Pharmacogenetics of Clozapine-induced Agranulocytosis: A Systematic Review and Meta-Analysis

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BACKGROUND

Although clozapine (CLZ) is the most effective pharmacotherapy for treatment-resistant schizophrenia, it is underutilized, and initiation is often delayed. One reason is the occurrence of a severe and potentially fatal adverse reaction, CLZ-induced agranulocytosis (CIA) defined as absolute neutrophil count < 500 cells/mm^3. Identifying genetic variations contributing to CIA would help determine patient risk of developing CIA and elucidate its unknown pathomechanism.

OBJECTIVES: (1) Review pharmacogenetic studies of CIA, (2) conduct meta-analyses on alleles reported to be associated with CIA, and (3) discuss the potential of findings for clinical implementation.

METHODS

A systematic literature search was performed using PubMed from database inception date to April 2021. The Boolean search string used was: (clozapine AND agranulocytosis).
Only peer-reviewed articles published in English and on human participants were considered.

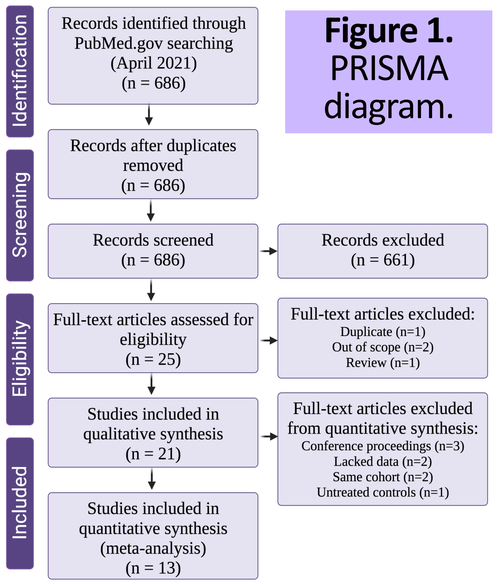

Figure 1. PRISMA diagram.

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RESULTS

Table 1. Summary statistics of meta-analyses.

Authors	Allele/Haplotype	CIA+	CIA-	Control+	Control-	NPV_C^B	OR [95% CI]	|Z|	I^2	p-vlaue	p_c^A
Dettling 2001, Turbay 1997	HLA-DRB1*04:02	14	40	8	123	99.3%	5.89 [2.20, 15.80]	3.5	0%	4.00E-04	0.03
Legge 2016, Yunis 1995, van der Weide 2017, Athanasiou 2011	HLA-DQB1*05:02	33	178	9	521	99.2%	7.12 [1.91, 26.51]	2.9	53%	3.00E-03	0.22
Theodoropoulou 1997, Yunis 1995	HLA-DR2, -DQ1	15	9	18	41	99.5%	5.40 [1.58, 18.43]	2.7	0%	0.01	0.5
Dettling 2001, Yunis 1995	HLA-DRB5*02	13	59	2	107	99.2%	6.44 [1.57, 26.39]	2.6	0%	0.01	0.7
Dettling 2001, Yunis 1995	HLA-DRB1*16:01	13	59	5	104	99.2%	3.62 [1.15, 11.45]	2.2	0%	0.03	1
Yunis 1995, Valevski 1998, Dettling 2001	HLA-B38	27	29	22	137	99.5%	10.01 [1.13, 88.55]	2.1	82%	0.04	1
Ostrousky 2003, van der Weide 2017	NQO2 1541 G>A	40	9	154	167	99.7%	7.16 [0.52, 98.34]	1.5	70%	0.14	1
Dettling 2001, Turbay 1997	HLA-DQB1*03:02	16	38	20	111	99.2%	2.31 [0.53, 10.09]	1.1	71%	0.26	1
Mosyagin 2004, van der Weide 2017	CYBA 640 A>G	78	31	246	70	98.8%	0.70 [0.36, 1.38]	1.0	27%	0.31	1
Lahdelma 2000, Yunis 1995	HLA-B7	10	32	5	33	99.2%	2.17 [0.14, 34.50]	0.6	75%	0.58	1
Dettling 2001, Yunis 1995	HLA-DRB4	20	26	53	78	99.1%	1.27 [0.35, 4.55]	0.4	69%	0.72	1
Dettling 2001, Lahdelma 2000	HLA-B35	10	42	19	87	99.1%	1.08 [0.45, 2.57]	0.2	0%	0.87	1
Mosyagin 2004, van der Weide 2017	MPO -463 G>A	42	70	125	193	99.1%	1.03 [0.63, 1.68]	0.1	0%	0.92	1

Abbreviations: CIA+, number of variant positive clozapine-induced agranulocytosis subjects; CIA-, number of variant negative clozapine-induced agranulocytosis subjects; Control+, number of variant positive control subjects; Control-, number of variant negative control subjects. [A]Bonferroni correction (m = 73) was applied based on the number of alleles/haplotypes analyzed in this review. [B]Negative Predictive Value was corrected for the prevalence of CIA in the US.

After correction for multiple testing (m=73), one of the thirteen meta-analyzed alleles (Table 1) was still a significant predictor of CIA, *HLA-DRB1**04:02 (OR = 5.89; 95% CI 2.20, 15.80; pc = 0.03).
Further, four of the 53 alleles for which no replication was found were still significant predictors of CIA after corrections for multiple testing, including *TNFb5* (OR = 0.08; pc = 1.64 x 10-6), *HLA-B*59:01* (OR = 7.21; pc = 3.06x10-6), *TNFb4* (OR = 7.69; pc = 1.71 x 10-5), and *TNFd3* (OR = 4.61; pc = 5.23 x 10-3).

SUMMARY

Individuals carrying the *HLA-DRB1**04:02 allele had 6-fold (95% CI 2.20, 15.80) odds of CIA. Therefore, *HLA-DRB1**04:02 is a promising target for clinical implementation, which needs to be further explored. Future research is necessary to identify reliable and reproducible genetic variants in diverse populations with large effects related to CIA that can be incorporated into a pharmacogenetic test to guide treatment decisions.

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