# Large-scale genome-wide association study of 398,238 women unveils seven novel loci associated with high-grade serous epithelial ovarian cancer risk

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# Large-scale genome-wide association study of 398,238 women unveils seven novel loci associated with high-grade serous epithelial ovarian cancer risk

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## ABSTRACT

*Background*: Nineteen genomic regions have been associated with high-grade serous ovarian cancer (HGSOC). We used data from the Ovarian Cancer Association Consortium (OCAC), Consortium of Investigators of Modifiers of *BRCA1*/*BRCA2* (CIMBA), UK Biobank (UKBB), and FinnGen to identify novel HGSOC susceptibility loci and develop polygenic scores (PGS).

*Methods*: We analyzed >22 million variants for 398,238 women. Associations were assessed separately by consortium and meta-analysed. OCAC and CIMBA data were used to develop PGS which were trained on FinnGen data and validated in UKBB and BioBank Japan.

*Results*: Eight novel variants were associated with HGSOC risk. An interesting discovery biologically was finding that *TP53* 3'-UTR SNP rs78378222 was associated with HGSOC (per T allele relative risk (RR)=1.44, 95%CI:1.28-1.62, $P=1.76\times10^{-9}$). The optimal PGS included 64,518 variants and was associated with an odds ratio of 1.46 (95%CI:1.37-1.54) per standard deviation in the UKBB validation (AUROC curve=0.61, 95%CI:0.59-0.62).

*Conclusions*: This study represents the largest GWAS for HGSOC to date. The results highlight that improvements in imputation reference panels and increased sample sizes can identify HGSOC associated variants that previously went

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undetected, resulting in improved PGS. The use of updated PGS in cancer risk prediction algorithms will then improve personalized risk prediction for HGSOC.

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## INTRODUCTION

Globally, epithelial ovarian cancer (EOC) is the seventh most common cancer diagnosed in women, with approximately 314,000 new cases diagnosed each year[1]. It is the most lethal gynecological cancer, responsible for approximately 207,000 deaths annually[1]. EOC is a collection of five major histotypes, namely high-grade serous (HGSOC), endometrioid, clear cell, low-grade serous (LGS) and mucinous, which are thought to have distinct etiology[2]. HGSOC is the most prevalent accounting for 60-70% of EOC diagnoses[2,3], and accounting for most EOCs diagnosed in *BRCA1* and *BRCA2* pathogenic variant (PV) carriers[4-11]. Furthermore, HGSOC accounts for the majority of EOC mortality[12,13].

To date, 40 genomic regions associated with EOC have been identified through genome-wide association studies (GWAS)[14-27][OCAC fine-mapping article, accepted AJHG]. For 19 of these regions, HGSOC is the most strongly associated histotype[14-22,26,27][OCAC fine-mapping article, accepted AJHG]. These studies have relied on imputation efforts that used the 1000 Genomes Project[28] and Haplotype Reference Consortium[29] reference panels, yielding up to approximately 11 million well-imputed genetic variants. The Trans-Omics for Precision Medicine (TOPMed) reference panel[30] and imputation server[31] have recently become publicly available. The TOPMed panel consists of approximately 308 million variants, yielding greater genomic coverage than previously available reference panels, with the added benefit of containing many more low-frequency and rare variants. This prompted us to re-impute genetic variant data from the population-based Ovarian Cancer Association Consortium (OCAC)[32], and *BRCA1*/*2* carriers from the Consortium of Investigators of

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Modifiers of *BRCA1* and *BRCA2* (CIMBA)[33,34] to assess whether the larger coverage of the genome from the TOPMed reference panel leads to detection of novel loci associated with HGSOC risk. We additionally made use of the UK Biobank (UKBB)[35,36] to boost the sample size and power to detect associations. We combined these data with summary statistics from FinnGen[37,38] and BioBank Japan[39,40] to develop and validate polygenic models (PGM) and scores (PGS) for non-mucinous OC.

## METHODS

*Study samples*

OCAC participants were enrolled in 65 studies from 16 countries and a large European multinational nested case-control study (Supplementary Table 1). OCAC individual participant data were used for GWAS discovery analyses and developing polygenic models (PGMs).

CIMBA study participants were enrolled in 64 studies from 28 countries (Supplementary Table 2). Eligibility was restricted to women aged at least 18 years at the time of recruitment who carried a PV in either *BRCA1* or *BRCA2*. Data collected included year of birth, PV description, age at recruitment, age at last follow-up, and age at breast and ovarian cancer (invasive, fallopian tube and peritoneal) diagnoses, and age or date of prophylactic surgeries (bilateral mastectomy and bilateral oophorectomy). Most participants were recruited through cancer genetics

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clinics and enrolled in regional/national research studies. CIMBA individual participant data were used in the GWAS discovery and in PGM development.

The UK Biobank (UKBB) is a large-scale biomedical research resource, with detailed genetic and health data on half a million UK participants[35,36]. For the purposes of these analyses, data from 245,377 female participants of European ancestry were used. UKBB individual participant data were used in the GWAS discovery analyses and to independently validate PGS.

FinnGen is a large collection of newly recruited and legacy samples from Finnish biobanks, research institutes, universities, university hospitals, international pharmaceutical partners, the Finnish Blood Service, the Finnish Biobank Cooperative, and the Finnish Institute for Health and Welfare, utilizing Finnish longitudinal health register data collected on every resident of Finland since 1969[37,38]. FinnGen summary statistics based on 150,658 women (149,394 controls, 1,264 EOC cases of any histotype) were used to train PGM hyperparameters.

BioBank Japan (BBJ) is a large biobank resource containing clinical and genetic data on over 300,000 participants[39,40]. BBJ summary statistics based on 61,457 women (60,614 controls, 843 EOC cases) were used for assessing PGS associations for women of East Asian ancestry.

*Genotyping and re-imputation using the TOPMed reference panel*

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Genotyping for OCAC and CIMBA was performed on one of two custom single nucleotide polymorphism (SNP) arrays (iCOGS and OncoArray), described in the Supplementary Methods. OCAC had additional samples genotyped on GWAS arrays[14-16]. These data were imputed to the TOPMed reference panel[30] after standard quality control (Supplementary Methods). Details of the UKBB genotyping and imputation to a combined UK10K[41,42] and HRC[29] reference panel have been described elsewhere[35,36]. The OCAC, CIMBA and UKBB analyses were based on 142 million, 104 million and 60 million well-imputed (imputation $r^2$>0.30) variants, respectively (Table 1). Downstream meta-analyses were restricted to variants that had minor allele counts (MACs) of MAC>5 and did not have heterogeneous effects ($P_{het}$>1x10$^{-8}$) in the meta-analysis of OCAC studies.

Analyses including FinnGen and BBJ data made use of summary statistic data only. Details of FinnGen and BBJ genotyping and imputation have been described elsewhere[37-40].

*Statistical analyses of OCAC and UKBB data*

We examined the associations between genotypes and HGSOC risk in the OCAC data using logistic regression. Analyses were conducted separately for OncoArray, iCOGS, and five GWAS datasets and were combined by fixed-effects inverse-variance weighted meta-analysis (Figure 1). We included project-specific principal components (PCs) as covariates in the model with the number of PCs based on the inflection point observed in a scree plot. All women were of European ancestry, determined using genetic data (Supplementary Methods)[22,43].

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The UKBB analysis was restricted to women with European ancestry, selected based on their PCs. EOC histotypes were classified using diagnostic codes provided by UKBB, with “serous”, “undifferentiated”, or “other” classified as HGSOC, a methodology similar to that used in OCAC[22]. Association analyses between genotypes and HGSOC risk were assessed by logistic regression (Figure 1). We adjusted for the top four PCs and age at recruitment.

*Statistical analyses of BRCA1 and BRCA2 pathogenic variant carriers*

Analyses of CIMBA data were limited to carriers of European ancestry, determined by genetic data and multidimensional scaling (Supplementary Methods)[22,43]. Association analyses were performed separately by genotyping array (iCOGS or OncoArray), and separately for *BRCA1* and *BRCA2* PV carriers (Figure 1). iCOGS and OncoArray associations were combined by fixed-effects inverse-variance weighted meta-analysis to estimate *BRCA1* and *BRCA2* PV carrier specific associations. The association analysis was carried out within a survival analysis framework, by modelling the retrospective likelihood of observing the genotypes conditional on the disease phenotypes to adjust for the non-random ascertainment with respect to disease phenotypes[44,45]. The censoring process followed carriers from birth until the first occurrence of: EOC (including fallopian tube and peritoneal cancers) diagnosis, risk-reducing salpingo-oophorectomy, or study entry. Breast cancer diagnoses were not considered to be a censoring event and EOC was the endpoint of interest. Associations were then assessed using the score test statistic based on the retrospective likelihood[44,45] assuming *BRCA1* and *BRCA2* PV carrier

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specific and age-cohort specific EOC incidences[46]. Analyses were stratified by country and Ashkenazi Jewish ancestry, and to account for relatedness between individuals we calculated kinship adjusted variances[47]. Only variants that were available through OncoArray genotyping and imputation were considered, as the majority of samples were available from this genotyping platform (Table 1). As HGSOC is the predominant histotype for both *BRCA1* and *BRCA2* PV carriers, the associations were combined by fixed-effects and inverse variance weighted meta-analysis using the METAL software[48].

*Meta-analyses*

We pooled the combined OCAC and UKBB summary association data (per-allele odds ratios, ORs) with the combined *BRCA1* and *BRCA2* PV carrier summary association data (per-allele hazard ratios, HRs) by fixed-effects inverse-variance weighted meta-analysis using METAL[48] to give per-allele relative risks (RRs, a combination of population-based ORs and *BRCA1*/*2* carrier HRs) (Figure 1).

*Eliminating likely statistical artifacts*

The associations of all variants with genome-wide significant associations and falling outside known regions were re-evaluated to eliminate likely spurious associations potentially due to unstable effect estimates from strata with small numbers. For this purpose, the associations were re-analysed, pooling individual level data from OCAC and UKBB (Supplementary Methods), whilst the associations for *BRCA1*/*2* PV carriers were reassessed assuming all study participants came from a single stratum.

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We also re-evaluated potentially novel associations with variants in regions proximal to known regions by performing approximate conditional analysis[49]. This approach utilized summary statistics from the combined OCAC, UKBB and *BRCA1/2* PV carrier meta-analysis and the linkage disequilibrium (LD) structure from 111,304 women genotyped on the OncoArray from OCAC and CIMBA.

For variants passing these checks, we calculated Bayes false discovery probabilities (BFDPs), assuming prior probabilities of 1:1,000 and 1:10,000 variants being truly associated[50].

*Defining credible causal variants*

The sentinel variant (variant with the smallest P-value) at each novel region may not be causal. Therefore, we identified lists of credible causal variants (CCVs) that are likely to contain the genetic variant responsible for altering HGSOC risk defined as the set of variants within ±500kb of the sentinel variant whose likelihood was within a 100-fold range of the sentinel variant's likelihood[51].

*Development of polygenic risk models*

We developed several PGMs (sets of variants and their weights) for non-mucinous OC using the Select and Shrink with Summary Statistics (S4) method[52,53], using P-value to LD $r^2$ ratios 0.02 and 0.15 to select variants, and each model taking different combinations of model hyperparameters (Figure 2, Supplementary Methods).

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Polygenic scores (PGS) are PGMs applied to observed or imputed genotypes. Previous analyses of PGMs specific to HGS, LGS, and mucinous histotypes showed that all histotypes, except mucinous, were associated with either the HGSOC PGS or LGSOC PGS. Thus, the non-mucinous histotypes were combined here[53]. The PGM was developed on summary statistics using associations obtained from a meta-analysis of the OCAC and CIMBA data. For this purpose, to maximize sample size and genetic diversity, the OCAC summary statistics were based on a meta-analysis of associations from East Asian (3,871 controls, 2,736 cases), African (1,099 controls, 556 cases), and European (133,369 controls, 25,707 cases) populations. The LD structure was weighted to reflect the average effects from each ancestry. Model hyperparameters (shrinkage parameters controlling small and large variant effect sizes, and an overall shrinkage parameter) were trained using summary association statistics based on 150,658 women (149,394 controls, 1,264 EOC cases) from FinnGen (release 8)[37,38]. EOC histotype data was not available for FinnGen, hence we used the associations with overall EOC for the PGM training. Finally, we used the resultant PGM to calculate PGS in the UKBB[35,36] data, to test its association with HGSOC and calculated its discriminatory ability for HGSOC by estimating the area under the ROC (AUROC) curve.

We assessed the performance of the PGS for women of East Asian ancestry using association summary statistics from BBJ. The reference panel consisted of individuals of East Asian ancestry from the 1000 Genomes Project[28]. This method has been described in detail elsewhere[53].

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We also created candidate PGMs consisting of genotyped variants that could be more easily applied in clinical settings (Supplementary Methods).

*Absolute risks of EOC by PGS percentile*

We calculated predicted lifetime risks (to age 80 years) of developing EOC for the general population, *BRCA1* and *BRCA2* PV carriers at the 1$^{st}$, 5$^{th}$, 20$^{th}$, 50$^{th}$ (median), 80$^{th}$, 95$^{th}$ and 99$^{th}$ percentiles of the various PGS distributions, following previously published methodology[54]. To ensure consistency with known EOC risks for the general population, *BRCA1* and *BRCA2* PV carriers, average age-specific EOC incidence rates were constrained over PGS percentiles to agree with external EOC incidence rates for the general population[55] and *BRCA1*/*2* carriers[56].

We examined the number of *BRCA2* PV carriers genotyped on the OncoArray that would transition between risk groups (low (<10%) or high (≥10%) lifetime risk) of developing EOC, based on their observed PGS percentile. These risk reclassification analyses were limited to *BRCA2* carriers as their lifetime risks transition over the 10% lifetime risk threshold, whereas a *BRCA1* carrier is already at substantially increased lifetime risk.

*Ethics statement*

All study participants provided written informed consent and participated in research or clinical studies at the host institute under ethically approved protocols. The studies

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and their approving institutes are listed in the Supplementary Material (Ethics Statement).

## RESULTS

The genome-wide association analyses for HGSOC were based on up to 398,238 women from OCAC (N=120,248, 30.2%), UKBB (N=245,377, 61.6%) and CIMBA (N=32,613, 8.2%) (Table 1, Supplementary Tables 1-2). A total of 19,883 (5.0%) women were classified as being diagnosed with HGSOC. The mean (standard deviation, SD) age at diagnosis for women in OCAC and UKBB were 60.2 (10.9) years and 63.5 (10.0) years, respectively. The mean (SD) censoring ages for BRCA1 and BRCA2 PV carriers were 43.7 (SD=12.0) years and 46.2 (SD=12.9) years, respectively.

*Reexamining previously identified associations with EOC*

We looked up the associations for the lead variants previously identified as being associated with EOC in our new results (Supplementary Table 3, Supplementary Figure 1). Most lead variants previously reported to be associated specifically with HGSOC risk replicated in the present meta-analysis of OCAC, UKBB and *BRCA1/2* carriers at the significance threshold $P<5x10^{-8}$. Exceptions were chr2:111138666 (rs17041869)[26], chr2:113216387 (rs895412), chr11: 62126500 (rs7937840)[26] and chr22:28538325 (rs6005807)[22] (Supplementary Table 3). However, the chr2:110525257..111658369 and chr2:112716387..113716387 regions contained other variants that were associated at the genome-wide significance level in the

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present analysis, whilst the chr11:61626500..62626500 and chr22:28038325..29038325 regions did not contain any variants associated with HGSOC at the genome-wide significance level. It should be noted, however, that the chr2:111138666 (rs17041869) and chr11:62126500 (rs7937840) variants were identified through a cross-cancer (breast, ovarian, and prostate) GWAS[26] and were not specifically identified as HGSOC associated variants.

*Novel loci associated with HGSOC*

Associations with a total of 5,786 variants from 44 loci were significant at $P<5x10^{-8}$. We excluded 5,778 variants at 37 loci from further consideration, as they were either near known associated regions (Supplementary Table 3), were not conditionally independent of the sentinel variant in a nearby known region, or were likely statistical artifacts arising from strata specific effects.

There were eight variants associated ($P<5x10^{-8}$) with HGSOC, at 5q11, 6p12, 8p21, 9p24-23, 16q22, 17p13 and 19q12 (Table 2, Figure 3, Supplementary Tables 4-5).

The associations at 5q11 (rs528577783-G; RR=5.15, 95%CI:2.96-8.96), 6p12 (rs1013698558-T; RR=2.35, 95%CI:1.76-3.14), 8p21 (rs191420549-A; RR=25.60, 95%CI:9.32-70.31), and 9p24-p23 (rs768719522-T; RR=10.04, 95%CI:4.38-22.99) were all single rare variants (MAF≤0.15%) associated with large HGSOC effects. The single SNPs associated with HGSOC at 16q22 (rs6979-G; RR=1.07, 95%CI:1.04-1.09) and 19q12 (rs62107113-A; RR=1.08, 95%CI:1.05-1.11) were

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common and conferred modest effects on HGSOC risk. There were two moderately correlated (TOPMed European[57] $r^2$=0.46, D'=0.89) low-frequency (MAF: 1.2% and 2.1%) variants at the 17p13 locus. The *TNFS13*/*TNFSF12*-*TNFSF13* intronic variant rs143094271-G was associated with a per-allele RR=1.28 (95%CI:1.18-1.39, P=7.61x10$^{-9}$); and rs78378222-T, a *TP53* 3'-UTR variant, with a per-allele RR=1.44 (95%CI:1.28-1.62, P=1.76x10$^{-9}$). The association effect size estimates at 16q22, 19q12 and 17p13 were consistent between OCAC/UKBB and *BRCA1/2* PV carriers.

BFDPs indicated that the majority of these associations are likely to be true, although two rare variants, rs191420549 and rs768719522, had noticeably larger BFDPs (Table 2). Under a model assuming 1:1,000 truly associated variants, the BFDPs were 3.2% for rs191420549 and 11% for rs768719522. The other variants all had BFDP≤0.42%.

*Credible causal variants*

We defined 52 CCVs across the seven novel regions (Supplementary Table 6, Supplementary Figure 2). Four regions (5q11, 6p12, 8p21, 9p24-23) had only the sentinel variant as a CCV, whilst the 16q22 (N=5), 17p13 (N=3) and 19q12 (N=40) loci had several CCVs.

*Association of the PGS with HGSOC*

Of the 1,102 PGMs developed using OCAC and CIMBA data, the PGM that performed best in the FinnGen data comprised of 64,518 variants (Supplementary

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Table 7), and is denoted $PGS_{64518}$. In the UKBB validation, the OR per SD of $PGS_{64518}$ was estimated to be 1.46 (95%CI:1.37-1.54), with discriminatory ability of AUROC=0.607 (95%CI:0.590-0.623) (Table 3). The association of $PGS_{64518}$ was strongly attenuated in the BBJ validation (East Asian ancestry women), where the OR per SD was 1.12 (95%CI:1.05-1.20).

When restricting the PGS to include only genotyped variants from the 64,518 genotyped and imputed variants, which may make their implementation easier, PGS with 5,957 (all genotyped variants from the 64,518) and 400 variants had similar performance characteristics. Relative to the $PGS_{64518}$, a PGS considering the 400 most strongly associated genotyped variants, denoted $PGS_{400}$, resulted in a small decrease in the AUROC to 0.603, and a marginally attenuated OR per SD (OR=1.43, 95%CI:1.35-1.52) in the UKBB.

*Predicted absolute risks for the general population and BRCA1/2 pathogenic variant carriers*

The absolute lifetime risks (at age 80 years) for *BRCA1* PV carriers were predicted to be 25.9%, 42.8% and 64.7% at the $5^{th}$, $50^{th}$ and $95^{th}$ percentiles of the $PGS_{64518}$ distribution, respectively (Table 3, Figure 4). The corresponding risks for $PGS_{64518}$ for *BRCA2* PV carriers at the same PGS percentiles were predicted to be 9.3%, 16.7% and 28.9%, respectively (Table 3, Figure 4). The range of predicted percentile specific risks for the previously published 36 variant PGS[52] was narrower, with risks for the same percentiles of 27.7%, 43.0% and 62.3% for *BRCA1* PV carriers, respectively, and 10.1%, 16.9% and 27.5% for *BRCA2* PV carriers, respectively. The

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$PGS_{400}$ yielded absolute risks which were approximately at the midpoint of the 36 and 64,518 variant PGS absolute risks (*BRCA1* PV carriers: 26.7%, 42.9% and 63.6% at the 5$^{th}$, 50$^{th}$ and 95$^{th}$ percentiles, respectively; *BRCA2* PV carriers: 9.7%, 16.8% and 28.3% at the 5$^{th}$, 50$^{th}$ and 95$^{th}$ percentiles, respectively).

There was a net reclassification of *BRCA2* PV carriers at the 10% risk threshold when considering $PGS_{400}$ and $PGS_{64518}$ of 4.8% and 5.4%, respectively, compared to the 36 variant PGS (Supplementary Table 8).

## DISCUSSION

We conducted the largest GWAS to date for HGSOC, both in terms of the sample size and the number of genetic variants assessed. To do this, we made use of large international consortia (OCAC and CIMBA), and harnessed data from the UKBB to bolster the sample size. We also utilized recent advances in imputation reference panels, namely the TOPMed panel, which allowed us to investigate the largest number of genetic variants to date. We identified eight independent variants at seven loci to be genome-wide statistically significant for association with HGSOC risk, including four rare variants (MAF<1%) and two low-frequency polymorphisms (MAF 1-5%), demonstrating that GWAS with greater coverage imputation can identify previously undiscovered rare variant associations. Based on these associations, we defined 52 CCVs that have the strongest statistical evidence for being the likely causal variant for each locus. We also developed a polygenic model that exhibited improved discriminatory ability compared to previously published models.

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The four rare variants were associated with large effect sizes, with RR estimates ranging from 2.35 to 25.6. The large effect sizes seem implausible and may reflect a winner's curse effect with true effect sizes actually being lower than the estimates that we obtained[58]. Moreover, they may represent false positive associations, hence we estimated BFDPs[50] for the eight novel variants to determine the likelihood of this. Six variants had low BFDPs, indicating they are likely true associations. However, 8p21 rs191420549 and 9p24-p23 rs768719522 had noticeably larger BFDPs and are more likely to represent false positive associations.

Variant rs78378222, in the *TP53* 3'-UTR, with the major T-allele (AF 98.8%) is associated with an increased risk of HGSOC. The same allele has been associated with an increased risk of triple-negative breast cancer[59] with a per-allele relative risk of 1.45, similar to its association with HGSOC (RR=1.44). In contrast, the minor (G) allele of rs78378222 is associated with increased risks of skin[60-64], brain[64-68] and prostate cancers[60,69]. One study also found rs78378222 to be associated with standing height, lean body mass and basal metabolic rate[64]. The minor allele has been shown to impede *TP53* 3'-end processing, resulting in downregulated p53 mRNA levels and protein levels, and decreased apoptosis[70]. Furthermore, germline and somatic variations in *TP53* are well established factors in cancer development and progression through its role as a tumor suppressor[71-74] and the *TP53* 3'-UTR germline variant has been shown to interact with tumor *TP53* mutation status[75]. A previous study by the OCAC found five SNPs in the *TP53* region, within ±21kb of

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rs78378222, to be associated with invasive EOC[76]. However, none of these SNPs are in LD with rs78378222.

rs528577783 is a rare intergenic variant between the *FST* and *NDUFS4* genes. *FST* encodes follistatin, a single-chain gonadal protein that specifically inhibits follicle-stimulating hormone release and is moderately expressed in human reproductive tissues (Supplementary Table 5)[77]. A linkage study identified *FST* as a candidate gene for polycystic ovary syndrome (PCOS)[78]. PCOS may be associated with an increased risk of borderline or postmenopausal ovarian cancer[79], although a recent Mendelian Randomization study found that genetically predicted PCOS was associated with decreased risk of ovarian cancer[80]. A GWAS of African ancestry women found rs37792 near *FST* to be genome-wide statistically significantly associated with HGSOC in African ancestry women[81].

The 6p12 variant rs1013698558, located ~9.7kb from the *GCLC* gene, was moderately associated with HGSOC. A study found a synthetic lethality relationship between *GCLC* and *ARID1A*-deficient OC cells[82], whilst another reports that *GCLC* inhibition causes apoptosis in *ARID1A*-deficient cancer cells[83]. *ARID1A* has been implicated as a tumor suppressor gene[84]. It may be that the association we find for rs1013698558 with HGSOC is a result of the interplay between *GCLC* and *ARID1A*. The 8p21 variant rs191420549 is 156kb from *CDCA2* and was associated with HGSOC with the largest RR that we report. *CDCA2* is involved in the cell division cycle and response to DNA damage. One study found *CDCA2* expression is upregulated in ovarian tumor tissue compared with normal tissue[85]. This study also

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found that *CDCA2* and its 100 most co-expressed genes were primarily involved in cell cycle, oocyte meiosis, progesterone-mediated oocyte maturation, p53 signaling and pyruvate metabolism pathways. We found that the *PTPRD* intronic variant rs768719522 at the 9p24-p23 locus had a large association RR with HGSOC. *PTPRD* has been implicated as a tumor suppressor gene[86]. This gene encodes a protein from the protein tyrosine phosphatase (PTP) family – PTPs are signaling molecules regulating processes such as cell growth, cell differentiation, the mitotic cycle and oncogenic transformation[87]. The common *ACD* missense variant rs6979 at 16q22 conferred a small per-allele RR to HGSOC risk. This gene encodes telomere protein TPP1, which is involved in maintenance of telomere length and protecting telomere ends. In addition to the 17p13 *TP53* 3'-UTR variant association, there was another independent variant associated with HGSOC risk at this locus. The rs143094271 variant is intronic in *TNFSF13*/*TNFSF12-TNFSF13*. These genes are members of the tumor necrosis factor family, which are involved in various cellular processes, including survival, proliferation, differentiation, and apoptosis. rs143094271-G has been associated with a decreased risk of having uterine fibroids (OR=0.70)[88]. Women with uterine fibroids have been found to be at increased risk of developing OC[89]. However, despite rs143094271-G being associated with women being less likely to have uterine fibroids, we found that rs143094271-G yielded an increased risk of developing HGSOC. The 19q12 common variant rs62107113 is located ~15kb from the *CCNE1* gene and was associated with a modest increased risk of developing HGSOC. *CCNE1* encodes cyclin E1, which regulate cyclin-dependent kinases. Overexpression of *CCNE1* has been observed in genomically unstable tumors, notably HGSOC[90-94] and triple-negative breast cancer[91,95-97]. Moreover, it has been shown that replication stress in cells overexpressing *CCNE1*

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is likely a consequence of replication initiation, ultimately resulting in DNA damage and genomic instability[98]. There is evidence indicating *CCNE1* amplification is mutually exclusive to BRCA inactivation[92]. *CCNE1* is an exciting novel therapeutic target, Gallo *et al* developed an orally bioavailable PKMYT1 inhibitor that activated CDK1 in *CCNE1* overexpressed cells, promoting early mitosis in cells undergoing DNA synthesis[99].

In addition to the 40 loci previously found to be associated with EOC[14-27], we have identified genetic variants at a further seven loci associated with HGSOC, taking the number of loci associated with EOC to 47, 26 specifically with HGSOC. The previous known loci (52 variants at 40 loci) explained 8.5% of the polygenic variance of OC, assuming a total polygenic variance of 2.004 from Lee *et al*[100]. The six variants that we report to be associated with HGSOC with low BFDP explain an additional 2.8%, making the total variance explained by GWAS identified variants to be 11.3%.

For previously identified variants, the estimated associations from general population data (combined OCAC and UKBB) ORs were broadly consistent with the estimated HRs for *BRCA1* and *BRCA2* PV carriers (Supplementary Table 3). Furthermore, testing for heterogeneity of effects resulted in a small number of variants exhibiting differences in effect sizes between population-based ORs and carrier HRs. None of the eight novel associations exhibited any heterogeneous effects between population-based ORs and *BRCA1*/*2* PV carrier HRs (Supplementary Table 4).

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Using the S4 method, we developed a 64,518 variant PGM, whose PGS was associated with a per SD OR of 1.46 (95%CI:1.37-1.54) and had discriminatory ability of AUROC=0.607 (95%CI:0.590-0.623). There was a small improvement over the previous best performing PGM developed by Dareng *et al*[52] (18,007 variants; OR per unit SD = 1.42; AUROC=0.596) developed using similar methodology. The $PGS_{400}$ could be more practical to implement in a clinical setting, since it contains fewer variants, all of which are known to successfully genotype from the OncoArray experiment, compared to the best performing $PGS_{64518}$ which requires imputation. We found that the $PGS_{400}$ had similar performance to the optimal $PGS_{64518}$. This also suggests that most of the predictive ability of the PGS may derive from genotyped SNPs with the largest variance contributions.

When each of the PGS were tested in individuals of East Asian ancestry from BBJ, the PGS associations were strongly attenuated, each to a similar degree. For women of East Asian ancestry, the PGS consisting of genotyped variants with 5,957 and 3,448 variants performed marginally better, with a slightly larger OR per PGS SD. The observed attenuations for East Asian women compared with European women are likely a result of the PGM derivation data being strongly weighted towards Europeans, as the majority of OCAC and CIMBA samples came from this ancestry group.

We calculated lifetime risks of developing EOC by PGS percentiles for the optimal 64,518 variant PGS for *BRCA1*/*2* carriers. The risks ranged from 25.9% to 64.7% for *BRCA1* carriers, and 9.3% to 28.9% for *BRCA2* carriers, at the 5$^{th}$ and 95$^{th}$

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percentiles, respectively. The range of risks for the 36 variant PGS that is currently implemented in the CanRisk ovarian cancer risk prediction algorithm[52,100] were narrower than those for the $PGS_{64518}$. The lifetime risks based on the $PGS_{400}$ that used a subset of 400 reliably genotyped variants included in the $PGS_{64518}$ at these percentiles sat approximately at the midpoints of the risks from the 64,518 and 36 variant PGS. We compared what risk reclassification (lower risk, <10%, or higher risk, ≥10% lifetime risk) would occur when using the $PGS_{64518}$ or $PGS_{400}$ versus the 36 variant PGS for *BRCA2* PV carriers. We were unable to assess reclassification for *BRCA1* carriers as the lifetime absolute risks at the lowest percentiles of the PGS distributions were always above 10%. We found that the $PGS_{64518}$ and $PGS_{400}$ led to net reclassification of risk groups of around 5% versus the 36 variant PGS. Most reclassification shifted women from lower risk (<10%) using the 36 variant PGS to higher risk (≥10%) using the alternative $PGS_{64518}$ or $PGS_{400}$. Taken together, these estimated lifetime risks and risk reclassifications will be useful in more accurately determining a carriers' risk and informing clinical management of risk.

Strengths of this study include using the TOPMed imputation reference panel, enabling us to assess a larger number of low-frequency and rare variants than previous studies. A further strength was its power to detect low-frequency and rare variant associations, as well as previously unidentified common variant associations. This was facilitated by additional genotyped samples included in both OCAC and CIMBA and using population-based data from UKBB, resulting in the largest sample size analysed for assessing genetic variant associations with HGSOC risk.

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Limitations include the fact that the GWAS discovery data available were primarily of European ancestry; the associations of these variants are likely to differ for women of non-European ancestries, as they are likely to have different frequencies and LD patterns. A limitation of the PGM was that the derivation data differed from the GWAS discovery data presented here. Ideally, all the discovery GWAS data would have been used for PGM development. However, it was essential to validate the PGM on independent data, hence the OCAC and CIMBA data were used for development, whilst the UKBB data were reserved for validation. Lastly, the PGM training data (FinnGen) did not have specific histotypes available, meaning we were only able to consider overall EOC in the PGM training. As we were investigating non-mucinous OC, we would ideally have had specific EOC histotypes available at each stage of the PGM development, training and validation. However, given that HGSOC is the most prevalent EOC histotype, it is unlikely to have a major impact on the PGM hyperparameter fine-tuning.

Future research may aim to fine-map the novel loci identified here, to refine the candidate causal variants associated with HGSOC risk; and in-silico analyses may identify candidate target genes or pathways for further experimental studies[101]. Additionally, future research could aim to identify novel variants associated with other OC histotypes and to discover novel associations for other ancestries.

We have shown that improvements in imputation reference panels and increased sample sizes can identify novel HGSOC associated variants that previously went undetected, either from absence from genotyping or imputation reference panels, or

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from lack of power to detect associations. Furthermore, these associations can be used to develop PGM that outperform previous best efforts that can be incorporated into cancer risk prediction algorithms to improve personalized risk prediction for HGSOC.

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# FIGURE LEGENDS

*Figure 1*: Schema describing the analytical process for the GWAS analyses from OCAC, UKBB and CIMBA, and subsequent meta-analyses.

*Figure 2*: Schema describing the development of polygenic models, determining the optimal model, and validating the resultant polygenic score in European ancestry women from UKBB and East Asian ancestry women from BBJ.

*Figure 3*: Manhattan plot showing the associations with HGSOC from the meta-analysis of OCAC, UKBB and CIMBA summary association data. The dashed line is the genome-wide statistical significance level ($P=5x10^{-8}$). The eight independent genome-wide statistically significant variants at seven novel loci are shown as red triangles.

*Figure 4*: Predicted cumulative risks of developing EOC based on the $PGS_{64518}$ at various percentiles of the PGS distribution for: (a) the general population (0.7% for 1$^{st}$ percentile to 3.9% for the 99$^{th}$ percentile), (b) *BRCA1* PV carriers (20.7% for 1$^{st}$ percentile to 74.1% for the 99$^{th}$ percentile), and (c) *BRCA2* PV carriers (7.3% for 1$^{st}$ percentile to 35.7% for the 99$^{th}$ percentile).

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# SUPPLEMENTARY TABLE LEGENDS

*Supplementary Table 1*: Numbers of controls and EOC cases by genotyping array and country from population-based studies. The "cases" column (column E) is a total of the histotypes in columns F-K. LMP = low malignant potential, HGSOC = high-grade serous ovarian cancer, ENOC = endometrioid ovarian cancer, CCOC = clear cell ovarian cancer, MOC = mucinous ovarian cancer.

*Supplementary Table 2*: Numbers of unaffected *BRCA1*/*2* carriers and carriers diagnosed with EOC, by CIMBA study.

*Supplementary Table 3*: Previously identified genomic regions associated with EOC. Lookups are presented for the variant's association with its most strongly associated EOC histotype from the OCAC. Lookups are also presented from the present HGSOC meta-analysis of OCAC, UKBB and *BRCA1*/*2* carriers, and its component parts (associations from OCAC and UKBB combined, associations from *BRCA1* carriers, and associations from *BRCA2* carriers).
Chr = chromosome. Positions are on build 38. SNP = rsID of the most strongly associated variant with "best histotype". Alleles = reference/effect alleles. EAF = effect allele frequency. RR = relative risk (per effect allele). CI = confidence interval. P = P-value for association with HGSOC. $P_{het}$ = P-value for heterogeneity between the general population OR (OCAC and UKBB meta-analysis, column U) and the PV carrier HRs (*BRCA1* PV carriers, column Z; *BRCA2* PV carriers, column AF).

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SNPs and positions (columns E-F) highlighted in yellow are most strongly associated with HGSOC in OCAC that did not replicate ($P<5x10^{-8}$) in the OCAC+UKBB+CIMBA meta-analysis (columns N and S).

Histotypes: NMOC = non-mucinous, HGSOC = high-grade serous, LGSOC = low-grade serous, MOC = mucinous, CCOC = clear cell, EnOC = endometrioid.

* Previously identified through meta-analysis of OCAC and CIMBA. ** Previously identified through multi-cancer meta-analysis. *** When combining result with most recent results from CIMBA (unpublished).

*Supplementary Table 4*: Novel associations by major analysis units (OCAC, UKBB, *BRCA1* carriers and *BRCA2* carriers).

Positions are on build 38. EAF = effect allele frequency. OR = odds ratio per effect allele. HR = hazard ratio per effect allele. CI = confidence interval. P = P-value for association. UKBB did not contribute associations for rs1013698558 (chr6:53554782:A:T). * HRs were estimated but had large estimated standard errors resulting in wide CIs – these associations were used in the meta-analysis between OCAC, UKBB and CIMBA, but contributed little as the inverse variance weights were extremely small.

*Supplementary Table 5*: Further details for eight novel variants associated with HGSOC risk.

Positions are on build 38. Gene descriptions are taken from dbSNP[87].

Phenoscanner[102-104] and PheWeb[105] are lookups of relevant associations for these

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variants/genes. GTEx[77] gene expression data is reported for human reproductive tissues with TPM (transcripts per million) > 5. eQTLGen[106,107] lookups for cis- and trans-eQTLs for variants and genes were performed.

*Supplementary Table 6*: List of credible causal variants (CCVs) at each novel region. Sentinel variants are highlighted in green. These data are presented graphically in Supplementary Figure 2.

*Supplementary Table 7*: List of variants contributing to the polygenic models (PGMs). Positions are on build 38. Weights are given for five PGMs and are per effect allele. Instances in which weights are not present (NA) means that that variant does not contribute to that PGM. The weights are taken from the OCAC, UKBB and CIMBA meta-analysis effect size estimates with the hyperparameters applied. Four of the eight variants found in the discovery GWAS were directly included in the 64,518 variant PGM (rs6979 chr16:67657765, rs143094271 chr17:7559785, rs78378222 chr17:7668434 and rs62107113 chr19:29797136, highlighted in green in the table).

*Supplementary Table 8*: Risk reclassification based on different polygenic scores for *BRCA2* carriers. Lifetime risks were categorized as lower risk (lifetime risk below 10%) or higher risk (10% or greater). The $PGM_{64518}$ and $PGM_{400}$ were compared with the 36 SNP PGS currently used in the CanRisk prediction algorithm.

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# SUPPLEMENTARY FIGURE LEGENDS

*Supplementary Figure 1*: Regional association plots for 40 genomic regions previously associated with any EOC histotype. Regions are described in Supplementary Table 3.

*Supplementary Figure 2*: Regional association plots for seven novel genomic regions associated with HGSOC. Credible causal variants (CCVs) are highlighted in blue. Lists of CCVs are presented in Supplementary Table 6.

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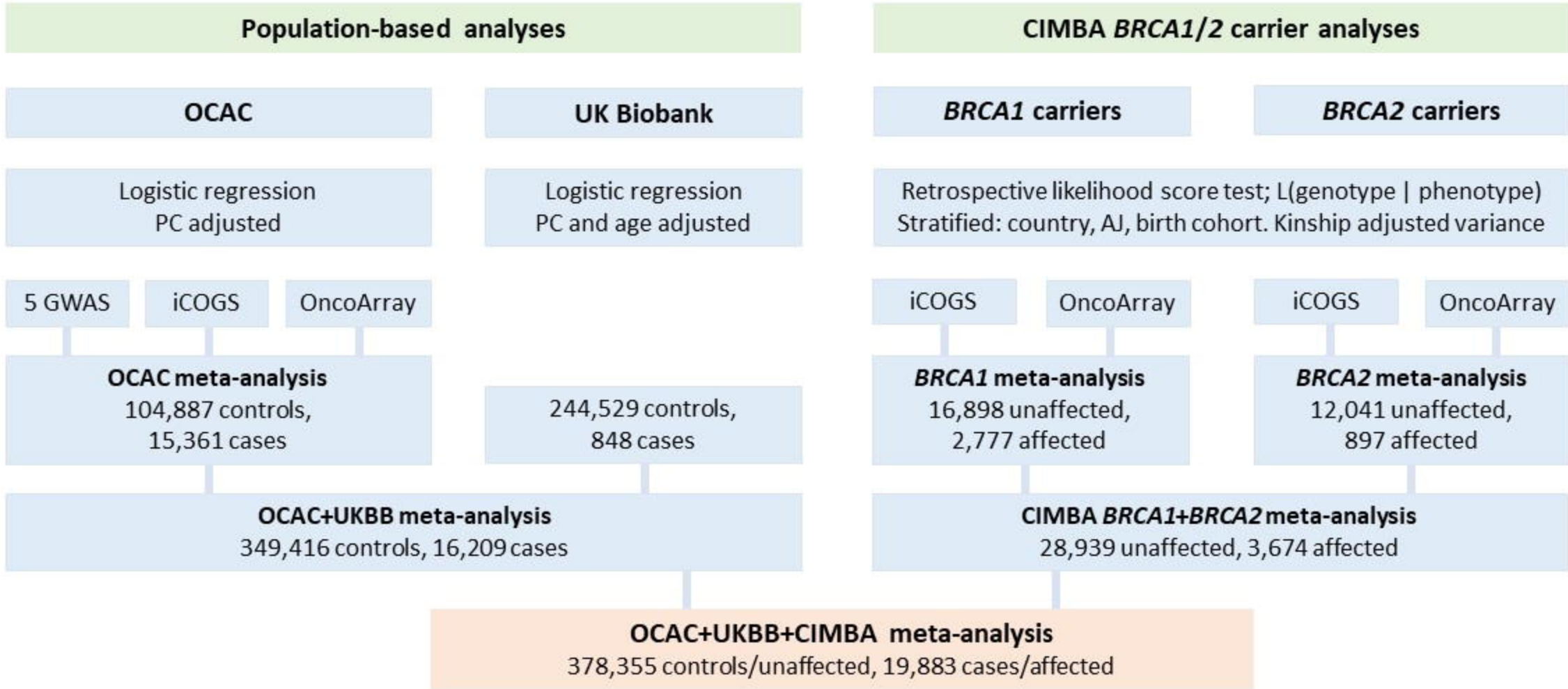
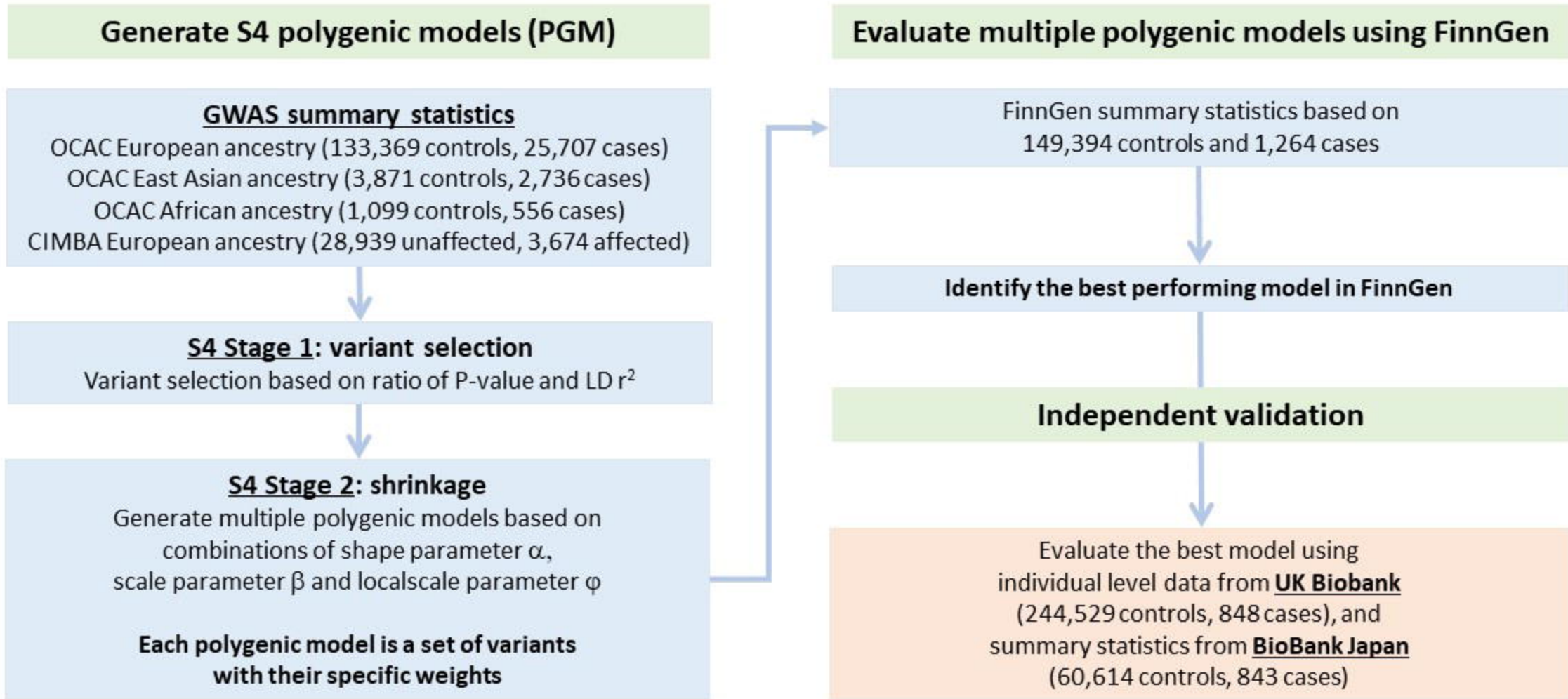
# Figure 1


Population-based analyses
CIMBA BRCA1/2 carrier analyses
OCAC
UK Biobank
BRCA1 carriers
BRCA2 carriers
Logistic regression
PC adjusted
Logistic regression
PC and age adjusted
Retrospective likelihood score test; L(genotype | phenotype)
Stratified: country, AJ, birth cohort. Kinship adjusted variance
5 GWAS
iCOGS
OncoArray
iCOGS
OncoArray
iCOGS
OncoArray
OCAC meta-analysis
104,887 controls,
15,361 cases
244,529 controls,
848 cases
BRCA1 meta-analysis
16,898 unaffected,
2,777 affected
BRCA2 meta-analysis
12,041 unaffected,
897 affected
OCAC+UKBB meta-analysis
349,416 controls, 16,209 cases
CIMBA BRCA1+BRCA2 meta-analysis
28,939 unaffected, 3,674 affected
OCAC+UKBB+CIMBA meta-analysis
378,355 controls/unaffected, 19,883 cases/affected

# Figure 2


Generate S4 polygenic models (PGM)
GWAS summary statistics
OCAC European ancestry (133,369 controls, 25,707 cases)
OCAC East Asian ancestry (3,871 controls, 2,736 cases)
OCAC African ancestry (1,099 controls, 556 cases)
CIMBA European ancestry (28,939 unaffected, 3,674 affected)
S4 Stage 1: variant selection
Variant selection based on ratio of P-value and LD r2
S4 Stage 2: shrinkage
Generate multiple polygenic models based on combinations of shape parameter α, scale parameter β and localscale parameter φ
Each polygenic model is a set of variants with their specific weights
Evaluate multiple polygenic models using FinnGen
FinnGen summary statistics based on 149,394 controls and 1,264 cases
Identify the best performing model in FinnGen
Independent validation
Evaluate the best model using individual level data from UK Biobank (244,529 controls, 848 cases), and summary statistics from BioBank Japan (60,614 controls, 843 cases)

# Figure 3

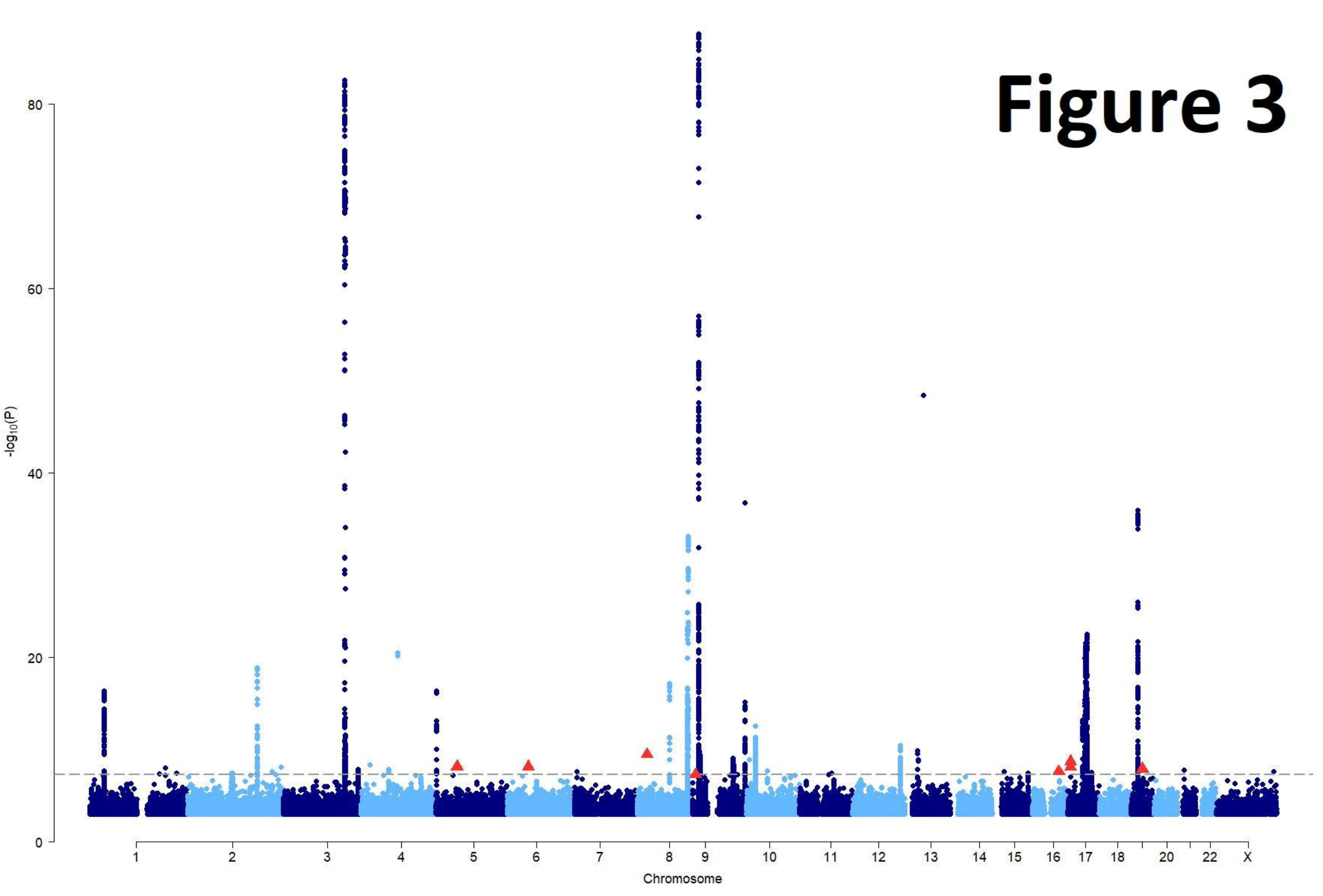
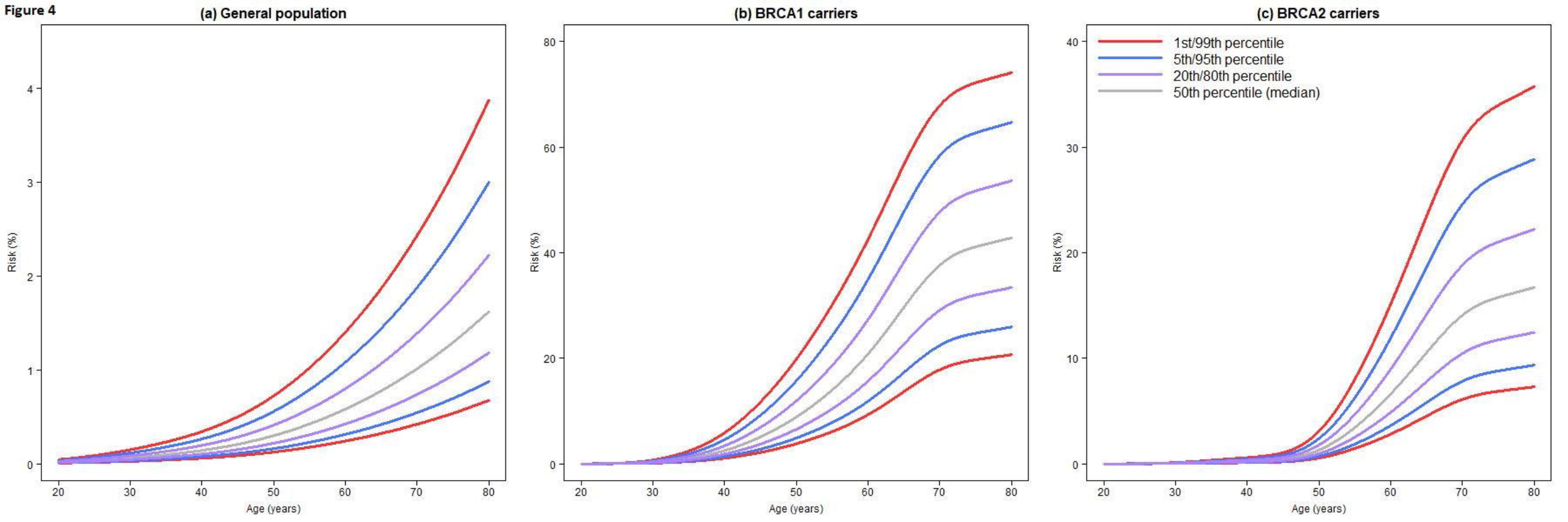
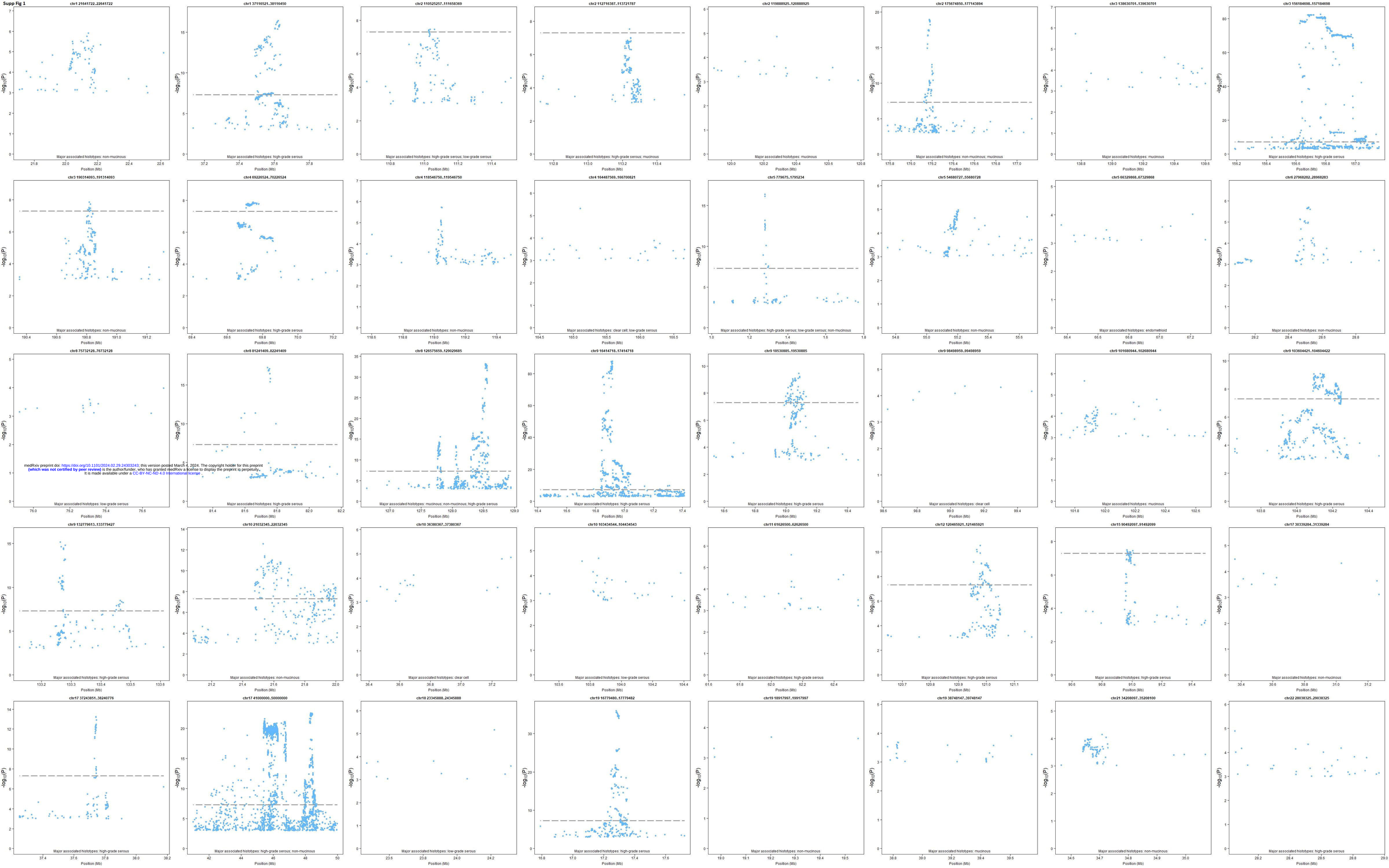

80
60
40
20
0
-log10(P)
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
20
22
X
Chromosome

Figure 4


(a) General population
(b) BRCA1 carriers
(c) BRCA2 carriers
1st/99th percentile
5th/95th percentile
20th/80th percentile
50th percentile (median)
Risk (%)
Age (years)

**Supp Fig 1**

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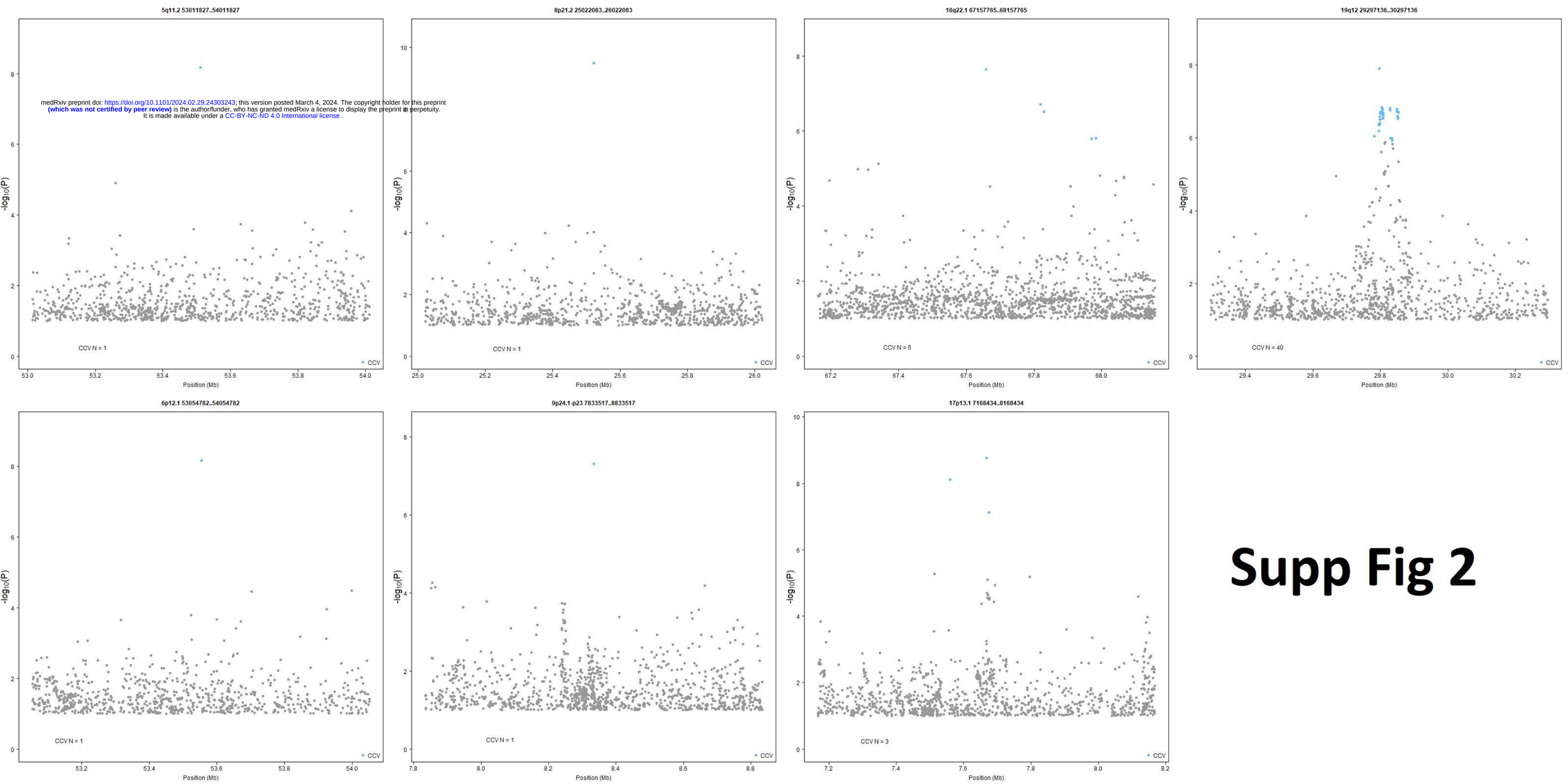


# Supp Fig 2