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Distribution of Genetic Polymorphism in the CCR5 among Caucasians, Asians and Africans: A Systematic Review and Meta-Analysis

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Abstract

Background: Cysteine-Cysteine Chemokine Receptor 5 (CCR5), also referred to as CD195, is a component of the mammalian cell membrane and is receptor for chemokines that are activated during cell damage and inflammations. This receptor is coded by a gene located in the human chromosome 3. A Mutation on this CCR5 through deletion of 32 base pairs results into a non-destructive gene CCR5Δ32. It enables protection against HIV infection to its homozygous carriers and slows progression of the disease to heterozygous carriers. **Objective**: To systematically review and establish global distribution of CCR5Δ32 allele in HIV-1 infected individuals over the history of the epidemic and compare regions inhabited by Caucasians, Asians and Africans. **Methodology:** This meta-analysis comprised of published papers with over 10,000 individuals from whom CCR5-Delta 32 allele was successfully genotyped and recorded. The study review period was from 1984 to 2017. The search targeted online sources such as Hinari specifically PubMed Central, Google scholar, Science Direct, Research4Life, National Center for Biotechnology Information (NCBI), OVID databases, AIDS Journal and Google. The searches were not limited to a particular publication language or study design but excluded letters of correspondence and conference presentations. Search strategy using key words from a combination of Medical Subject Heading (MeSH) and free text including terms related to CCR5, CCR5Δ32 and HIV were performed in Medical Literature Analysis and Retrieval System Online (MEDLINE) through Ovid Open Access. Additional studies were identified by perusing the reference list of relevant and included articles. The review considered studies conducted among general population, both HIV positive and HIV negative individuals, exposed seronegatives (ESN), exposed seropositives (ESP) and highly exposed seronegatives (HESN) and resultant data

pooled using a fixed effect model. **Results:** A total of 40 studies comprising 10,871 participants were reviewed. These were from three main regions: Europe, Africa and Asia. Of the studies accessed and reviewed, Caucasians were 22.5%, Africans were 12.5%, Europeans were 27% and others (not specified) were 37.5%. The distribution of CCR5Δ32 allele among different populations in comparison to its heterozygosity displayed significant association with a pooled Odds Ratio (OR) of 0.08 (95% CI, 0.03 - 0.18, P < 0.00001), test of subgroup differences at I^2 = 0% and a P value of 0.50. Among the Caucasians alone the OR was at 0.04 (95% CI, 0.01 - 0.19, I^2 = 96%) and a significant P value of < 0.00001 displaying a high presence of CCR5Δ32 homozygosity as compared to Europeans with OR of 0.09 (95% CI, 0.04 - 0.19, I^2 = 21%, P = 0.25) and Africans with OR 0.25 (95% CI, 0.03 - 2.29, I^2 = 0%, P = 0.81); an indication that race can be a factor that determines CCR5Δ32 homozygosity or heterozygosity and it highly favors the Caucasians. Out of 136 homozygous carriers found in the review Europeans had 6%, Caucasian 93%, Africans 0% and others combined 0.7%. **Conclusion:** The distribution of CCR5Δ32, an allele that is associated with lower acquisition of HIV/AIDS is at 93% among the Caucasians. The remaining 7% is shared amongst the rest of the populations, hence high susceptibility to the disease. Minimal availability of recorded data experienced in this study is a clear indication that there exist major gaps in studies that could further associate CCR5Δ32 allele frequency and HIV infection in different populations. The review recommends a mixture of population genetics and epidemiological studies in trying to understand the increasing rates of HIV prevalence among selected groups.

Keywords

CCR5, CCR5Δ32, HIV, Genetic Polymorphism, Allele Frequency

1. Introduction

Mammalian cell membranes have cysteine-cysteine chemokine receptor 5 (CCR5) as a component. They are also referred to as CD195 and are popularly known for allowing in chemokines that signal cellular response during inflammation and after cellular damages [1]. The receptor (CCR5) is coded by a gene located in the human chromosome 3. Several known mutations of CCR5 result into damage of the expressed receptor either by deletion, insertion and or omission. The CCR5-Delta 32 (CCR5Δ32) is a damage resulting from a deletion of 32 base pairs of the CCR5 gene but the mutation is non-deleterious. This is unlike other genes that cause serious and harmful damages such as sickle cell anemia, cystic fibrosis, diabetes when knocked out. CCR5Δ32 mutation is suspected to confer various advantages to the host in relationship to HIV acquisition [2]. Previous studies have shown that individuals having homozygosity in CCR5Δ32 are hindered from HIV acquisitions while their heterozygous counterparts are slow progressers of the disease [3].

In human, the distribution of CCR5Δ32 has a high geographical variation

indicating adaptive traits and the co-evolution of HIV and the human genome [4]. This mutation results into a shortened protein that cannot be expressed on the surface hence giving a perceived resistance to HIV-1 infection, which in turn hinders faster progression to AIDS among infected persons [5].

Population genetic surveys earlier estimated the existence of CCR5Δ32 allele among the Europeans at 10% while it was found missing among the black populace except African Americans who descended from admixture with Europeans [1] [2] [6]. The estimates were reached upon studying equally minimal samples of 747 non-European individuals against 4000 European or Caucasian [6].

A meta-analysis on the accrued data on the distribution of CCR5Δ32 allele covering the critical HIV study period would help in generating statistics for advising on the best method to counter the spread of HIV across different populations. It would further assist in formulating a much better way of channeling prevention and treatment strategies taking into consideration current frequent travels across the globe and possible cross infections and gene flow among travelers.

2. Materials and Methods

2.1. Search Criteria and Study Selection

We searched available online sources such as Hinari specifically PubMed Central, English database of Google scholar, Science Direct, Research4Life, National Center for Biotechnology Information (NCBI), OVID databases, AIDS Journal and Google. The period of search was tailored to range from 1984 to 2017, however other relevant papers that were published before 1984 and after 2017 were enlisted to boost on literature review. Suitable published papers were identified and assembled using Mendeley desktop application. Search strategy using key words from a combination of Medical Subject Heading (MeSH) and free text including terms related to CCR5, CCR5Δ32 and HIV were performed in Medical Literature Analysis and Retrieval System Online (MEDLINE) through Ovid Open Access. Studies conducted among the following populations were accepted for review; general population, both HIV positive and HIV negative individuals, exposed seronegatives (ESN), exposed seropositives (ESP) and highly exposed seronegatives (HESN). To reduce reporting bias only studies with participants successfully genotyped for CCR5Δ32 and results accurately recorded were included. The PRISMA 2009 flow diagram [7] was used to summarize details on data identification, screening and eligibility. A predetermined and comprehensive inclusion and exclusion criteria was arrived at to facilitate objective screening of different articles. Only published and original articles on the distribution of CCR5Δ32 allele in HIV-1 infected individuals from various countries were included for the review. Letters of correspondence, papers with missing relevant data and conference presentations were excluded in this review.

2.2. Data Abstraction and Statistical Analysis

For accurate data abstraction, an excel sheet was used.

Odds Ratios (OR) were used to assess the distribution of CCR5Δ32 allele among different populations grouped as Caucasians, African, Europeans and Others. The ratio was also used to evaluate the association of CCR5Δ32 heterozygotes and homozygotes with vulnerability to HIV infection. The Chi-square (X^2) and I^2 were used to test for the presence of, quantify and determine heterogeneity across studies [8]. P-Value of less than 0.10 was used to indicate statistical significance and publication bias accessed by a simple graphical test by Egger and Begg [9].

3. Results

A total of 544 relevant and non-duplicate articles were retrieved. From this, 144 articles were subjected to further analysis. The final 37 articles with 17,353 participants were accepted for inclusion in the meta-analysis (**Figure 1**). The search was conducted in two main phases; first a group of three reviewers independently cataloguing articles as per the agreed criteria. The result of the initial phase was cross checked by an independent reviewer to ensure an agreement accuracy of 90% and above. The second phase involved full text review and confirmation for inclusion suitability. Uncertainties and conflict of opinions were discussed and resolved in consensus by the reviewers.

Major and complete studies available for review were realized among the Caucasian population totaling to eighteen (18). The earliest study to be reviewed was conducted by Martison and group in 1997. It was done after successful characterization of the mutant allele and on realization that isolated cases of HIV positive homozygotes were still emerging. This study involved 3324 unrelated individuals from a globally distributed population and remains the largest so far in this review; studies that followed are relatively smaller and not so globally constituted. Nine studies with complete genotyped individuals were available for analysis from Asia while six studies covered Africa population and four studies under the ungrouped (others) category (**Table 1**). The largest share of the population reviewed were the Caucasians at 50% with a total of 52 CCR5Δ32 Homozygotes (**Figure 2**).

From the forest plot, there is a clear indication that most studies reviewed and meta-analyzed were from Caucasians population (**Figure 3**). These studies carried a lot of weight and significance as evidenced by the size and visibility of the small squares in the plot. With heterogeneity at 62%, it is observable that being a Caucasian is a factor for CCR5Δ32 homozygosity hence it can be assumed that this is a protected population in terms of the allele. With heterogeneity at 31% being an Asian is not a sure factor for CCR5Δ32 homozygosity hence no protection from HIV infection; few cases presenting the allele here could be as a result of gene flow or descendants of admixture with Caucasians. Scanty data was seen among the African population, out of six studies analyzed only three had events complete for estimation, others were at zero for both homozygosity and heterozygosity. Studies carried out among African population had heterogeneity of 0%

hence being an African is clearly not a factor for CCR5Δ32 homozygosity. The overall outcome for all the populations meta-analyzed indicates that race can be a factor that determines CCR5Δ32 homozygosity or heterozygosity and it highly favors the Caucasians.

A correlation and a strong indication that CCR5Δ32 homozygosity can be a shield to HIV virulence is realized from the results of the analysis for both HIV Positive and HIV negative individuals genotyped (Figure 4).

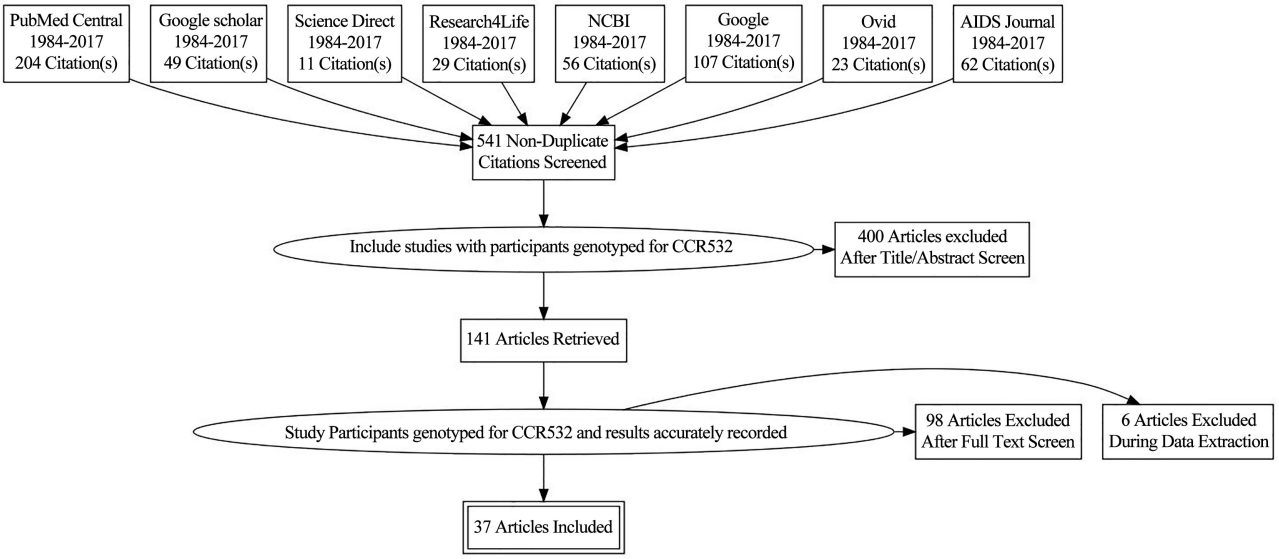


Figure 1. Summary study selection by PRISMA Flow Diagram.

Table1. Characteristics of all studies selected and grouped for review and meta-analysis (GP—General Population, SN—Seronegatives, SP—Seropositives, ESN—Exposed Seronegatives, HESN—Highly Exposed Seronegatives).

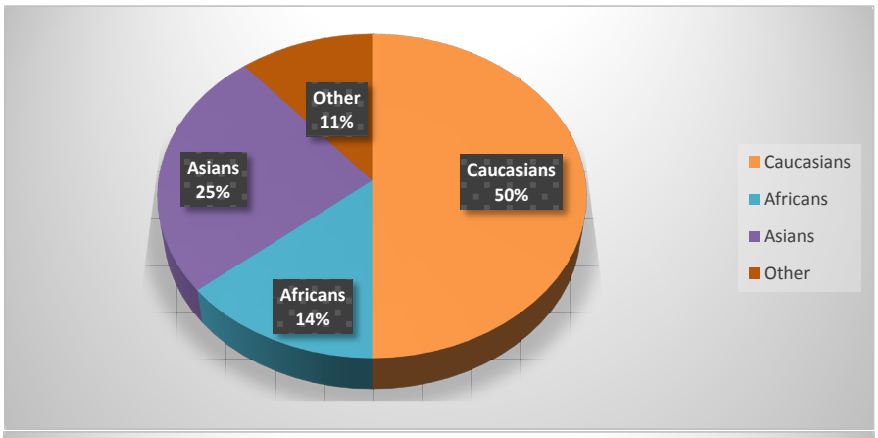
									CCR5 Heterozygous			CCR5 Homozygous		
Author	Yr	Population Genotyped	Study Category	Sample Size	Case Group	HIV +ve	HIV −ve	GP	HIV+ Wt/Δ32	HIV− Wt/Δ32	GP Wt/Δ32	HIV+ Δ32/Δ32	HIV− 32/Δ32	GP Δ32/Δ32
Martison *et al.* [6]	1997	Europeans	Caucasians	788	GP			788			134			7
Martison *et al.* [6]	1997	Africans	Africans	598	GP			598			1			0
Martison *et al.* [6]	1997	Asian	Asians	837	GP			837			13			2
Oh, D.-Y *et al.* [10]	2008	German	Caucasians	1200	HIV +ve	595	352		115	75		1	1	
Oh, D.-Y *et al.* [10]	2008	Africans	Africans		HIV +ve	35	25		1	1		0	0	
Al-Mahruqi, S *et al.* [11]	2013	Omani	Asian	115	GP			115						Rare
Trecarichi, E. M *et al.* [12]	2006	Italians	Caucasians	150	ESN & HIV +ve	120	30 ESN	120	9	6	12	0	0	0
Smoljanović, M., *et al.* [13]	2006	Dalmatia, Croatia	Caucasians	200	GP			200			13			1

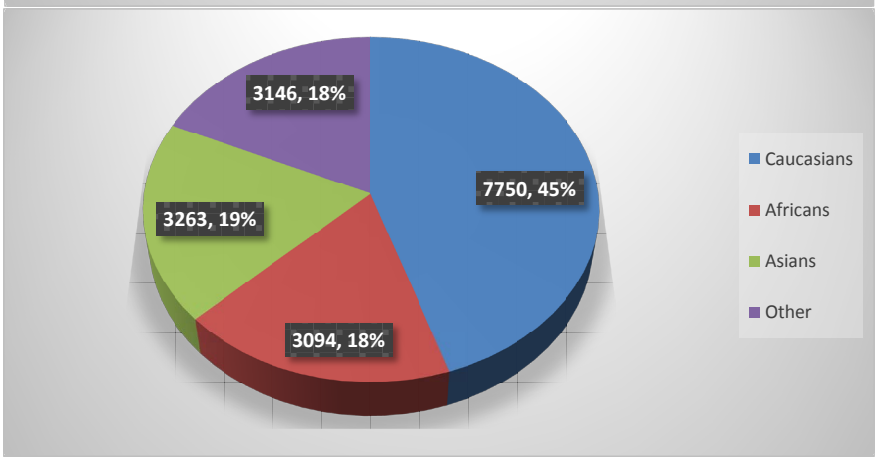
Continued

Lopes, M. P., *et al.* [14]	2014	Afro-Brazilian	Other Brazillian	1042	SCD GP			1042			809			0
Chavhan, A.B., *et al.* [15]	2013	Indians	Asian	108	GP			108			2			0
Rahimi, H., *et al.* [16]	2014	Iranian	Asian	570	HIV+ & −ve	530	40			6			1	
Biloglav, Z., *et al.* [17]	2009	Croatia	Caucasians	1000	GP			942						95
Kostrikis, L. G., *et al.* [18]	1999	African-Americans	Asian	1442	HIV +ve & −ve	1235	207			5			0	
Nkenfou, C. N., *et al.* [19]	2013	Cameroon	Africans	179	HIV +ve & −ve	32	147		0	0		0	0	
Bharti, D., *et al.* [20]	2015	India	Asian		SN		200			0			0	
Heydarifard, Z., *et al.* [21]	2017	Iranian	Asian	400	HIV +ve & −ve	140	300		1	9		0	0	
Roy, P., *et al.* [22]	2016	Indians	Asian	571	HIV+ & −ve	181	568					0	0	
Zapata,W., *et al.* [23]	2013	Colombia	Caucasians	239	SP and HESN	57	70	112				0	0	
Mehlotra, R. K., *et al.* [24]	2016	Papua New Guinea	Other	620	GP			620			0			0
Corado, André de Lima, *et al.* [25]	2016	Brazilian	Caucasians	177	HIV +ve		177		11			0		
Angelis, Daniela Souza *et al.* [26]	2007	Brazilian	Caucasians	51	HIV +ve		51		2			0		
Vargas, A.E., *et al.* [27]	2006	Brazilian	Caucasians	*103*	*GP*			103			*7*			*1*
Carvalhaes, F *et al.* [25]	2005	Brazilian	Caucasians	*249*	*Both SP and SN*	110	139		6	0		0	0	
Patrícia Munerato *et al.* [28]	2003	Brazilian	Caucasians	*298*	HIV +ve	183		115	21		15	0		0
Díaz, Francisco J, *et al.* [29]	2002	Brazilian	Caucasians	*68*	*Both SP and SN*	29	39		1	1		0	1	
Pereira, Rinaldo W., *et al.* [30]	*2000*	Brazilian	Caucasians	907	GP			907			93			2
Rugeles, María T *et al.* [31]	2011	Colombia	Caucasians	65	HIV +ve & −ve	28	37		1	1		0	1	
Rugeles, María T *et al.* [31]	2011	Colombia	Caucasians	80	HIV+ & −ve	33	47		3	2		0	1	
Nina Valadez-González., *et al.* [32]	2011	Mexico	Caucasians	*355*	HIV +ve & −ve	62	51	242	11	7	15	0	2	0

Continued

Abdel Halim Salem *et al.* [33]	2009	Bahraini	Asian	*304*	HIV −ve		304			15			1
Yudin, N., *et al.* [34]	1998	Russian	Caucasians	531	GP			531		59			12
Grigory S. Ryabov., *et al.* [35]	2004	Russian	Caucasians	171	GP			171		31			0
Grace C. John, *et al.* [36]	2001	Kenya	Africans	276	HIV +ve	276			1		0		
Sidoti, A., *et al.* [37]	2005	Sicilian	Other	1015	HIV +ve & −ve	114	901		5	70	0	5	
Mangano A,. *et al.* [38]	2001	Amerindian	Other	42	GP			42		1			1
Torimiro, J N., *et al.* [39]	2007	Cameroon	Africans	1390	GP			1390		0			0
Al-Jaberi, S A,. *et al.* [40]	2013	Emiratis	Asian	253	GP			253		0			0
Al-Jaberi, S A,. *et al.* [40]	2013	Tunisians	Africans	150	GP			150		0			0
Kalev, I., [41]	2000	Estonians	Caucasians	504	GP			504		117			16





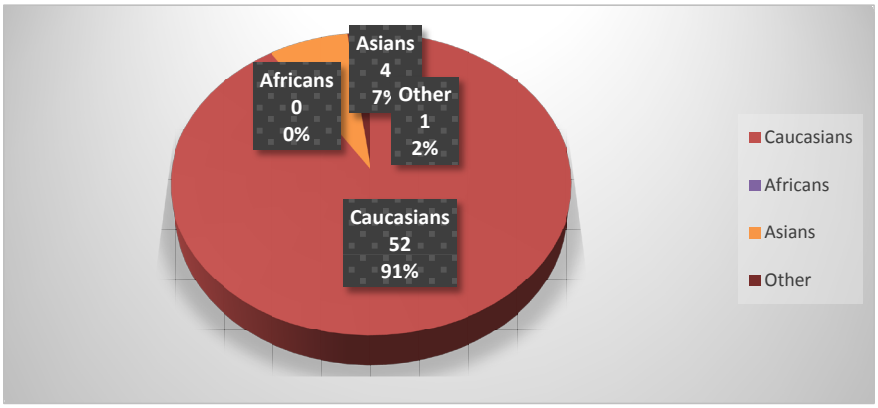


Figure 2. Distribution of reviewed studies (top) cumulative samplesize by category (middle) and CCR5Δ32 Homozygotes by category (bottom).

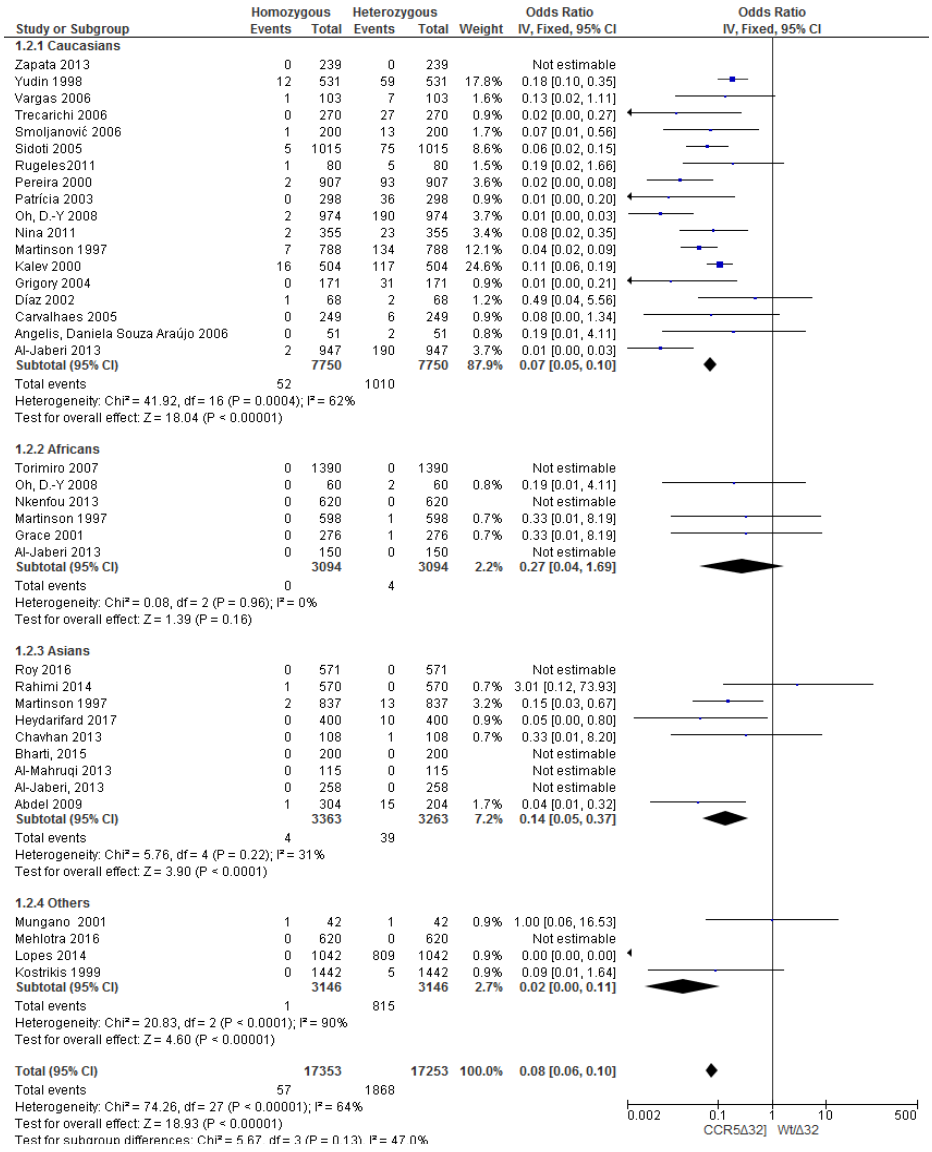


Figure 3. Forest plot comparing the distribution of CCR5 Homozygosity and Heterozygosity among various populations (Caucasians, Asians, Africans and Others).

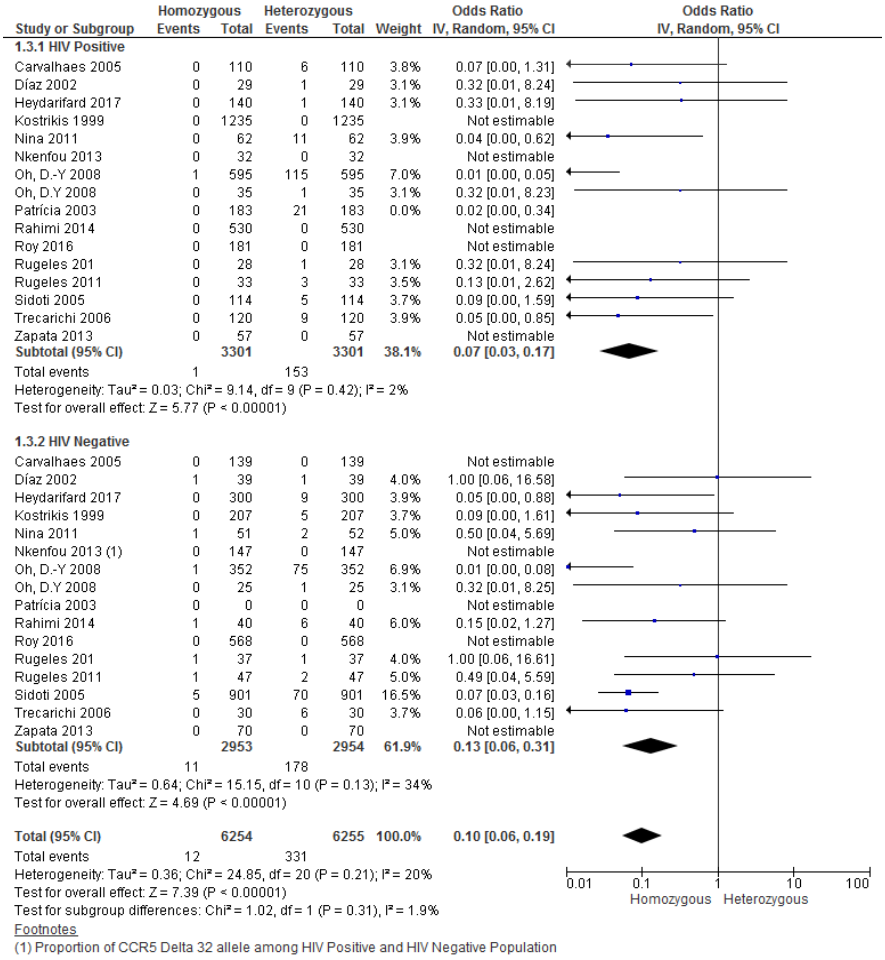


Figure 4. Forest Plot detailing the comparison of CCR5 Homozygosity and Heterozygosity among HIV positive and HIV Negative individual in the reviewed data.

4. Discussions

This review correlated data from studies on the distribution of CCR5Δ32 which is a natural selection allele acting in humans against HIV/AIDS as demonstrated by previous studies [6]. The result of this meta-analysis involving 37 articles with 17,253 participants from diverse backgrounds sheds great lights on the distribution of this allele globally as well its association with HIV-1 epidemiology. The study undoubtedly demonstrates that there is a wide knowledge gap on CCR5Δ32 especially in African where HIV burden is highest but further confirms that CCR5Δ32 heterozygosity does not protect individuals against HIV-1 infection but rather slows progression of the disease [16] [42].

High concentration of studies on CCR5Δ32 is seen among the Caucasians. Globally 50% of the articles available for review covered this population while only three complete articles from African population were found representing less that 10%. Details from the study equally indicate that there is a likelihood of being homozygous of the allele when a Caucasian than any other race since most CCR5Δ32 homozygotes were Caucasians. However the few homozygotes seen

among the Asian group could have been as a result of gene flow [6]. Notably, among African population no one was positive for the allele while in the remaining un-grouped population only one individual was present in Nigeria as recorded by Martison and group in 1997 [6].

There is a possibility that the results in our study may be regionally and racially biased based on the data available online. Language bias, especially on manuscripts published in other languages other than English may also be another factor that could have affected our analysis.

5. Conclusion

This meta-analysis is in line with previous various studies and concludes that CCR5Δ32 is highly concentered among the Caucasians as compared to other populations. From the systematic review conducted; 91% of the total number of individuals who were found to be CCR5 homozygous are Caucasians and 50% of articles available for review were also from that same region. Likewise, results presented here indicate that Caucasians as compared to other populations are less susceptible to HIV virus infection due to the expression rates of CCR5Δ32 while the rest of the populations experience a much higher prevalence of the disease. However, scanty data experienced is Africa is a clear indication that minimal work has been done in trying to associate the allele and HIV infection in different populations. This study recommends further studies on relevant contextual factors including but not limited to social, economic and nutritional factors given that a lot of cross-border travels and inter-race marriages has occurred over the years. A mixture of population genetics and epidemiological studies can also be explored.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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