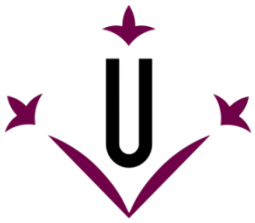

Title: *Vitamin D Receptor* Polymorphisms and Risk of Enveloped Virus Infection: a Meta-Analysis

Running title: VDR and viral infection meta-analysis

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Abstract

Introduction: Vitamin-D plays a role regulating the immune response against to viral infection. In this sense, vitamin-D deficiency may confer increased susceptibility to enveloped virus infection such as HIV, Hepatitis, Dengue and Respiratory Syncytial virus infection, among others. Vitamin D activity is mediated by its receptor (VDR), which acts as a transcription factor modulating the expression of genes triggering the response against viruses. To date, six major VDR polymorphisms (Cdx, A1012G, FokI, BsmI, ApaI and TaqI) have been studied in the context of viral infection susceptibility. Reported studies show controversial results probably due to statistical lack of power and population genetic differences.

Aims: To do a systematic review of the published data and to perform a meta-analysis examining the role of six VDR polymorphisms on infection susceptibility to enveloped virus.

Results: From all markers and virus considered an association of FokI polymorphism with RSV infection emerges as significant. The worldwide distribution of risk T-allele reveals a lower prevalence in African populations that runs parallel with the relative lower incidence of RSV-associated severe ALRI in children <1 year described in African samples.

Conclusion: The results disclose FokI polymorphism as a relevant variant capturing the association of VDR polymorphisms with viral infection.

Keywords

Vitamin D receptor, VDR, polymorphism, *FokI*, Enveloped virus infection risk, RSV

1. Introduction

Vitamin D (1-α-25-dihydroxyvitamin-D3) has been known for its physiological role in regulating mineral metabolism and its pleiotropic effects involving regulation of cell proliferation and differentiation. In addition, vitamin D has an important role in the modulation of the immune response inducing microbicide factors against bacterial infections (Wang et al., 2004) and controlling the exacerbation of the cellular immune response (Deluca and Cantorna, 2001; Wang et al., 2004). Vitamin D balance has been described as involved in life-limiting diseases (Garland et al., 2009; Wang et al., 2004) such as bacterial (Deluca and Cantorna, 2001; Gao et al., 2010; Wang et al., 2004) and viral infections (de la Torre et al., 2008), cancer (Garland et al., 2009), cardiovascular diseases (Gouni-Berthold et al., 2009), osteoporosis (Lash et al., 2009), sarcopenia (S. M. Roth et al., 2004) and diabetes (Danescu et al., 2009). Sources of vitamin D are on the dietary intake, mainly oily fish such as salmon, mackerel and sardines (T. C. Chen et al., 2007) and egg yolks (Lamberg-Allardt, 2006), and undergo endogenous synthesis by photolytic reaction of vitamin D precursors in the skin (Lips, 2006).

Genomic actions of vitamin D are mediated by its nuclear receptor, vitamin D receptor (VDR), which acts as a ligand-dependent transcription factor modulating the expression of vitamin D responsive genes (Pike, 1991). VDR is present on monocytes, dendritic cells, and activated T and B lymphocytes. Upon vitamin D binding, VDR translocate to the nucleus determining cell type specific genomic responses. VDR plays a pivotal role in different gene networks and has been reported to be involved in immune response modulation. More specifically, vitamin D acts as an immunoregulatory hormone associated with monocyte activation, stimulation of cell-mediated immunity and suppression of lymphocyte proliferation, antibody production, and cytokine synthesis (Deluca and Cantorna, 2001).

VDR gene maps to chromosome 12q12-14 and several *VDR* polymorphisms with functional effects have been described in the promoter, coding and 3´ untranslated region (UTR) (Uitterlinden et al., 2004). So far, most of the genetic studies that investigated the association between viral infection and *VDR* gene polymorphisms were performed using six common variants: two of them, rs11568820 (*Cdx*) and rs4516035 (*A1012G*), are located in the 5´ regulatory region and affect binding of transcription factors. *Cdx* polymorphism is a G to A transition between exons 1f and 1e that alters the recognition site for the intestinal-specific

transcription factor ‘‘caudal-related homeodomain protein-2’’, affecting vitamin D-VDR mediated intestinal calcium absorption (Arai et al., 2001). *A1012G* polymorphism is an A to G transition located between 1e and 1a exons that modifies the GATA-3 transcription factor recognition sequence, involved in the regulation of Th2 polarization (Halsall et al., 2004). A third variant, rs2228570 (*FokI*) polymorphism, has been described in the *VDR* coding region, affecting the first ATG start site and forcing translation to initiate in an alternate ATG sequence, giving rise to a VDR protein that is three amino acids (aas) shorter (427 *vs.* 424 aas) (Gross et al., 1996). *FokI* genotypes implicate functional alterations such as a more efficient interaction of the VDR protein coded by the C-allele (short 424 aas) with TFIIB and a greater transcriptional activity than the full-length VDR protein coded by *FokI* T-allele (long 427 aas) (Jurutka et al., 2000). Finally, three restriction fragment length polymorphisms (RFLP) have been described in the 3´UTR region, rs1544410 (*BsmI*), rs7975232 (*ApaI*) and rs731236 (*TaqI*), with functional effects linked to alterations in *VDR* mRNA stability (Fang et al., 2005; Morrison et al., 1994).

Vitamin D-VDR mediated action might modulate the immune response and subsequently *VDR* polymorphisms are candidates to be associated with differential risk to both viral and bacterial infections. In this sense, most association studies performed to date have been addressed in small cohorts, which lead to both controversial and/or non-conclusive results. Some studies may have been underpowered to detect small allelic effects, which in contrast are quite common among complex traits such as those involving host-pathogen interactions. Meta-analyses are powerful tools to combine results from different studies by producing a single estimate of the major effect with increased precision. One of the major advantages of these studies is to increase sample size, what reduces random errors that cause false-positive and false-negative associations. The association of *VDR* polymorphisms has been previously evaluated in meta-analyses of bacterial infection studies such as tuberculosis (Gao et al., 2010; Lewis et al., 2005; Wu et al., 2013) and in severe Respiratory Syncytial virus (RSV) bronchiolitis (McNally et al., 2014), however, the evaluation of the role of VDR polymorphisms in the risk to enveloped-virus infection, from a global perspective, remains to be addressed.

We have conducted a meta-analysis of all eligible case-control studies of *VDR* gene polymorphisms and risk of viral infection comprising studies of Human Immunodeficiency virus (HIV), Hepatitis B virus (HBV), Dengue virus (DENV) and Respiratory Syncytial virus

(RSV) infections. Although these viruses belong to different viral families and present differences in the infection process, they all share two critical similarities: being enveloped viruses and having the ability to impair or escape immune response (Fibla and Caruz, 2010; Mella et al., 2013; Morrison et al., 1992). Our study can contribute to the understanding of the role of vitamin D in the modulation of the viral immune response.

2. Methods

2.1 Literature and search strategy

Genetic studies investigating the association of *Cdx* (rs11568820), *A1012G* (rs4516035), *Fok*I (rs2228570), *Bsm*I (rs1544410) and TaqI (rs731236) polymorphisms in the *VDR* gene with susceptibility to viral infection published before January 2017 were considered in the meta-analysis. The studies were identified by extended computer based search of the PubMed database. The search strategy to identify all possible articles involved the use of combination of the following key words: "vitamin d receptor" or "vit D receptor" or "VDR" AND "variant" or "variation" or "polymorphism" or "association" or "susceptibility" or "correlation" AND "infection" or "virus" or "viral". All references cited in the publications were also reviewed to identify additional published studies not indexed in PubMed. The selection process is shown in Figure 1. Only publications in English were considered. Abstracts, case reports, editorials and review articles were excluded. The eligibility criteria were: (i) primary case-control studies; (ii) papers exploring the association of at least one of the six SNPs considered with viral infection; (iii) studies presenting sufficient data to estimate odds ratio (OR); (iv) published in English. If more than one article was published using the same study data, only the study with the largest sample size was considered. Studies presenting cases complicated with other diseases were excluded from the meta-analysis. Two researchers performed literature search independently. Once extracted from Pubmed, data were joined to reach a consensus list containing the articles to be included in the study (Table 1). From each article we extracted the following information: first author, publication year, country of origin and distribution of alleles and genotypes in cases and controls for each polymorphism.

2.2 Statistical analysis

For each of the six *VDR* gene polymorphisms (*Cdx*, *A1012G*, *FokI*, *BsmI*, *ApaI* or *TaqI*), we explored the significance of the associations for the allele contrast (minor allele *vs.* major allele) as well as the dominant (minor allele homozygote + heterozygote *vs*. major allele homozygote), recessive (minor allele homozygote *vs*. heterozygote + major allele homozygote) and overdominant (homozygotes *vs*. heterozygotes) genotype models with viral infection susceptibility. Statistical analyses were performed using the OpenMeta[Analyst] free software (Wallace et al., 2012). The OR was used as the summary statistics. The significance of the pooled ORs was determined using Z-tests and were considered statistically significant when $P<0.05$. The heterogeneity among studies was evaluated by the Q-statistic test and I^2-statistic test (Higgins et al., 2003). A random effects (DerSimonian-Laird) (DerSimonian and Laird, 1986) or a fixed effects (Inverse-variance) (Marin-Martinez and Sanchez-Meca, 2010) model was used to calculate pooled effect estimates in the presence (P-value for Q-test (P_Q)≤ 0.05) or absence ($P>0.05$) of heterogeneity based on the Q-statistic test. In addition, the inconsistency index I^2 was used to quantify inter-study variability. This statistic ranges from 0-100%, where a value of 0% indicates no observed heterogeneity (cut-off points include: I^2=0–25%, no heterogeneity; I^2=25–50%, moderate heterogeneity; I^2=50–75%, large heterogeneity; I^2=75–100%, extreme heterogeneity) (DerSimonian and Laird, 1986). Begg's Funnel plot and Egger's test were conducted to assess for publication bias in the studies included in our meta-analysis (Begg and Mazumdar, 1994; Egger et al., 1997). We determined the statistical power of each meta-analysis as a measure of the probability of detecting the association between *VDR* polymorphism and the risk of virus infection for each specific trial condition. The statistical power of an experiment is directly affected by sample size, the effect size (equivalent to OR in the association studies) and the significance level chosen (P=0.05). Using these values as input parameters we computed the achieved power of meta-analysis for each SNP/virus combination by G*Power 3.1.9.2 software (Faul et al., 2007). In order to evaluate the reliability of future association studies, we have also estimated the power achieved if the sample size will be increased in a factor of 5x, 10x and 50x.

2.3 Recovering relevant genetic data of VDR locus and RSV epidemiological data from database resources

Linkage disequilibrium (LD) structure of the *VDR locus* was obtained from 1000 genomes project retrieved by *Locus*Zoom web facility (Pruim et al., 2010). LD was estimated from

correlation coefficient (r^2) between representative markers at 5' UTR region (*A1012G*), exon 2 (*FokI*) and 3'UTR region (*BsmI*) with neighboring markers. Population frequency data for *FokI* polymorphism was recovered from 1000 genomes Browser and HapMart data mining tool. Data from a total of 16 worldwide populations was available from databases.
Epidemiological data from worldwide RSV incidence was recovered from a systematic review of the global burden of respiratory infections (Nair et al., 2010). Graphical representation of geographic data was performed by GeoChart using Google spreadsheet.

3. Results

3.1 Selection process and study characteristics

Articles selection process is illustrated in Figure 1. An initial set of 113 articles was retrieved from PubMed based on the search criteria described in the methods section. 90 of them were discarded upon examination, leaving 23 suitable articles that underwent the reviewing procedure. 9 studies were eligible to be included in the meta-analysis (Alagarasu et al., 2012; Bellamy et al., 1999; Cohen, 2004; Janssen et al., 2007; Kresfelder et al., 2011; de la Torre et al., 2008; D. E. Roth et al., 2008; Suneetha et al., 2006; Zhu et al., 2012). Characteristics of the studies fitting the inclusion criteria are reported in Table 1 and include a total of 1898 cases affected by viral infection and 2149 non-infected controls. Subjects were recruited in Canada, China, Gambia, India, Spain, Netherlands and South Africa. The major countries of origin were Netherlands and India contributing with 37.3% and 15.4% of subjects, respectively. The studies included in this meta-analysis comprise infection by Human Immunodeficiency virus (HIV), Hepatitis B virus (HBV), Dengue virus (DENV) and Respiratory Syncytial virus (RSV) with a higher frequency of RSV infection. The polymorphisms that have been more frequently evaluated in relation to viral infection are *FokI* and *TaqI* and were genotyped in 6 of the selected studies. Genotype and allele distribution of the 6 polymorphisms evaluated in the different studies are shown in Table 1.

3.2 Meta-analysis of relationship between VDR gene polymorphisms and the risk of each specific virus infection

Table 2 shows the meta-analysis results for the association of each SNP with viral infection susceptibility evaluated under four genetic models: allele, dominant, recessive and

overdominant. From all markers and virus considered an association of *FokI* polymorphism with RSV infection emerges as significant. Meta-analysis show that *FokI* T-allele was associated with RSV infection assuming fixed effects, under allelic (T-allele; Odds Ratio (OR)=1.28, 95% Confidence Interval (CI)= 1.11-1.48, P=0.001) and dominant (TT+CT *vs.* CC; OR=1.36, 95%CI=1.11-1.66, P=0.003) and recessive (TT *vs.* CT+CC; OR=1.42, 95%CI=(1.07-1.88), P=0.016) models (Table 2). As I^2-statistic test revealed heterogeneity between studies (I^2>50%), we evaluated *FokI* association assuming random effects. Association remains significant under both, allelic (OR=1.50, 95%CI= 1.06-2.14, P=0.023) and dominant (OR=1.56, 95%CI= 1.03-2.38, P=0.037) models. Figure 2 shows the forest plot of the association of *FokI* polymorphism and RSV infection under allelic (A) and dominant (B) models.

3.3 Meta-analysis of relationship between VDR gene polymorphism and the risk of infection to enveloped virus

FokI, *BsmI*, *ApaI* and *TaqI* polymorphisms were tested independently for association with enveloped viral infection by conducting a meta-analysis between each single SNP and available viral infection data (Table 3). The analysis revealed an association between *FokI* polymorphism with enveloped virus infection susceptibility under recessive model (TT *vs.* CT+CC) (OR=1.29, 95%CI= 1.01-1.66, P=0.042) evaluated assuming fixed effects (Table 3 and Figure 2, C).

3.4 Meta-analysis statistical power

In order to evaluate the capability of our meta-analysis to detect association we determined the power achieved by each specific meta-analysis taken into account the estimated effect size (OR) and sample size at a level of significance of 0.05. Figure 3 shows power values obtained for the meta-analysis association of each polymorphism to virus infection under allelic (A), dominant (B), recessive (C) and overdominant (D) models. If we consider a threshold value of 80% power, meta-analysis only reaches enough power to detect association on 6 of the 44 analysis performed, corresponding to the association study of *Fok*I polymorphism with RSV (allelic, dominant and recessive models) and enveloped virus infection (allelic and recessive models), as well as for the association study of *TaqI* polymorphisms with HBV infection (recessive model). In order to evaluate the capability of

future studies to assess association in the remaining 38 underpowered studies we found that 13 of them will reach enough power with a 5x increase in sample size; 12 will needs a 10x increase in sample size; 6 will needs a 50x increase in sample size and 7 will remains underpowered (Figure 3 A-D).

3.5 Linkage disequilibrium pattern of VDR region

Figure 4 shows *VDR* genomic structure depicting the linkage disequilibrium (LD) pattern for American (AMR), Asian (ASN), European (EUR) and African (AFR) populations constructed by data obtained from 1000 genomes project (Pruim et al., 2010). All populations show a differential LD pattern at the *VDR locus*, giving rise to the definition of different population-specific LD blocks at 5'UTR and 3'UTR regions. Nonetheless *FokI* polymorphism shows a common pattern in all populations that reflects a lack of LD with all neighboring markers.

3.6 Worldwide distribution of FokI T-allele frequency and RSV infection incidence

*Fok*I T-allele frequency distribution was obtained from 16 human populations at 1000 Genomes Browser and HapMart resource. Samples recruited have geographical origin from Africa (four populations), Europe (five populations), Asia (four populations) and Central and South America (three populations). In addition, data from control samples of studies included in the meta-analysis were also considered, representing five additional geographical origins from Europe (two populations), Asia (one population), Africa (one population) and North America (one population). T-allele frequency was lower in African samples (mean T-allele frequency = 0.185; rank min: 0.13; max: 0.21), intermediate in Asian (mean T-allele frequency = 0.383; rank min: 0.26; max: 0.41), European (mean T-allele frequency = 0.397; rank min: 0.33; max: 0.46) and North American samples (T-allele frequency = 0.34) and higher in Central and South American samples (mean T-allele frequency of 0.452; rank min: 0.40; max: 0.49) (Figure 5, A).

Data from RSV and acute lower respiratory infection (ALRI) due to RSV in children younger than 5 years was obtained from a systematic review of studies published between January 1995, and June 2009, and ten unpublished population-based studies performed by Nair et al. (Minsky, 1994; Nair et al., 2010). This study constitutes a crucial effort of the World Health

Organization (WHO) and Bill & Melinda Gates Foundation to known the global burden of disease. We recovered data from this study referring to the worldwide incidence of RSV-associated severe ALRI in children <1 year in 20 human populations from Africa (four populations), Asia (five populations), Europe (six populations), North America (three populations) and Central and South America (two populations).

Incidence (cases per 1000 children per year) was lower in samples from Africa (rank min: 10; max: 18), intermediate in samples from Austral-Asia (rank min: 10; max: 28) and Europe (rank min: 10; max: 30) and higher in samples from Central and South America (rank min: 47; max: 60). Data from North American samples reveals intermediate values in Eastern countries (rank min: 10; max: 27) while the highest values coming from the Northern (Alaska and White Mountain) samples (rank min: 34; max: 91) (Figure 5, B).

4. Discussion

The two general types of immune response, the rapid-onset "innate" response and the "adaptive" response are key elements against the virus infection. However, immune responses differ between non-enveloped and enveloped viruses. While non-enveloped viruses induce a predominant humoral response, enveloped viruses promote both, cell-mediated and humoral immune responses. In this way, the role of vitamin D as modulator of the Th1/Th2 balance should be a relevant element on the control of enveloped virus infection. Vitamin D VDR-mediated effects in the immune response modulation have been largely studied in immune related diseases by the assessment of *VDR* polymorphisms. There are a number of studies evaluating *VDR* polymorphisms in bacterial and viral infection; however, most of them have a small number of subjects limiting its statistical power to detect associations. A meta-analysis achieve a higher statistical power by increasing the sample size which allows to detect new associations and reinforce previous results contributing to a better understanding of the genetic variability in these diseases. There are some meta-analyses evaluating the association of *VDR* polymorphisms with tuberculosis, HBV and RSV (Gao et al., 2010; Lewis et al., 2005, McNally et al., 2014; He et al., 2018), however our study is the first addressing its association with enveloped viral infection in a global perspective.

Among all comparisons performed, the meta-analysis showed association of *FokI* polymorphism with susceptibility to RSV infection under allelic and dominant models. Our

results are in accordance with those shown by a recent meta-analysis of RSV in children (McNally et al., 2014). In addition, when considering as a whole the data available for three enveloped virus including RSV, HIV and DENV the association of *FokI* remains statistically significant. According to this, *FokI* T-allele confers risk to RSV infection as well as TT homozygotes are at risk for enveloped virus infection.

FokI variant alleles have been associated with changes in TFIIB-VDR interaction and in transcription efficiency (Jurutka et al., 2000). In addition, there is evidence that *FokI* polymorphism affects immune cell behavior, with a bolstered active immune system assigned to the protein isoform derived from the C-allele (van Etten et al., 2007). In this line, the risk T-allele may have lower transcription of *VDR* decreasing the efficiency of the vitamin D pathway by hampering the binding of vitamin D to VDR and affecting the expression of vitamin D responsive genes. As recovered from 1000 Genomes data, *FokI* shows the same LD structure in all populations considered revealing that alleles at this *locus* are randomly distributed in relation to nearest polymorphisms. This allows us to consider any effect attributed to *FokI* polymorphism as causative on its own.

Functional evidences, genomic LD pattern and our meta-analysis results supports for a relevant role of *FokI* polymorphism in the vitamin D VDR-mediated effects in the immune response modulation that confers susceptibility to enveloped viral infection. Previous meta-analysis of *VDR* polymorphisms and pulmonary tuberculosis risk (C. Chen et al., 2013; Fibla and Caruz, 2010; Lewis et al., 2005) and severe RSV bronchiolitis (McNally et al., 2014) showed a trend for association of *FokI* T-allele with infection. Taking it together with our results, these points to a relevant role of *VDR FokI* polymorphism in both bacterial and viral infections.

RSV infection is the most prevalent cause of lower respiratory tract infection during infancy. Epidemiological and clinical evidences have suggested a role of vitamin D in respiratory viral infections. Skin pigmentation and, thus, vitamin D production, explained the variations in risk of childhood respiratory infections in Hawaii (Grant, 2008), and RSV infection activity has been inversely correlated with solar UV-B (UVB) doses in a latitudinal varying manner that will be linked to differences on vitamin D synthesis (Fibla and Caruz, 2010; Welliver, 2007). Infants with the lowest concentrations of vitamin D had six times the risk of developing RSV infections compared to infants with the highest levels of vitamin D

(Belderbos et al., 2011). Our meta-analysis reveals that the vitamin D receptor functional polymorphic variant *FokI* is consistently associated with RSV infection with T-allele being less efficient to mediate vitamin D immune action conferring risk to RSV infection.

The worldwide regional incidence of episodes of ALRI due to RSV has been reviewed in a comprehensive meta-analysis (Nair et al., 2010). In 2005 near to 34 million of new episodes of RSV-associated ALRI occurred worldwide in children younger than 5 years. From them, a 10% representing severe RSV-associated ALRI required hospital admission. While meta-estimate of incidence on developing countries was higher than in industrialized countries, regional distribution of incidence is highly variable within countries or regions and between regions. The lowest regional values were observed in African countries while highest values were from northern countries in North America. Although methodological, environmental and social factors could be considered as the main explanation of worldwide regional differences on RSV incidence, we could not discard a potential role of population specific genetic factors as those disclosed in our meta-analysis. As population genetic data reveals, worldwide distribution of risk T-allele frequency mimics regional incidence of RSV infection. Although our analysis is based on the comparison of regional incidence of RSV infection and T-allele frequency between unpaired populations, a common trend is observed that points towards to consider *FokI* polymorphism as a candidate genetic factor contributing to worldwide regional differences on RSV incidence.

We recognize limitations of the present meta-analysis such as the limiting power to detect meta-analysis association for some markers and models tested. The capability to detect association depends on several factors including the effect size of the tested variant (OR) and the sample size. Considering values used in the present study, enough power to detect meta-analysis association with susceptibility to infection (i.e. a standard 80% power) was achieved for HBV (*TaqI*), RSV (*FokI*), and enveloped virus (*FokI*) infections. This forces us to be cautious when rejecting meta-analysis association for those cases with limiting power. Nevertheless, if association exists with an effect size as detected in the present meta-analysis, the required sample size of the majority of studies should be increased in a factor between 5 to 10, which is a major challenge for future studies. We also recognize a possible bias in the selection of control subjects due to the pooling of populations with different origin and to the differences in gender and age distributions between the studies. Future studies on the field should allow reaching larger sample sizes, helping to clarify the role of *VDR* genetic

variability in viral infection susceptibility. Nevertheless, our meta-analysis underlines the importance of *FokI* as causative polymorphisms in this process.

5. Conclusion

In conclusion, we have used a meta-analysis strategy to evaluate the association of *VDR* genetic variants with susceptibility to infection to several enveloped virus. Among markers analyzed, *FokI* polymorphism emerges as consistently associated with susceptibility to infection to RSV. A common trend is observed between worldwide incidence of RSV infection and *FokI* allele frequency distribution that points towards *FokI* polymorphism as a candidate genetic factor contributing to worldwide regional differences on RSV incidence.

Acknowledgements

ML was recipient of a fellowship from the University of Lleida. This work was supported by grants to the University of Lleida (J.F. principal investigator) from Fondo de Investigación Sanitaria (FIS PI051778) and Ministerio de Ciencia e Innovación (CGL 2007-62875).

Conflict of Interest

The authors state no conflict of interest.

Web site resources

OpenMeta[Analyst]: http://www.cebm.brown.edu/open_meta

1000 Genomes Browser at NCBI: http://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/

HapMart: http://hapmap.ncbi.nlm.nih.gov/biomart/martview/

LocusZoom: http://csg.sph.umich.edu/locuszoom/

Geochart: https://developers.google.com/chart/interactive/docs/gallery/geochart?hl=fr

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Table 1. Genotype and allele distribution of *VDR* polymorphisms and main characteristics of selected case-control studies.

				Cases						Controls					
Polymorphism	**Author (Year)**	**Country**	**Virus type** [a]	**N**	**GG**	**GA**	**AA**	**G**	**A** [b]	**N**	**GG**	**GA**	**AA**	**G**	**A** [b]
Cdx	Alagarasu et al. (2009)	India	HIV	242	97	125	20	319	165	146	69	60	17	198	94
(rs11568820)	de la Torre et al. (2008)	Spain	HIV	320	192	109	16	493	147	124	75	42	7	193	55
				Cases						**Controls**					
				N	AA	AG	GG	A	G [b]	N	AA	AG	GG	A	G [b]
A1012G	Alagarasu et al. (2009)	India	HIV	243	155	75	13	385	101	146	103	36	7	242	50
(rs4516035)	de la Torre et al. (2008)	Spain	HIV	320	106	157	57	365	269	124	42	60	22	144	104
				Cases						**Controls**					
				N	CC	CT	TT	C	T [b]	N	CC	CT	TT	C	T [b]
FokI	Alagarasu et al. (2009)	India	HIV	243	149	81	13	379	107	144	81	59	4	221	67
(rs2228570)	Alagarasu et al. (2012)	India	DENV	112	60	46	6	166	58	105	54	41	10	149	61
	de la Torre et al. (2008)	Spain	HIV	320	147	138	32	435	205	124	57	54	13	168	80
	Janssen et al. (2007)	Netherlands	RSV	470	165	223	82	553	387	1007	397	471	139	1265	749
	Kresfelder et al. (2011)	South Africa	RSV	296	177	109	10	463	129	113	86	24	3	196	30
	Roth et al. (2008)	Canada	RSV	56	14	29	13	57	55	64	24	37	3	85	43
				Cases						**Controls**					
				N	GG	GA	AA	G	A [b]	N	GG	GA	AA	G	A [b]
BsmI	Alagarasu et al. (2009)	India	HIV	238	46	122	70	214	262	146	45	62	39	152	140
(rs1544410)	Alagarasu et al. (2012)	India	DENV	112	35	43	34	113	111	105	33	45	27	111	99
	de la Torre et al. (2008)	Spain	HIV	320	118	141	61	378	262	124	46	54	24	147	101
	Janssen et al. (2007)	Netherlands	RSV	468	160	234	74	382	554	1008	368	469	171	1205	811
				Cases						**Controls**					
				N	TT	TA	GG	T	G [b]	N	TT	TA	GG	T	G [b]
ApaI	Alagarasu et al. (2009)	India	HIV	242	83	121	38	287	197	146	44	81	21	169	123
(rs7975232)	Alagarasu et al. (2012)	India	DENV	112	43	59	10	145	79	105	26	53	26	105	105
	Suneetha et al. (2012)	India	HBV	204	80	101	23	261	147	408	201	177	30	579	237
				Cases						**Controls**					
				N	TT	TC	CC	T	C [b]	N	TT	TC	CC	T	C [b]
TaqI	Alagarasu et al. (2009)	India	HIV	241	89	119	33	297	185	146	70	62	14	202	90
(rs731236)	Alagarasu et al. (2012)	India	DENV	112	51	51	10	153	71	105	45	54	6	144	66
	Bellamy et al. (1999)	Gambia	HBV	206	104	87	15	295	117	324	137	141	46	415	233
	Janssen et al. (2007)	Netherlands	RSV	470	159	242	69	560	380	1004	366	472	166	1204	804
	Roth et al. (2008)	Canada	RSV	56	24	28	4	76	36	64	32	28	4	92	36
	Suneetha et al. (2012)	India	HBV	214	93	96	25	282	146	408	178	191	39	547	269
	Zhu et al. (2012)	China	HBV	274	239	35	0	513	35	158	139	18	1	296	20

[a] Virus type: Human Immunodeficiency virus (HIV), Hepatitis B virus (HBV), Dengue virus (DENV) and Respiratory Syncytial virus (RSV).

[b] Minor allele

Table 2. Meta-analysis results of *VDR* polymorphisms association with single virus infection

Virus	Contrasted	Genetic model [a]	Fixed Effects			Random Effects			Heterogeneity			Publication
			OR (95%CI)	Z	P	OR (95%CI)	Z	P	Q	I^2	P (Q)	P_{bias}
HIV	*Cdx* (rs11568820)	Allelic (A *vs.* G)	1.04 (0.83-1.31)	0.34	0.737	1.04 (0.83-1.31)	0.34	0.737	0.19	0	0.659	NA
		Dominant	1.16 (0.86-1.56)	0.98	0.328	1.16 (0.86-1.56)	0.98	0.328	0.96	0	0.328	NA
		Recessive	0.75 (0.44-1.30)	1.03	0.304	0.75 (0.44-1.30)	1.03	0.304	0.20	0	0.652	NA
		Overdominant	0.79 (0.59-1.07)	1.53	0.126	0.79 (0.54-1.18)	1.15	0.252	1.72	41.69	0.190	NA
	A1012G (rs4516035)	Allelic (G *vs.* A)	1.10 (0.87-1.38)	0.80	0.427	1.10 (0.87-1.39)	0.80	0.427	0.92	0	0.336	NA
		Dominant	1.19 (0.87-1.62)	1.07	0.286	1.19 (0.87-1.62)	1.07	0.286	0.74	0	0.388	NA
		Recessive	1.03 (0.65-1.65)	0.14	0.893	1.03 (0.65-1.65)	0.14	0.893	0.04	0	0.842	NA
		Overdominant	0.86 (0.63-1.17)	0.97	0.333	0.86 (0.63-1.17)	0.97	0.333	0.80	0	0.372	NA
	FokI (rs2228570)	Allelic (T *vs. C*)	0.96 (0.76-1.21)	0.35	0.723	0.96 (0.76-1.21)	0.35	0.723	0.05	0	0.824	NA
		Dominant	0.89 (0.67-1.20)	0.75	0.456	0.89 (0.67-1.2)	0.75	0.456	0.41	0	0.522	NA
		Recessive	1.16 (0.65-2.08)	0.50	0.619	1.19 (0.62-2.26)	0.52	0.606	1.14	12.51	0.285	NA
		Overdominant	1.18 (0.87-1.58)	1.06	0.289	1.18 (0.85-1.62)	0.99	0.323	1.15	13.37	0.283	NA
	BsmI (rs1544410)	Allelic (G *vs.* A)	1.16 (0.94-1.42)	1.36	0.175	1.15 (0.87-1.53)	1.00	0.317	1.81	44.6	0.179	NA
		Dominant	1.33 (0.97-1.83)	1.74	0.082	1.36 (0.75-2.47)	1.00	0.316	3.49	71.31	0.062	NA
		Recessive	1.07 (0.76-1.51)	0.38	0.703	1.07 (0.76-1.51)	0.38	0.703	0.18	0	0.669	NA
		Overdominant	0.83 (0.62-1.11)	1.26	0.209	0.83 (0.60-1.15)	1.13	0.258	1.23	18.65	0.268	NA
RSV	*FokI* (rs2228570)	Allelic (T *vs.* C)	1.28 (1.11-1.48)	3.44	0.001	1.50 (1.06-2.14)	2.27	*0.023*	5.79	65.43	0.055	<0.001
		Dominant	1.36 (1.11-1.66)	3.00	0.003	1.56 (1.03-2.38)	2.09	*0.037*	4.89	59.07	0.087	<0.001
		Recessive	1.42 (1.07-1.88)	2.40	0.016	1.91 (0.80-4.56)	1.45	0.148	4.03	60.22	0.081	0.005
		Overdominant	0.89 (0.73-1.08)	1.17	0.243	0.82 (0.48-1.39)	0.74	0.461	7.95	74.83	0.019	0.141
	TaqI (rs731236)	Allelic (G *vs.* A)	1.03 (0.89-1.20)	0.38	0.706	1.03 (0.89-1.20)	0.38	0.706	0.36	0	0.551	NA
		Dominant	1.14 (0.92-1.42)	1.17	0.241	1.14 (0.92-1.42)	1.17	0.241	0.20	0	0.655	NA
		Recessive	0.88 (0.65-1.19)	0.85	0.398	0.88 (0.65-1.19)	0.85	0.398	0.14	0	0.704	NA
		Overdominant	0.83 (0.67-1.03)	1.73	0.083	0.83 (0.67-1.03)	1.73	0.083	0.04	0	0.851	NA
HBV	TaqI (rs731236)	Allelic (G vs. A)	0.89 (0.75-1.06)	1.35	0.177	0.89 (0.66-1.20)	0.77	0.444	4.82	58.53	0.090	0.224
		Dominant	0.89 (0.71-1.11)	1.07	0.286	0.89 (0.69-1.14)	0.95	0.341	2.32	13.91	0.313	0.362
		Recessive	0.81 (0.54-1.20)	1.06	0.288	0.71 (0.29-1.72)	0.76	0.448	6.29	68.19	0.043	0.137
		Overdominant	1.04 (0.83-1.30)	0.34	0.732	1.04 (0.83-1.30)	0.34	0.732	0.36	0	0.835	0.847

[a] Human Immunodeficiency virus (HIV), Hepatitis B virus (HBV) and Respiratory Syncytial virus (RSV).

[b] Genetic models tested: Allelic: minor allele *vs.* major allele; Dominant: (minor allele homozygote + heterozygote) *vs.* major allele homozygote, Recessive: minor allele homozygote *vs.* (heterozygote + major allele homozygote); Overdominant: homozygotes *vs.* heterozygotes. Random effects was selected when I^2 (%) >50% and/or P (Q) < 0.05.

Table 3. Meta-analysis results of *VDR* polymorphisms association with enveloped virus infection.

Contrasted polymorphism (rs code)	Virus considered[a]	Genetic model[b]	Fixed Effects			Random Effects			Heterogeneity			Publication bias
			OR (95%CI)	Z	P	OR (95%CI)	Z	P	Q	I^2 (%)	P (Q)	P_{bias}
FokI (rs2228570)	HIV, DENV, RSV	Allelic (T *vs. C*)	1.16 (1.03-1.30)	2.43	0.015	1.17 (0.94-1.45)	1.44	0.150	12.39	59.65	0.030	0.015
		Dominant	1.16 (0.99-1.36)	1.88	0.060	1.18 (0.90-1.54)	1.19	0.235	11.43	56.27	0.043	0.054
		Recessive	1.29 (1.01-1.66)	2.04	*0.042*	1.33 (0.83-2.11)	1.19	0.236	9.38	46.71	0.095	0.050
		Overdominant	0.96 (0.82-1.13)	0.47	0.637	0.95 (0.73-1.24)	0.38	0.707	11.46	56.36	0.043	0.584
BsmI (rs1544410)	HIV, DENV, HBV	Allelic (A *vs.* G)	1.07 (0.95-1.21)	1.16	0.245	1.07 (0.95-1.21)	1.16	0.245	2.64	0	0.451	0.177
		Dominant	1.16 (0.97-1.39)	1.65	0.100	1.18 (0.93-1.51)	1.34	0.180	4.56	34.23	0.207	0.081
		Recessive	1.01 (0.82-1.25)	0.11	0.912	1.01 (0.82-1.25)	0.11	0.912	1.20	0	0.753	0.724
		Overdominant	0.88 (0.75-1.04)	1.46	0.146	0.88 (0.75-1.04)	1.46	0.146	2.68	0	0.444	0.241
ApaI (rs7975232)	HIV, DENV, RSV	Allelic (G *vs.* T)	1.01 (0.85-1.20)	0.08	0.935	0.91 (0.55-1.49)	0.39	0.700	15.84	87.38	<0.00	0.563
		Dominant	1.04 (0.81-1.33)	0.32	0.752	0.90 (0.50-1.64)	0.34	0.731	10.71	81.32	0.005	0.711
		Recessive	0.97 (0.68-1.40)	0.15	0.883	0.84 (0.34-2.06)	0.38	0.703	11.82	83.08	0.003	0.543
		Overdominant	0.94 (0.74-1.18)	0.55	0.586	0.95 (0.71-1.27)	0.36	0.722	2.96	32.40	0.228	0.680
TaqI (rs731236)	HIV, DENV, RSV, HBV	Allelic (C *vs.* T)	1.01 (0.91-1.12)	0.18	0.860	1.02 (0.87-1.20)	0.22	0.823	11.64	48.45	0.070	0.717
		Dominant	1.05 (0.91-1.21)	0.70	0.484	1.05 (0.87-1.27)	0.51	0.608	9.23	35.02	0.161	0.469
		Recessive	0.93 (0.75-1.16)	0.63	0.532	0.97 (0.68-1.36)	0.84	0.844	10.11	40.67	0.120	0.652
		Overdominant	0.92 (0.80-1.06)	1.15	0.250	0.92 (0.80-1.06)	1.15	0.250	4.68	0	0.585	0.364

[a] Human Immunodeficiency virus (HIV), Hepatitis B virus (HBV), Dengue virus (DENV) and Respiratory Syncytial virus (RSV

[b] Genetic models tested: Allelic: minor allele *vs.* major allele; Dominant: (minor allele homozygote + heterozygote) *vs.* major allele homozygote, Recessive: minor allele homozygote *vs.* (heterozygote + major allele homozygote); Overdominant: homozygotes *vs.* heterozygotes. Random effects was selected when I^2 (%) >50% and/or P (Q) < 0.05

Figure legends online (color)

Fig. 1. Articles selection process.

Fig. 2. Forest plot of the meta-analysis association of *Vitamin D Receptor FokI* polymorphism and risk of Respiratory Syncytial Virus infection under allelic (A) and dominant (B) models. Forest plot of the meta-analysis association of *Fok*I polymorphism with susceptibility to infection with enveloped virus under allelic model (C).

Fig. 3. Graphical representation of the statistical power of each meta-analysis evaluating the association of *VDR* polymorphic markers with selected enveloped virus under allelic (A), dominant (B), recessive (C) and overdominat (D) models. Colored circles correspond to power estimates based on actual sample size of meta-analysis for Hepatitis B virus (HBV, orange), Human Immunodeficiency virus (HIV, red), Respiratory Syncytial Virus (RSV, green) and Enveloped virus (blue). Vertical lines represent power estimates based on sample size increased in a factor of 5x (continuous line), 10x (scattered line) and 50x (doted line). Horizontal dotted lines marks threshold power at 80% (P=0.05).

Fig. 4. Linkage disequilibrium (LD) pattern of *Vitamin D Receptor* gene region of four human populations. Colored dots corresponds to LD values measured by r^2 of (A) representative 5'UTR marker rs4516035 (*A1012G*), (B) representative 3' UTR marker rs1544410 (*BsmI*) and (C) exonic marker rs2228570 (*FokI*) based on 1000 genomes data from American (AMR), Asian (ASN), European (EUR) and African (AFR) populations. Recombination rate profile of this genomic region and exon-intron structure of *VDR* gene is depicted at the lower part of the figure (D).

Fig. 5. Worldwide distribution of *Fok*I T-allele frequency and RSV infection incidence. (A) Worldwide distribution of *Fok*I allele frequency in 22 human populations with geographical origin in Africa (AFR): ASW (African ancestry in Southwest USA), LWK (Luhya in Webuye, Kenya), MKK (Maasai in Kinyawa, Kenya), SAF (South Africa) and YRI (Yoruba in Ibadan, Nigeria); Europe (EUR): CEU (Utah residents with Northern and Western European ancestry from the CEPH collection), TSI (Toscans in Italy), IBS (Iberian population), FIN (Finnish in Finland), CAT (northeast Spain), NTH (Netherlands) and GBR (British in England); Asian (ASN): CHB (Han Chinese in Beijing, China), CHD (Chinese in

Metropolitan Denver, Colorado), IND (Indians), GIH (Gujarati Indians in Houston, Texas) and JPT (Japanese in Tokyo, Japan); Central-South America (SAM): MEX (Mexican ancestry in Los Angeles, California), CLM (Colombians from Medellin, Colombia) and PUR (Puerto Ricans from Puerto Rico) and North America (NAM): CAN (Canada). Population specific frequency (histogram), mean regional frequency (circles) and rank (min, max) of *Fok*I T-allele are represented. Data was recovered from 1000 Genomes and HapMap projects. (B) Worldwide incidence of RSV-associated severe acute lower respiratory infection (ALRI) in children <1 year in 20 human populations with geographical origin in Africa: SAF (South Africa), KEN (Kenya), MNZ (Mozambique) and GAM (Gambia); Austral-Asia: HKG (Hong Kong), IND (India), INO (Indonesia), THL (Thailand) and AUT (Queensland, Australia); Europe: NTH (Netherlands), AUS (Austria), SWD (Sweden), GER (German), IBS (Spain) and UK (United Kingdom); North America: USA (United States), ALK (Alaska) and WTM (White Mountain) and Central and South America: GUA (Guatemala) and BRZ (Brazil). Population specific incidence of RSV-associated severe ALRI (per 1000 children per year) (histogram), mean regional incidence (circles) and rank (min, max) are represented. Data was recovered from Nair et al. 2010.

Figure legends in print (black and white)

Figure 3. Graphical representation of the statistical power of each meta-analysis evaluating the association of *VDR* polymorphic markers with selected enveloped virus under allelic (A), dominant (B), recessive (C) and overdominat (D) models. Forms correspond to power estimates based on actual sample size of meta-analysis for Hepatitis B virus (HBV, triangles), Human Immunodeficiency virus (HIV, squares), Respiratory Syncytial Virus (RSV, circles) and Enveloped virus (diamonds). Vertical lines represent power estimates based on sample size increased in a factor of 5x (continuous line), 10x (scattered line) and 50x (doted line). Horizontal dotted lines marks threshold power at 80% (P=0.05).

Abbreviation list

AFR, african; ALRI, acute lower respiratory infection; AMR, american; ASN, asian; CI, confidence interval; DENV, dengue virus; EUR, european; HBV, hepatitis B virus ; HIV, human immunodeficiency virus; LD, linkage disequilibrium; OR, odds ratio ; SNP, single nucleotide polymorphism; RFLP, restriction fragment length polymorphisms; RSV, respiratory syncytial virus; UTR, untranslated region; VDR, vitamin D receptor;

Figure1

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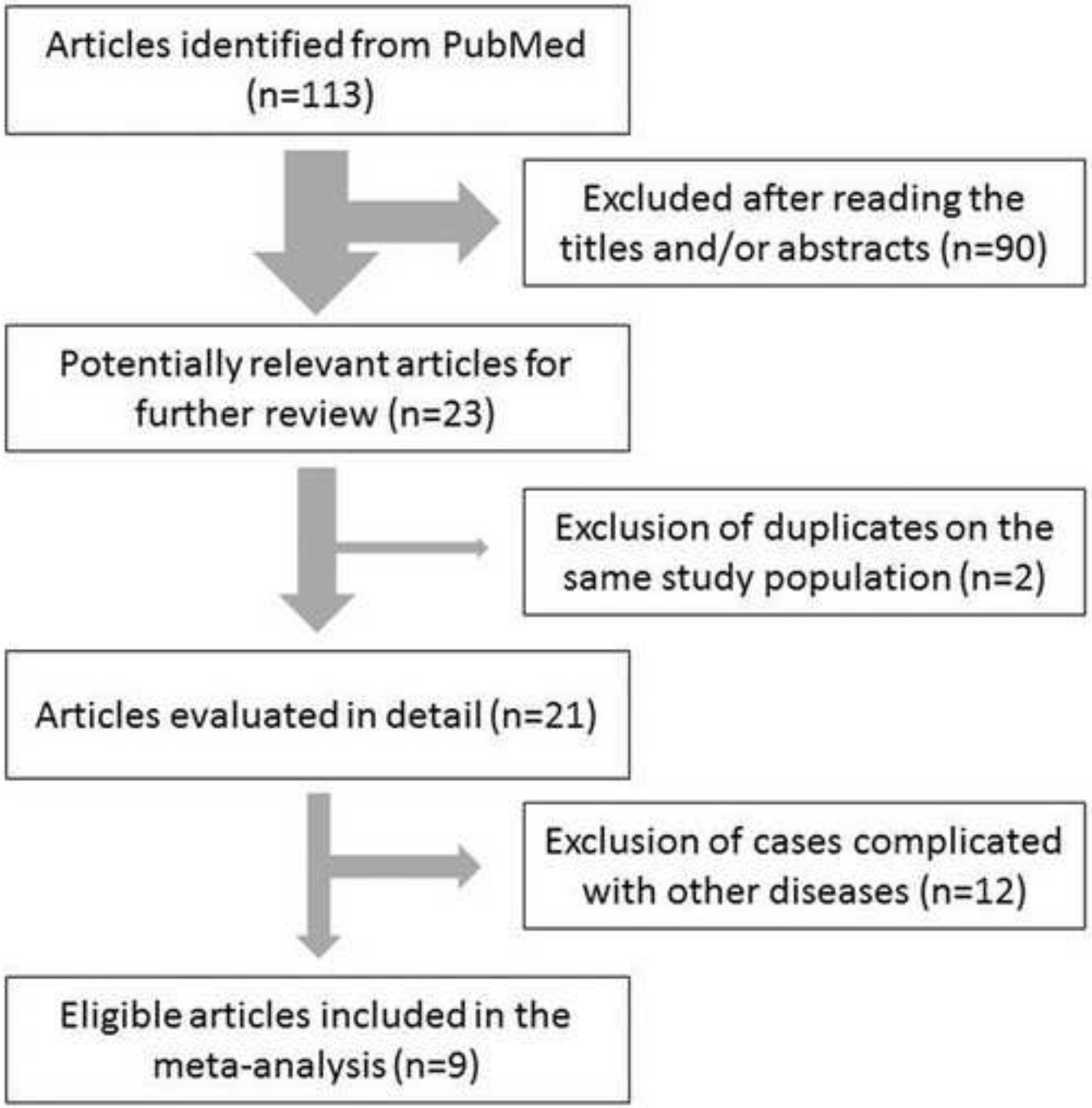

Figure2_color

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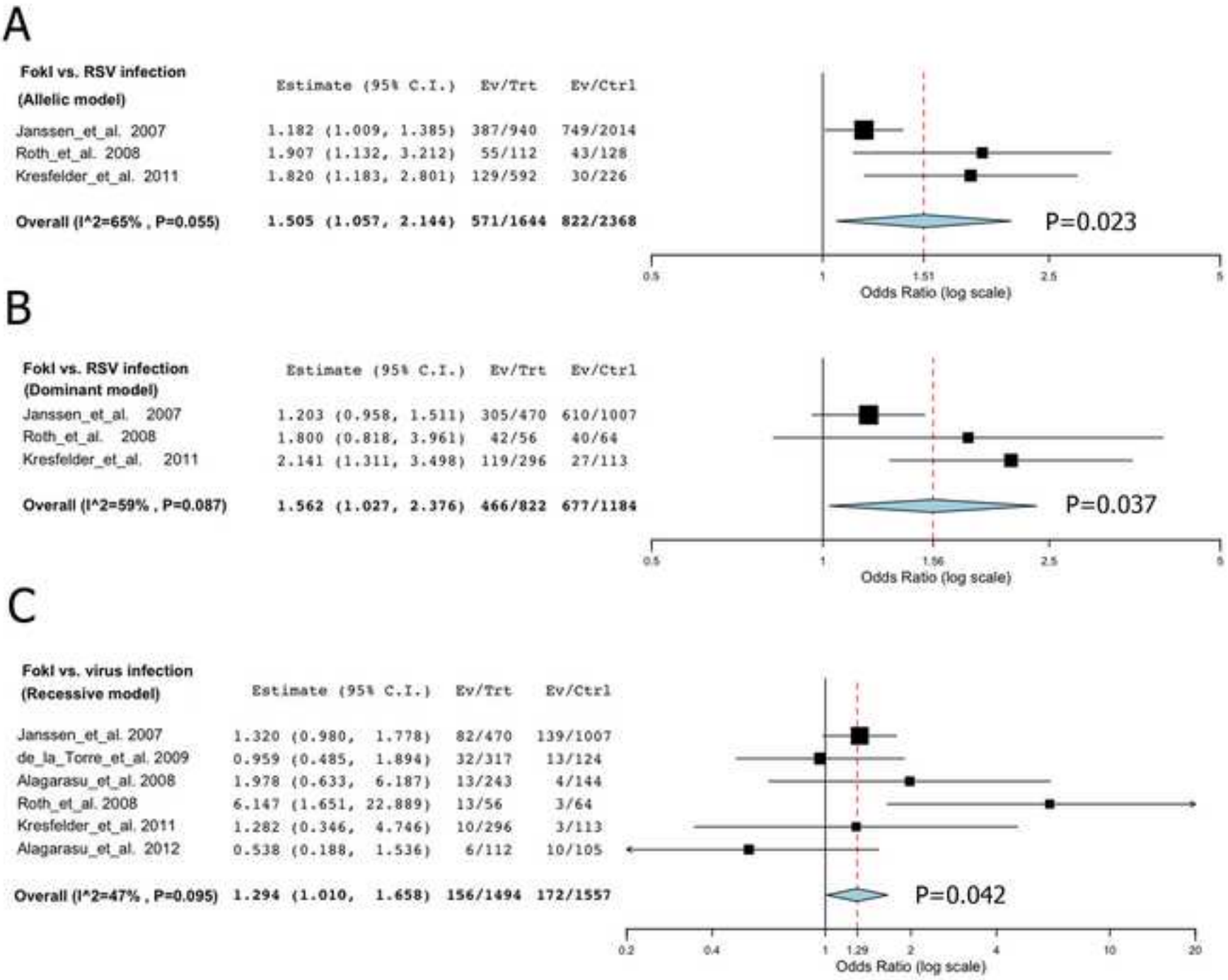

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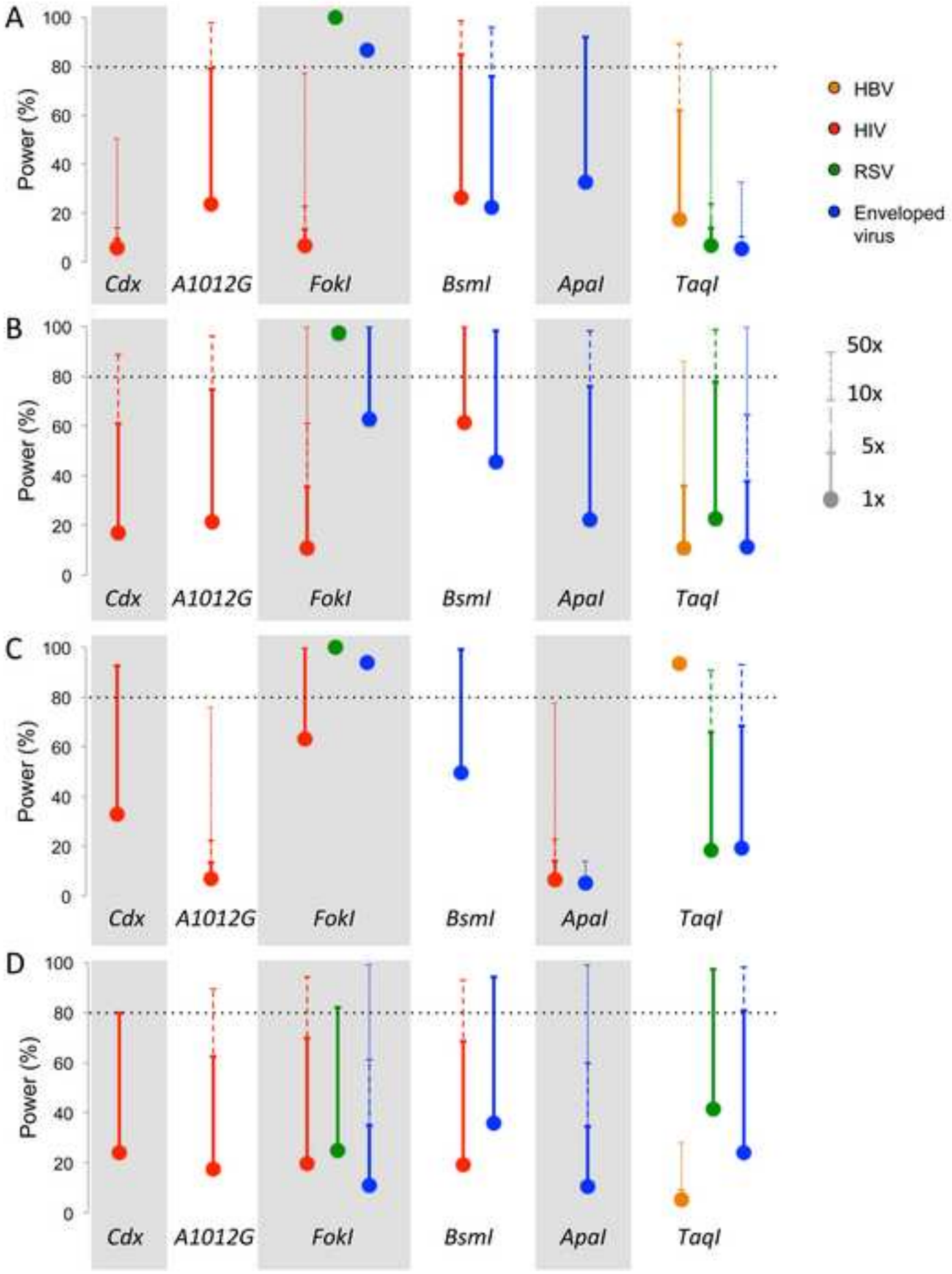

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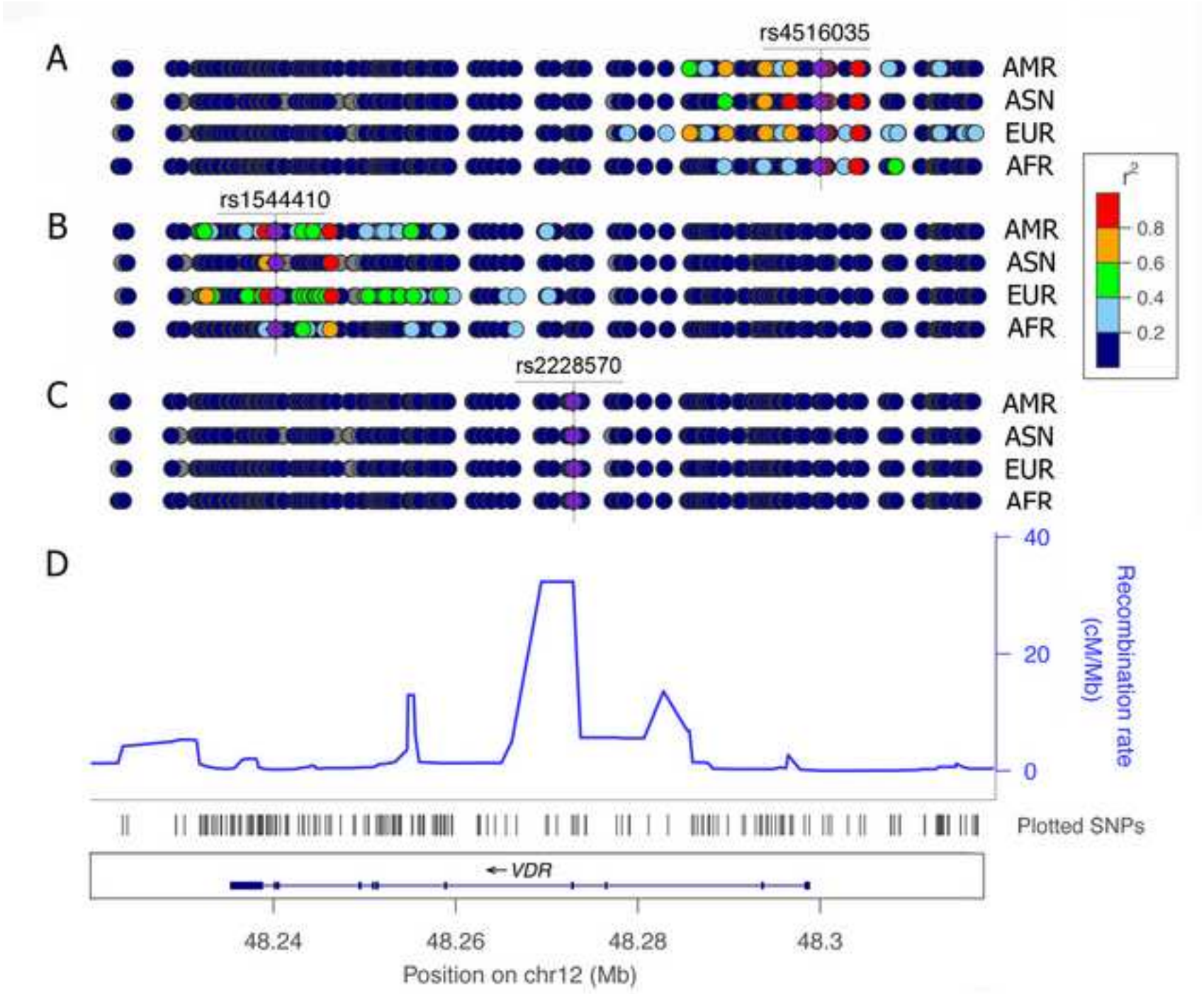

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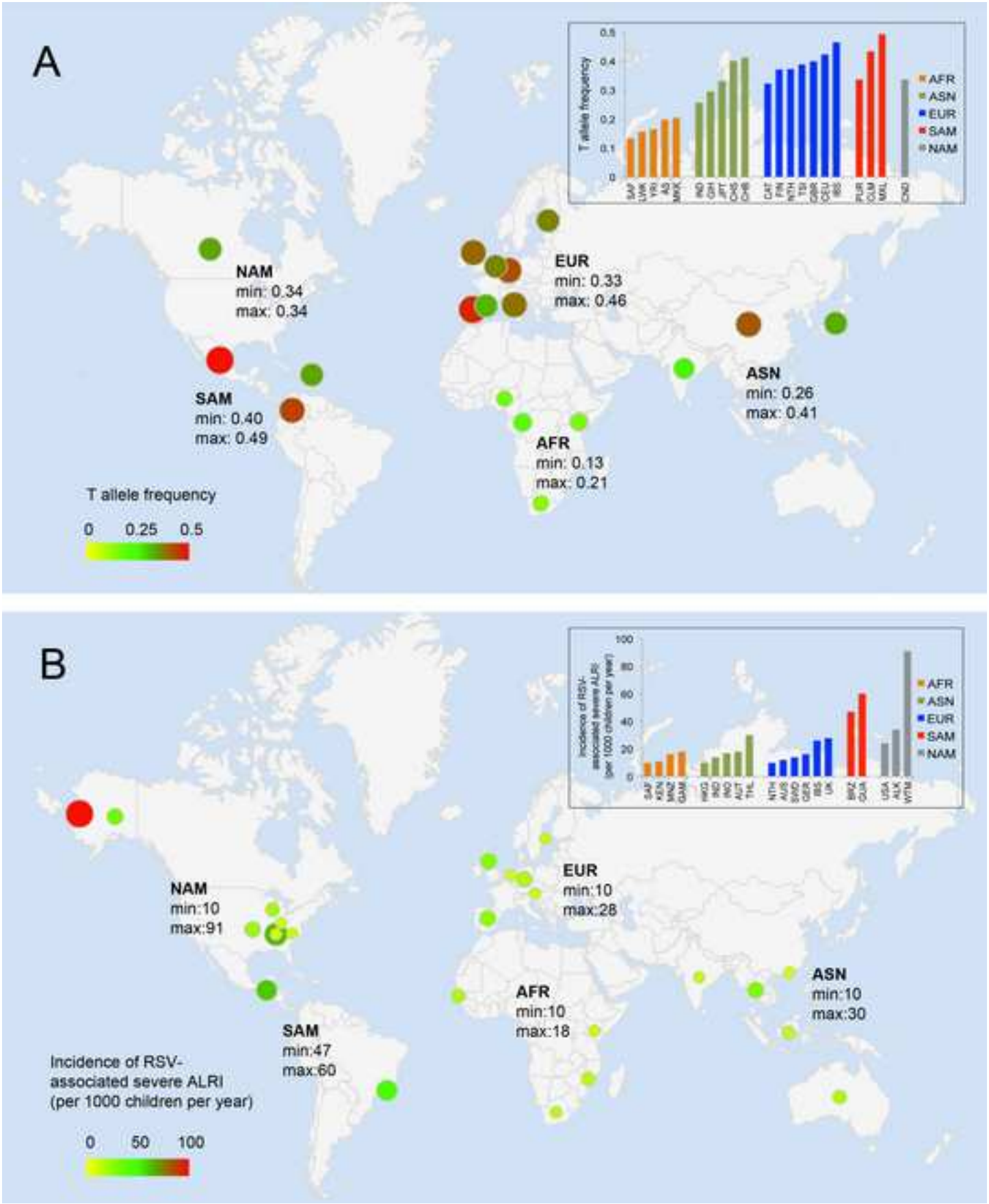

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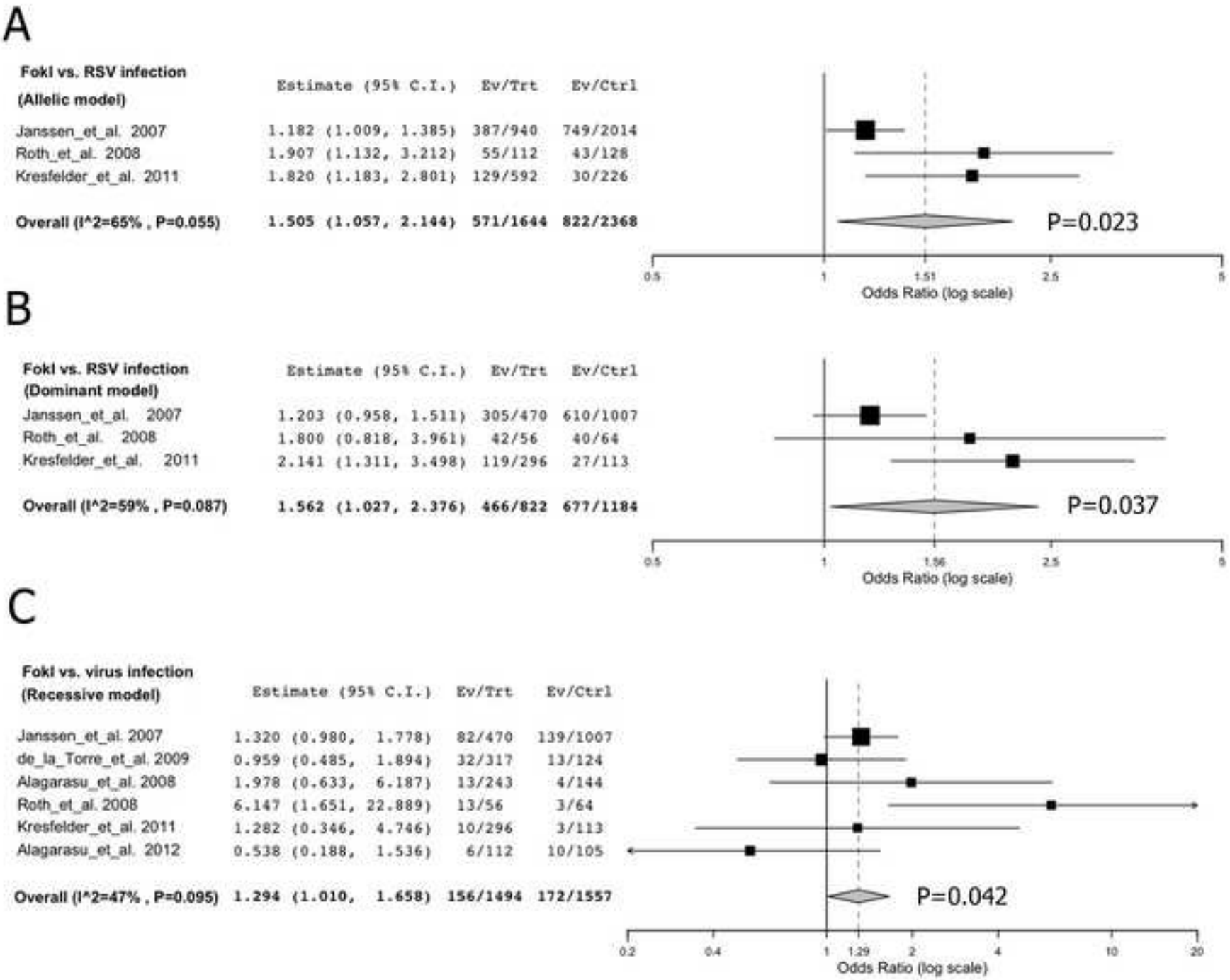

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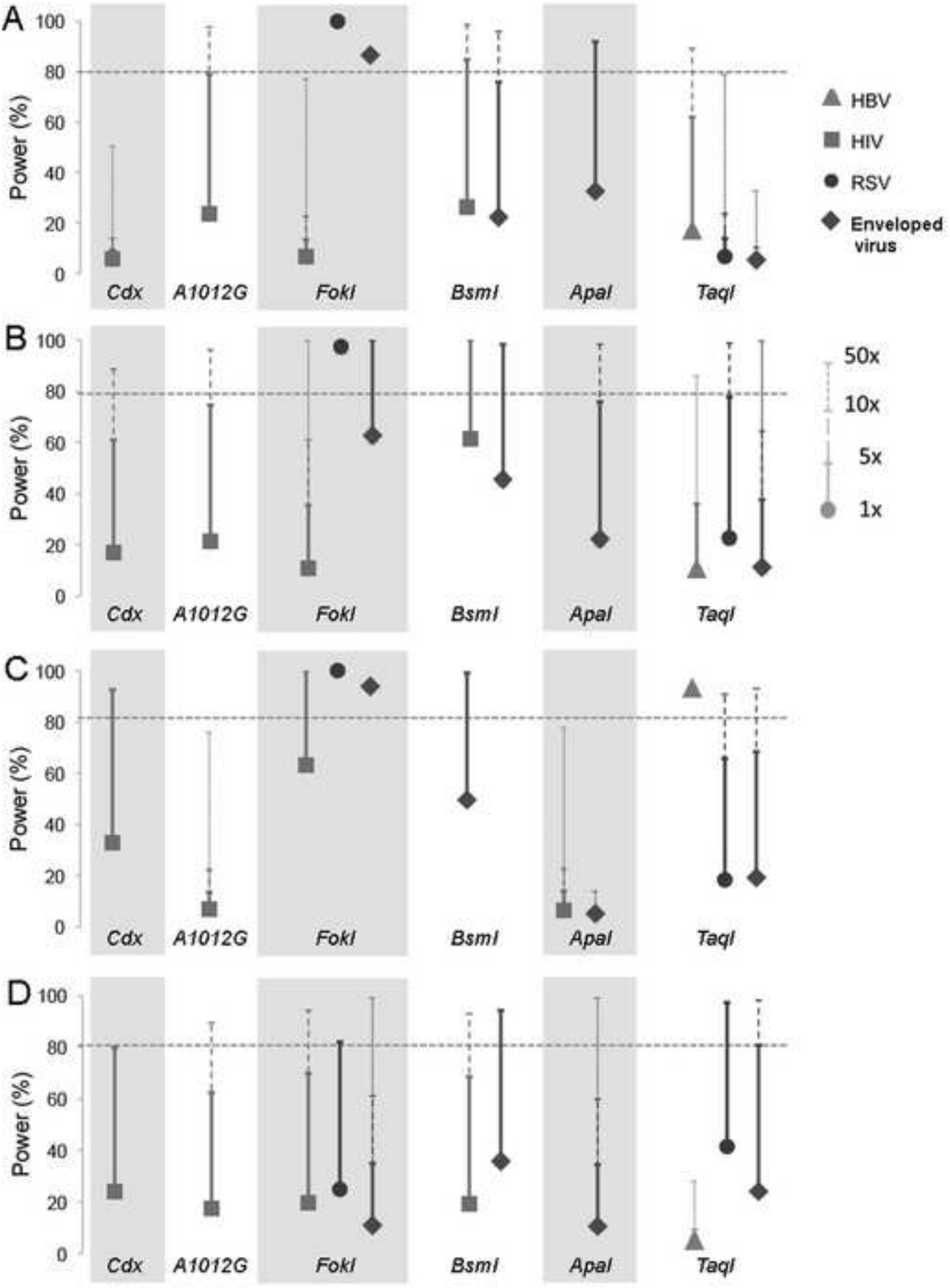

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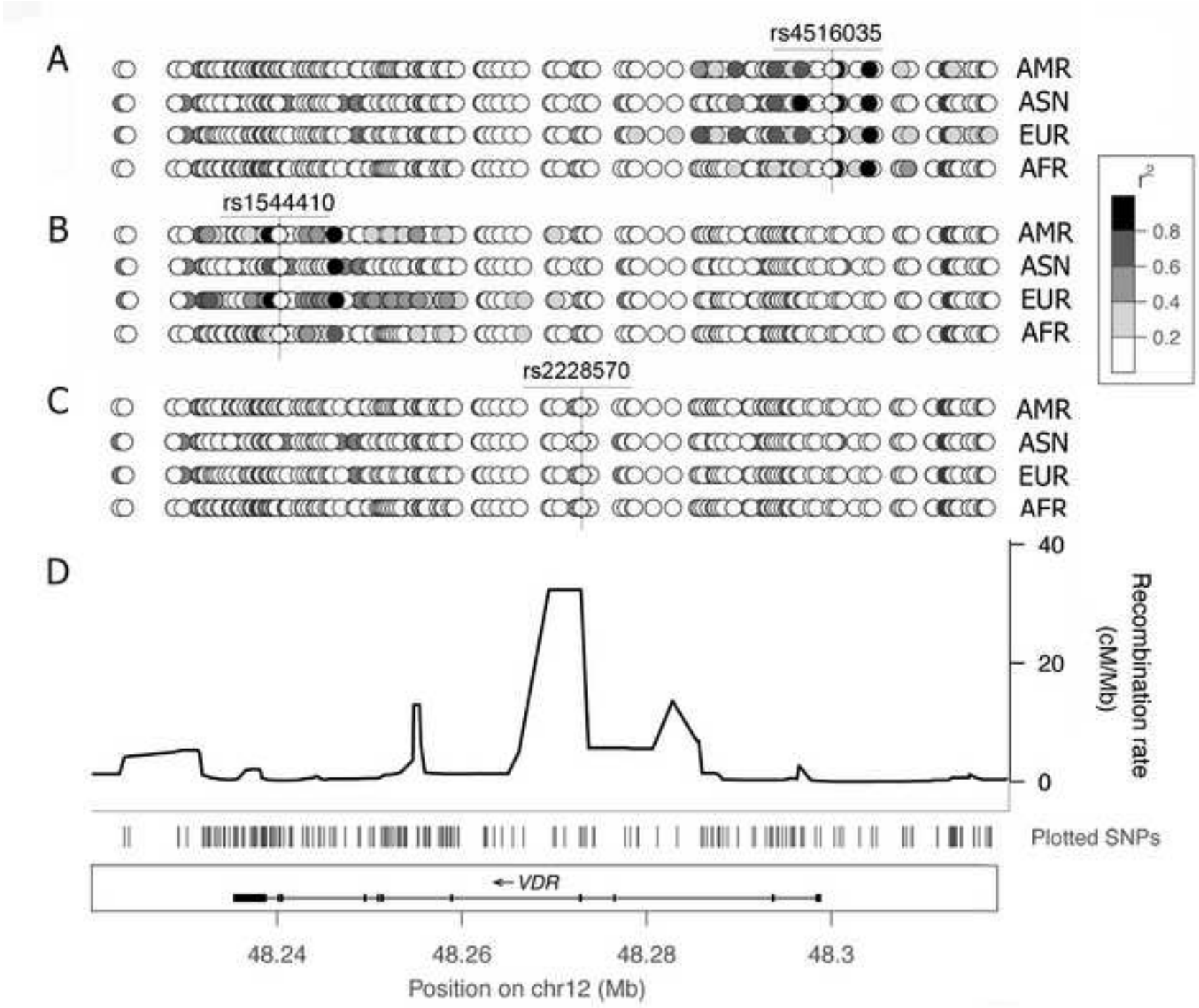

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