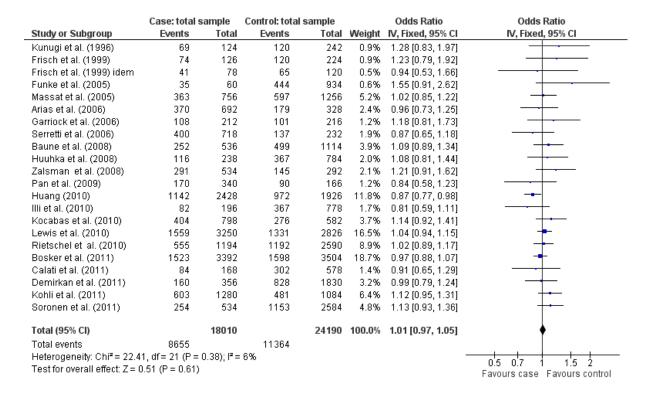
# **Supplementary figures 1-12:**

The supplementary figures 1-12 depict forest plots for all performed meta-analytic tests on allelic as well as genotypic level. The study of the total sample or stratification by gender is indicated in the title of each forest plot. Total events describe numbers of MDD cases and control subjects with the allele/genotype being analysed. The model used for each analysis is indicated on top of the diagram (fixed or random).



#### Supplementary figure 1: Forest plot - total sample Val vs. Met

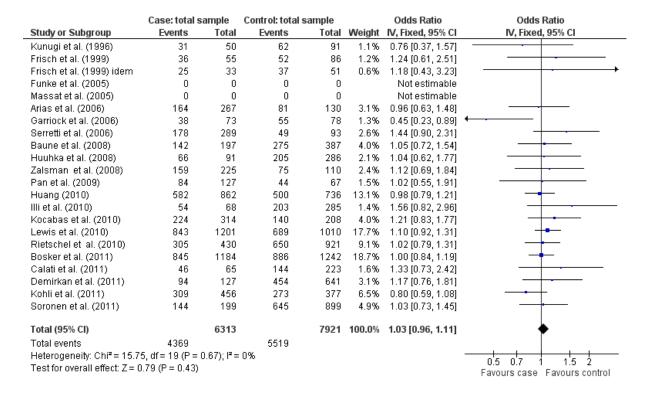
**Events: Val allele** 

	Case: total s	ample	Control: total	sample		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Kunugi et al. (1996)	19	31	29	59	0.9%	1.64 [0.68, 3.97]	-
Frisch et al. (1999)	19	27	34	60	0.8%	1.82 [0.69, 4.80]	-
Frisch et al. (1999) idem	8	14	14	23	0.4%	0.86 [0.22, 3.31]	+
Funke et al. (2005)	0	0	0	0		Not estimable	
Massat et al. (2005)	0	0	0	0		Not estimable	
Arias et al. (2006)	103	182	49	83	2.7%	0.90 [0.53, 1.53]	<del></del>
Garriock et al. (2006)	35	68	23	53	1.4%	1.38 [0.67, 2.85]	<del>-   -</del>
Serretti et al. (2006)	111	181	44	67	2.2%	0.83 [0.46, 1.49]	<del></del>
Baune et al. (2008)	55	126	112	282	4.1%	1.18 [0.77, 1.80]	<del></del>
Huuhka et al. (2008)	25	53	81	187	2.0%	1.17 [0.63, 2.15]	<del>-   ·</del>
Zalsman et al. (2008)	66	108	35	71	2.0%	1.62 [0.88, 2.96]	+
Pan et al. (2009)	43	86	23	39	1.3%	0.70 [0.32, 1.50]	<del></del>
Huang (2010)	280	632	236	463	12.8%	0.77 [0.60, 0.97]	
IIIi et al. (2010)	14	44	82	186	1.5%	0.59 [0.29, 1.19]	<del></del>
Kocabas et al. (2010)	90	175	68	151	3.9%	1.29 [0.84, 2.00]	<del>  •                                   </del>
Lewis et al. (2010)	358	782	321	724	18.0%	1.06 [0.87, 1.30]	<del></del>
Rietschel et al. (2010)	125	292	271	645	9.5%	1.03 [0.78, 1.37]	<del></del>
Bosker et al. (2011)	339	851	356	866	20.0%	0.95 [0.78, 1.15]	<del></del>
Calati et al. (2011)	19	38	79	145	1.5%	0.84 [0.41, 1.71]	<del></del>
Demirkan et al. (2011)	33	84	187	461	3.3%	0.95 [0.59, 1.53]	<del></del>
Kohli et al. (2011)	147	331	104	269	6.9%	1.27 [0.91, 1.76]	+
Soronen et al. (2011)	55	123	254	647	4.9%	1.25 [0.85, 1.85]	<del>  • • • • • • • • • • • • • • • • • • •</del>
Total (95% CI)		4228		5481	100.0%	1.02 [0.93, 1.11]	•
Total events	1944		2402				
Heterogeneity: Chi <sup>2</sup> = 20.4	7, df = 19 (P =	0.37); l² =					
Test for overall effect: Z = 0.35 (P = 0.73)							0.5 0.7 1 1.5 2
	( = )						Favours case Favours contro

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Supplementary figure 2: Forest plot -total sample Val/Val vs. Met/Met

**Events: Val/Val genotype** 



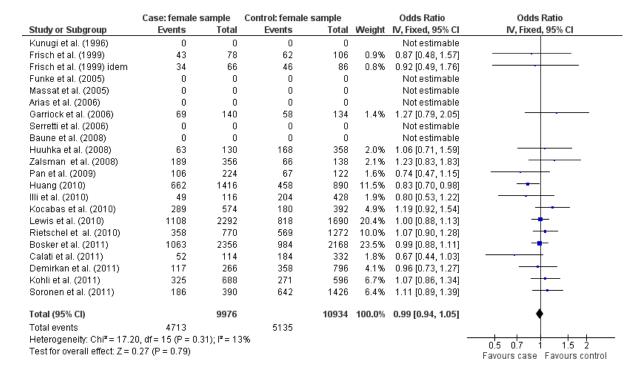
#### Supplementary figure 3: Forest plot - total sample Val/Met vs. Val/Val

**Events: Val/Met genotype** 

	Case: total s	ample	Control: total s	sample		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Kunugi et al. (1996)	31	43	62	92	1.6%	1.25 [0.56, 2.77]	<del></del>
Frisch et al. (1999)	36	44	52	78	1.3%	2.25 [0.92, 5.53]	+
Frisch et al. (1999) idem	25	31	37	46	0.8%	1.01 [0.32, 3.20]	<b>←</b>
Funke et al. (2005)	0	0	0	0		Not estimable	
Massat et al. (2005)	0	0	0	0		Not estimable	
Arias et al. (2006)	164	243	81	115	3.8%	0.87 [0.54, 1.41]	<del></del>
Garriock et al. (2006)	38	71	55	85	2.4%	0.63 [0.33, 1.20]	<del></del>
Serretti et al. (2006)	178	248	49	72	2.9%	1.19 [0.68, 2.10]	<del>-   ·</del>
Baune et al. (2008)	142	213	275	445	5.9%	1.24 [0.88, 1.74]	+-
Huuhka et al. (2008)	66	94	205	311	3.5%	1.22 [0.74, 2.01]	<del>-   •</del>
Zalsman et al. (2008)	159	201	75	111	3.3%	1.82 [1.08, 3.07]	
Pan et al. (2009)	84	127	44	60	2.2%	0.71 [0.36, 1.40]	<del></del>
Huang (2010)	582	934	500	727	9.7%	0.75 [0.61, 0.92]	<del></del>
Illi et al. (2010)	54	84	203	307	3.5%	0.92 [0.56, 1.53]	
Kocabas et al. (2010)	224	309	140	223	5.4%	1.56 [1.08, 2.26]	<del></del>
Lewis et al. (2010)	843	1267	689	1092	10.9%	1.16 [0.98, 1.38]	<del>  •  </del>
Rietschel et al. (2010)	305	472	650	1024	9.0%	1.05 [0.84, 1.32]	<del></del>
Bosker et al. (2011)	845	1357	886	1396	11.4%	0.95 [0.81, 1.11]	<del></del>
Calati et al. (2011)	46	65	144	210	2.6%	1.11 [0.60, 2.04]	<del></del>
Demirkan et al. (2011)	94	145	454	728	5.4%	1.11 [0.77, 1.61]	<del>-   •</del>
Kohli et al. (2011)	309	493	273	438	7.8%	1.01 [0.78, 1.32]	<del></del>
Soronen et al. (2011)	144	212	645	1038	6.6%	1.29 [0.94, 1.77]	<del>  •</del>
Total (95% CI)		6653		8598	100.0%	1.07 [0.96, 1.20]	<b>*</b>
Total events	4369		5519				
Heterogeneity: Tau <sup>2</sup> = 0.02 Test for overall effect: Z = 1		df= 19 (I	P = 0.03); I² = 42	!%			0.5 0.7 1 1.5 2 Favours case Favours control

Supplementary figure 4: Forest plot – total sample Val/Met vs. Met/Met

**Events:Val/Met genotype** 



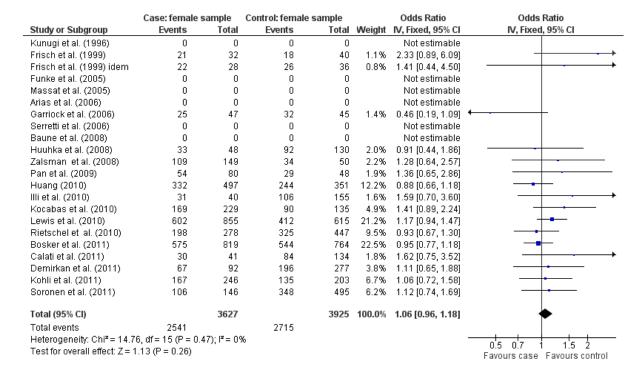
### Supplementary figure 5: Forest plot – female sample Val vs. Met

#### **Events:Val allele**

	Case: female sample		Control: female sample		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
Kunugi et al. (1996)	0	0	0	0		Not estimable		
Frisch et al. (1999)	11	18	22	35	1.0%	0.93 [0.29, 2.99]	ı <del></del>	
Frisch et al. (1999) idem	6	11	10	17	0.6%	0.84 [0.18, 3.88]	ı <del>←                                   </del>	
Funke et al. (2005)	0	0	0	0		Not estimable		
Massat et al. (2005)	0	0	0	0		Not estimable		
Arias et al. (2006)	0	0	0	0		Not estimable		
Garriock et al. (2006)	22	45	13	35	1.6%	1.62 [0.66, 3.99]	ı <del>-   </del>	
Serretti et al. (2006)	0	0	0	0		Not estimable		
Baune et al. (2008)	0	0	0	0		Not estimable		
Huuhka et al. (2008)	15	32	38	87	2.0%	1.14 [0.50, 2.57]		
Zalsman et al. (2008)	40	69	16	35	2.0%	1.64 [0.72, 3.72]	ı <del>-   </del>	
Pan et al. (2009)	26	58	19	32	1.7%	0.56 [0.23, 1.33]	i <del></del>	
Huang (2010)	165	376	107	201	11.2%	0.69 [0.49, 0.97]		
IIIi et al. (2010)	9	27	49	108	1.7%	0.60 [0.25, 1.46]	←	
Kocabas et al. (2010)	60	118	45	106	4.8%	1.40 [0.83, 2.38]	ı <del></del>	
Lewis et al. (2010)	253	544	203	433	20.8%	0.99 [0.76, 1.27]	ı <del>- †</del>	
Rietschel et al. (2010)	80	187	122	311	9.8%	1.16 [0.80, 1.67]	ı <del>-   •</del>	
Bosker et al. (2011)	244	603	220	540	23.8%	0.99 [0.78, 1.25]	ı <del>- •</del>	
Calati et al. (2011)	11	27	50	82	1.7%	0.44 [0.18, 1.07]	←	
Demirkan et al. (2011)	25	66	81	202	4.1%	0.91 [0.51, 1.61]	· · · · ·	
Kohli et al. (2011)	79	177	68	163	7.2%	1.13 [0.73, 1.73]	ı <del>-   •</del>	
Soronen et al. (2011)	40	89	147	365	6.1%	1.21 [0.76, 1.93]	-	
Total (95% CI)		2447		2752	100.0%	0.98 [0.88, 1.11]	•	
Total events	1086		1210			_	]	
Heterogeneity: Chi <sup>2</sup> = 16.7	0. df = 15 (P = 0.3	4): $I^2 = 10$					<del></del>	
Test for overall effect: Z = 0		.,,,					0.5 0.7 1 1.5 2	
							Favours case Favours control	

Supplementary figure 6: Forest plot – female sample Val/Val vs. Met/Met

**Events:Val/Val genotype** 



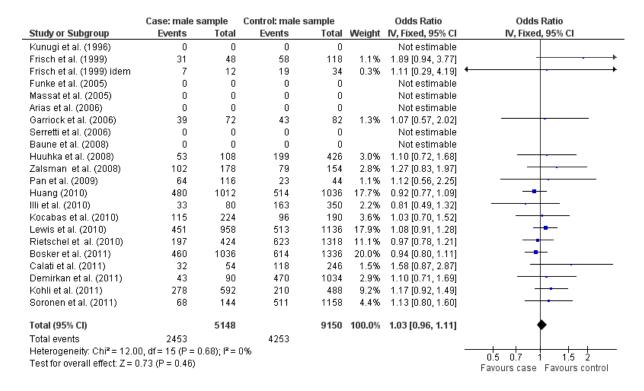
## Supplementary figure 7: Forest plot - female sample Val/Met vs. Val/Val

# **Events:Val/Met genotype**

	Case: female sample		Control: female sample		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Kunugi et al. (1996)	0	0	0	0		Not estimable	
Frisch et al. (1999)	21	28	18	31	1.9%	2.17 [0.71, 6.60]	<del></del>
Frisch et al. (1999) idem	22	27	26	33	1.5%	1.18 [0.33, 4.26]	<b>←</b>
Funke et al. (2005)	0	0	0	0		Not estimable	
Massat et al. (2005)	0	0	0	0		Not estimable	
Arias et al. (2006)	0	0	0	0		Not estimable	
Garriock et al. (2006)	25	48	32	54	3.4%	0.75 [0.34, 1.64]	
Serretti et al. (2006)	0	0	0	0		Not estimable	
Baune et al. (2008)	0	0	0	0		Not estimable	
Huuhka et al. (2008)	33	50	92	141	4.2%	1.03 [0.52, 2.04]	
Zalsman et al. (2008)	109	138	34	53	4.1%	2.10 [1.05, 4.21]	
Pan et al. (2009)	54	86	29	42	3.4%	0.76 [0.34, 1.66]	
Huang (2010)	332	543	244	338	9.8%	0.61 [0.45, 0.81]	<del></del>
Illi et al. (2010)	31	49	106	165	4.4%	0.96 [0.49, 1.86]	
Kocabas et al. (2010)	169	227	90	151	7.1%	1.97 [1.27, 3.07]	<del></del>
Lewis et al. (2010)	602	893	412	642	11.4%	1.15 [0.93, 1.43]	+-
Rietschel et al. (2010)	198	305	325	514	9.7%	1.08 [0.80, 1.45]	<del></del>
Bosker et al. (2011)	575	934	544	864	11.9%	0.94 [0.78, 1.14]	<del></del>
Calati et al. (2011)	30	46	84	116	3.8%	0.71 [0.34, 1.48]	
Demirkan et al. (2011)	67	108	196	317	6.9%	1.01 [0.64, 1.58]	
Kohli et al. (2011)	167	265	135	230	8.4%	1.20 [0.83, 1.72]	<del></del>
Soronen et al. (2011)	106	155	348	566	8.1%	1.36 [0.93, 1.98]	<del>                                     </del>
Total (95% CI)		3902		4257	100.0%	1.07 [0.91, 1.27]	•
Total events	2541		2715				
Heterogeneity: Tau <sup>2</sup> = 0.05	i; Chi² = 33.59. df	= 15 (P =	$0.004$ ); $I^2 = 55\%$				0.5 0.7 1 1.5 2
Test for overall effect: Z = 0		,					
							Favours case Favours control

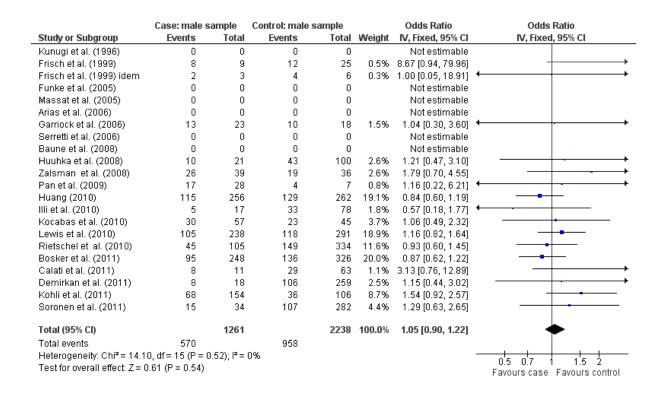
Supplementary figure 8: Forest plot – female sample Val/Met vs. Met/Met

**Events:Val/Met genotype** 



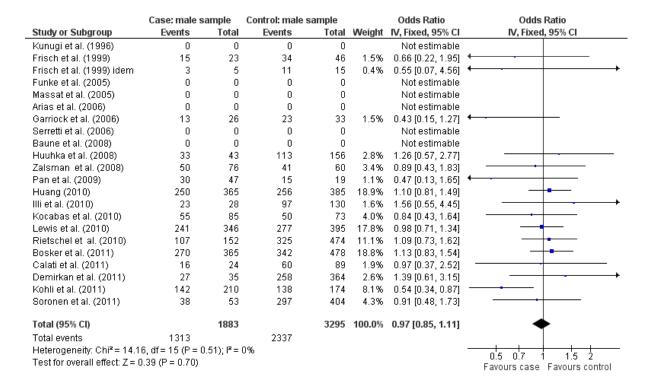
# Supplementary figure 9: Forest plot - Male sample Val vs. Met

### **Events:Val allele**



Supplementary figure 10: Forest plot - Male sample Val/Val vs. Met/Met

Events: Val/Val genotype



## Supplementary figure 11: Forest plot – male sample Val/Met vs. Val/Val

**Events: Val/Met genotype** 

	Case: male s	ample	Control: male	sample		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Kunugi et al. (1996)	0	0	0	0		Not estimable	
Frisch et al. (1999)	15	16	34	47	0.3%	5.74 [0.69, 47.91]	<del></del>
Frisch et al. (1999) idem	3	4	11	13	0.2%	0.55 [0.04, 8.27]	<del>-   -   -   -   -   -   -   -   -   -  </del>
Funke et al. (2005)	0	0	0	0		Not estimable	
Massat et al. (2005)	0	0	0	0		Not estimable	
Arias et al. (2006)	0	0	0	0		Not estimable	
Garriock et al. (2006)	13	23	23	31	1.1%	0.45 [0.14, 1.43]	<del></del>
Serretti et al. (2006)	0	0	0	0		Not estimable	
Baune et al. (2008)	0	0	0	0		Not estimable	
Huuhka et al. (2008)	33	44	113	170	2.7%	1.51 [0.71, 3.21]	<del></del>
Zalsman et al. (2008)	50	63	41	58	2.2%	1.59 [0.69, 3.66]	<del></del>
Pan et al. (2009)	30	41	15	18	0.8%	0.55 [0.13, 2.25]	<del></del>
Huang (2010)	250	391	256	389	17.5%	0.92 [0.69, 1.24]	<del></del>
Illi et al. (2010)	23	35	97	142	2.5%	0.89 [0.41, 1.94]	<del></del>
Kocabas et al. (2010)	55	82	50	72	3.3%	0.90 [0.45, 1.77]	<del></del>
Lewis et al. (2010)	241	374	277	450	18.7%	1.13 [0.85, 1.50]	<del></del>
Rietschel et al. (2010)	107	167	325	510	11.4%	1.02 [0.71, 1.46]	<del></del>
Bosker et al. (2011)	270	423	342	532	21.4%	0.98 [0.75, 1.28]	<del></del>
Calati et al. (2011)	16	19	60	94	0.9%	3.02 [0.82, 11.12]	<del></del>
Demirkan et al. (2011)	27	37	258	411	2.7%	1.60 [0.75, 3.40]	<del></del>
Kohli et al. (2011)	142	228	138	208	9.8%	0.84 [0.57, 1.24]	<del></del>
Soronen et al. (2011)	38	57	297	472	4.5%	1.18 [0.66, 2.11]	
Total (95% CI)		2004		3617	100.0%	1.02 [0.91, 1.16]	•
Total events	1313		2337				
Heterogeneity: Chi <sup>2</sup> = 14.1	4, df = 15 (P = 0	.52); l²=	0%				
Test for overall effect: Z = 0							0.5 0.7 1 1.5 2 Favours case Favours control
	,						ravours case ravours control

Supplementary figure 12: Forest plot – male sample Val/Met vs. Met/Met

**Events:Val/Met genotype**