Supplemental Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Study Populations and Analyses

Study populations

The eMERGEseq cohort is comprised of 24,956 biobank or prospectively recruited individuals from ten clinical sites under the eMERGE network between 2016 and 2018.[1] All sites consented participants under Institutional Review Board (IRB)-approved protocols and the two sequencing centers had IRB-approved protocols that deferred consent to the sites (Partners Healthcare (2015P000929), Baylor College of Medicine (#H-40455)).[1] These ten sites are Cincinnati's Children's Hospital and Medical Center (CCHMC), Children's Hospital of Philadelphia (CHOP), Columbia University (CU), Geisinger (GE), Kaiser Permanente of Washington (KPWA, formerly Group Health Cooperative)/University of Washington (UW), Mayo Clinic (MC), Northwestern University (NU), Partners HealthCare (PHC), and Vanderbilt University Medical Center (VUMC). Specifically, CHOP and CCHMC sites recruited pediatric patients. Approximately 2,500-3,000 participants were recruited from each site. The following sites recruited participants without specific populations or phenotypes of interest: VUMC, PHC and CCMC. The following sites enriched participants of specific indications, which include patients with diagnoses and/or family history. CHOP: autistic behaviors; CU: renal disease, liver disease and cancer; GE: participants from MyCode community health initiative;[2] KPWA/UW: colorectal polyps/cancer; MC: hypercholesterolemia, colon polyps and dyslipidemia; NU: lipid disorders, atrial fibrillation, breast cancer, ovarian cancer screening, and dermatologic disorders. For cancer-related phenotypes, a total of 211 participants with the indication for breast cancer, 186 for ovarian cancer and 2,437 for colorectal polyps/cancer were included in this cohort. Other common indications included autistic behaviors (n=722), chronic kidney diseases (n=996), hyperlipidemia (n=1,415) and intellectual disability (n=1,468).

The second dataset was obtained from the hereditary cancer registry (HCR) at Vanderbilt University Medical Center (VUMC). This study was approved by the IRB at VUMC. This cohort included 3,794 individuals who received clinical genetic testing for hereditary cancer[3] between 2012 and 2020. Testing results were returned to clinicians and patients and documented in the EHRs and recoded in the registry. Detailed information on personal and family history of cancer were also documented in the registry. This cohort was enriched for individuals at a high risk of hereditary cancer syndromes, with 98% reporting a family history of cancers and 65% reporting a personal history of cancer. Specifically, approximately 50% of all patients reported a breast cancer diagnosis. This cohort also included pediatric cancer patients. The ages at the first cancer diagnoses ranged from 1 year old to 90 years old, with a mean age at diagnosis of 50.4 years old, as documented in the EHRs.

The UK Biobank (UKB) is a prospective population-based cohort study of 500,217 participants aged 40-69 years at recruitment with 54% being female and 94% being of European ancestry, who were recruited between 2006-2010 and are continuously followed.[4] The UK Biobank has been approved by the NHS and National Research Ethics Service North West (11/NW/0382; 16/NW/0274), the National Information Governance Board for Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland. In addition, an independent Ethics and Governance Council oversees its continuous adherence to the Ethics and Governance Framework. Additional details on this framework have been described elsewhere.[5] More details can be found the UK biobank website. The current study was conducted under the UK Biobank application 68025.

Assessment of missing data and loss to follow-up

For the eMERGE and HCR cohorts, all available ICD data in EHRs were used for the included population and no missing data were found for their baseline characteristics. For the UKB biobank, we found no missing data in the baseline characteristics, and those with poor genotyping quality were removed. The loss to follow-up in UKB (0.2%) was rare. No evidence of associations is found between carrier status in this study and the loss to follow-up. This non-differential loss to follow-up is likely to lead bias towards to the null if any.

Reporting race/ethnicity

To account for potential confounding by population stratifications, we adjusted for race in our analyses, in addition to other covariates. In the eMERGE cohort, we used the genetically defined ancestry according to the first 4 principal components. We've previously determined that the first 4 principal components (PCs) were sufficient for accounting for population stratifications in this cohort.[6] In the HCR cohort, we used the self-reported race documented in the EHRs. In the UKB cohort, we used the first 16 PCs. Additional information on how UKB collected race data have been described previously.[4]

Gene panel and sequencing in eMERGEseq, genetic testing in HCR and whole exome sequencing in UKB

Details on the design of the sequencing panel of the eMERGEseq project have been previously described[6]. Briefly, this panel comprises a total of 109 genes and 1550 single nucleotide variants (SNVs). The 109 genes include 58 genes from the American College of Medical Genetics and Genomics (ACMG) actionable finding list.[7] Additionally, each of the participating sites nominated up to 6 genes relevant to site-specific research interest. In this study, we focused on hereditary cancer genes on this panel, including 25 genes related to cancer phenotypes determined by the ACMG working groups[7,8]. These genes included *APC*, *BMPR1A*, *BRCA1*, *BRCA2*, *MEN1*, *MLH1*, *MSH2*, *MSH6*, *MUTYH*, *NF2*, *PMS2*, *PTEN*, *RB1*, *RET*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TP53*, *TSC1*, *TSC2*, *VHL*, and *WT1*, and 6 genes related to cancer phenotypes determined by experts in the eMERGE network and nominated by participating sites. These genes were *ATM*, *BLM*, *CHEK2*, *PALB2*, *POLD1*, and *POLE*. Note that *PALB2* has been included in the most recent ACMG actionable gene list published in 2021.[8]

The genetic testing in the HCR was performed by commercial Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathologists (CAP)-accredited molecular diagnostic laboratories as part of clinical service.

Whole-exome sequencing data for UKB participants were generated at the Regeneron Genetics Center. Exomes were captured by paired-end 75-bp whole-exome sequencing using the IDT xGen v1 capture kit on the NovaSeq6000 platform. Details on the sequencing, data process and quality controls were described elsewhere.[9]

Classification of variants

Variant classifications in the eMERGEseq were performed by two CLIA/CAP-accredited laboratories at the sequencing centers of the eMERGE network, according to ACMG/Association of Medical Pathology (ACMG/AMP) guidelines and some specific modifications from ClinGen Sequence Variant Interpretation Working Group and ClinGen Expert Panels as previously described.[6] We only included variants with an allele fraction > 30%. Variants were classified into pathogenic (P), likely pathogenic (LP), variant of uncertain significance (VUS), likely benign (LB) and benign (B). No P/LP variants for cancer syndromes were detected for *BLM*, *BMPR1A*, *NF2*, *POLD1*, *POLE*, *SDHAF2*, *SMAD4*, and *STK11*.[6]

Variant classification in UKB was performed according to the ACMG/AMP guidelines. For shared variants with the eMERGEseq cohort, we make classification results from both cohorts identical according to the guidelines mentioned above.

Variant classification in the HCR was performed by commercial CLIA/CAP-accredited molecular diagnostic laboratories. Results were returned to clinicians and patients and were documented in the EHRs. We compared results of classification for the same variants identified in the eMERGEseq and HCR cohorts (n=11). The variant *VHL* p.R200W was classified as a VUS in the eMERGEseq/UKB dataset, while it was classified as a pathogenic variant (P) in the HCR dataset. Previous studies showed that this variant was not associated with the von Hippel Lindau (VHL) disease but congenital erythrocytosis.[10] Therefore, we considered this variant a VUS in the analysis in the HCR dataset. The interpretations for the remaining 10 variants were consistent between these two datasets.

For each gene, we defined patients with P/LP variants as carriers and patients with B/LB variants or no rare variants as non-carriers, and patients with VUS as VUS carriers. For *MUTYH*, we only considered biallelic mutation

carriers. The frequency of carriers identified in each cohort was consistent with previous studies under similar settings.[11-19]

To test the feasibility of testing the difference in the prevalence of carrier for each gene across ancestral groups, we performed power calculations through simulations. We found that this study is underpowered to detect the differences in the prevalence of carriers among ancestral groups (beta <30% for genes studied) assuming a χ^2 distribution. For distribution assumption-free tests, the currently available approaches, relying on Monte Carlo methods, such as Fisher-Freeman-Halton test, have not been equipped to perform in such a large sample size as in UKB. Caution should be exercised in interpreting results presented in eTable 3.

Phecodes for phenotyping using EHR-based data

PheWAS phenotypes were defined using phecodes, which are manually grouped ICD-9 and ICD-10 codes developed to facilitate EHR based genetic research. In this study, we modified and expanded our previous phecode map[20, 21] by adding more granular phenotypes, including those related to Mendelian disorders and other traits in the congenital, neonatal, developmental, ocular, and pregnancy categories. Using the EHR data from a cohort of 2.6 million patients from the Synthetic Derivative (SD) at VUMC[22], this new algorithm derived 3,368 phecodes from 16,245 unique ICD-9 codes and 18,893 unique ICD-10 codes, spanning the following categories: auditory, cardiovascular, congenital, dermatologic, developmental, digestive, endocrine, genitourinary, hematopoietic, infectious, musculoskeletal, neonate, neoplastic, ocular, pregnant, psychiatric, pulmonary, and symptoms/signs.

We derived 3186 unique PheWAS phenotypes from 2,134,933 unique dates of ICD-9 and -10 codes in the EHRs of the eMERGEseq cohort. We removed phenotypes with < 5 cases. A total of 3,017 phenotypes remained. To empirically estimate the phenome-wide significant *P*-value threshold, we conducted 10,000 PheWAS with a random variable using data from the eMERGEseq cohort and analyzed the distributions of minimum *P*-values (Pmin) for each PheWAS. The 95th percentile of Pmin was 2.5×10^{-5}, and we defined this *P*-value as the empirical phenome-wide significance threshold at a significance level of $\alpha = 0.05$ (eFigure 2), which was equivalent to the Bonferroni correction of 2000 independent tests.

Definition of known gene-phenotype associations

We retrieved the clinical synopses for each gene from the Online Mendelian Inheritance in Man (OMIM), a comprehensive, authoritative compendium of human genes and genetic phenotypes.[23] We retrieved data of gene-diseases validity from ClinGen.[24] We defined gene-cancer associations with definitive evidence of clinical validity by ClinGen working groups as primary gene-cancer associations.[25] We did not include WT1 with Wilms tumors as none of the WT1 carriers were from our pediatric cohorts.

As previously reported[21], to test the probability of replicating X out of Y known associations at $\alpha = 0.05$, we calculated based on the probability of drawing *P*-values randomly from a normal distribution with at least X of them having a $P < 0.05$ (X being the number of replicated associations). Thus, the probability of getting X gene-phenotype associations replicated ($P < 0.05$) out of Y tested associations is: $P(X) = C(Y, X)P^X(1-P)^{Y-X}$, where $P = 0.05$ and C (Y, X) represents the number of combinations selecting X items from among set of Y items.

PheWAS analyses

In each cohort, we used a minimum code count threshold of one phecode to define cases for a phenotype. We defined controls as those who never had the phecode. We included genes with at least 2 carriers. We focused on phenotypes that were documented in the carriers. The number of phenotypes found in carriers for each gene is shown in eFigure 1.

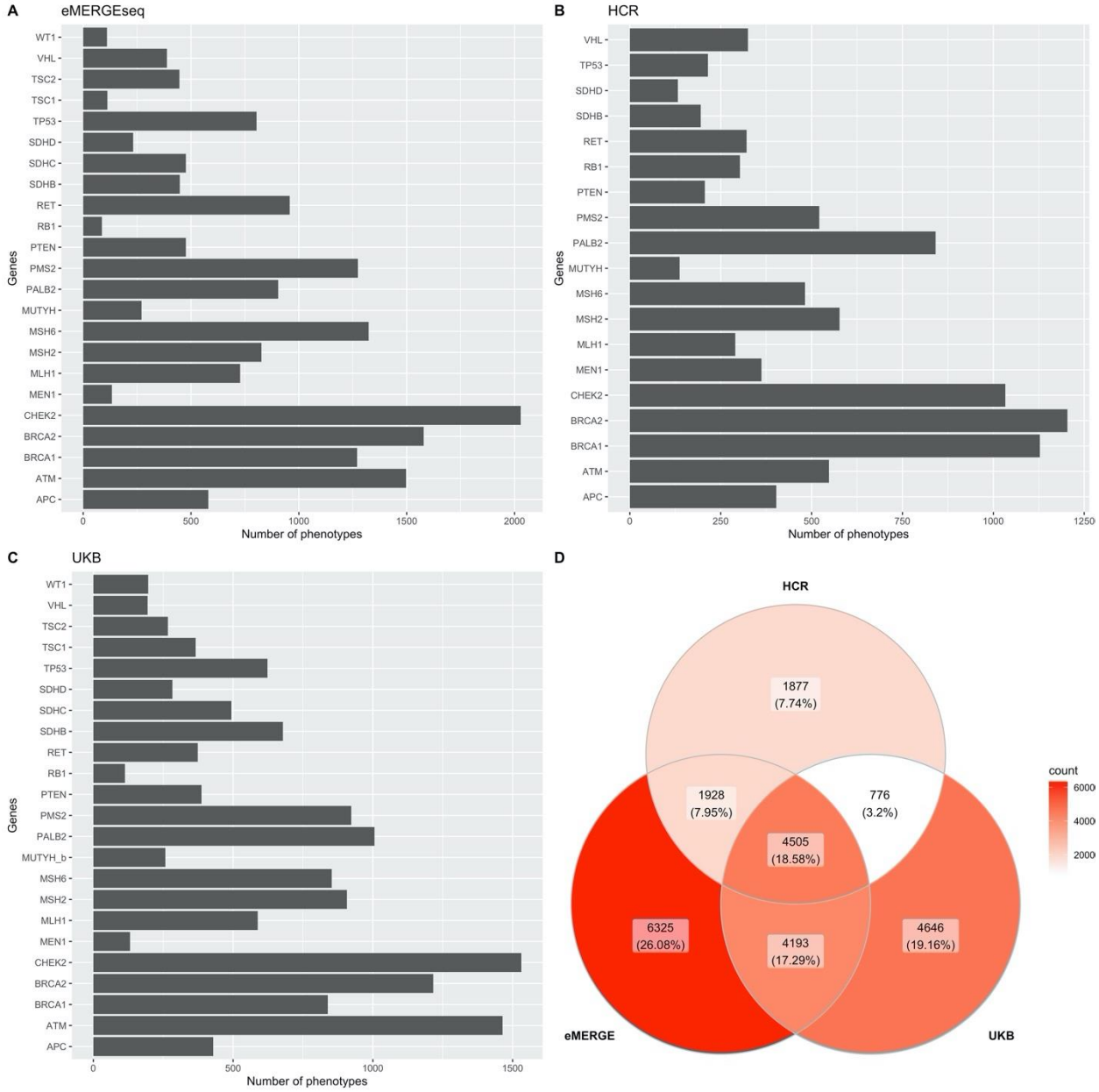
In the UKB dataset, phenotypes were derived from in-patient medical records, tumor/death registry and self-reported outcomes. Therefore, health outcomes related to out-patient settings were less likely to be collected than those in eMERGEseq and HCR cohorts which collected data unbiasedly from EHRs. For the outcome "Vitamin D deficiency", we used data of serum 25(OH)D concentrations measured from blood samples collected from

participants at baseline instead of ICD codes. Serum 25(OH)D concentration was categorized as <25.0, 25.0–49.9, and >=50 nmol/L. To be consistent with the definition of Vitamin D deficiency in clinical settings and previous studies using the data,[26] we defined participants with <25.0nmol/L as "Vitamin D deficiency" cases, participants with >=50 nmol/L as controls and removed those within 25.0–49.9 nmol/L from the analysis. Details of vitamin D measurements in UKB were described elsewhere.[26]

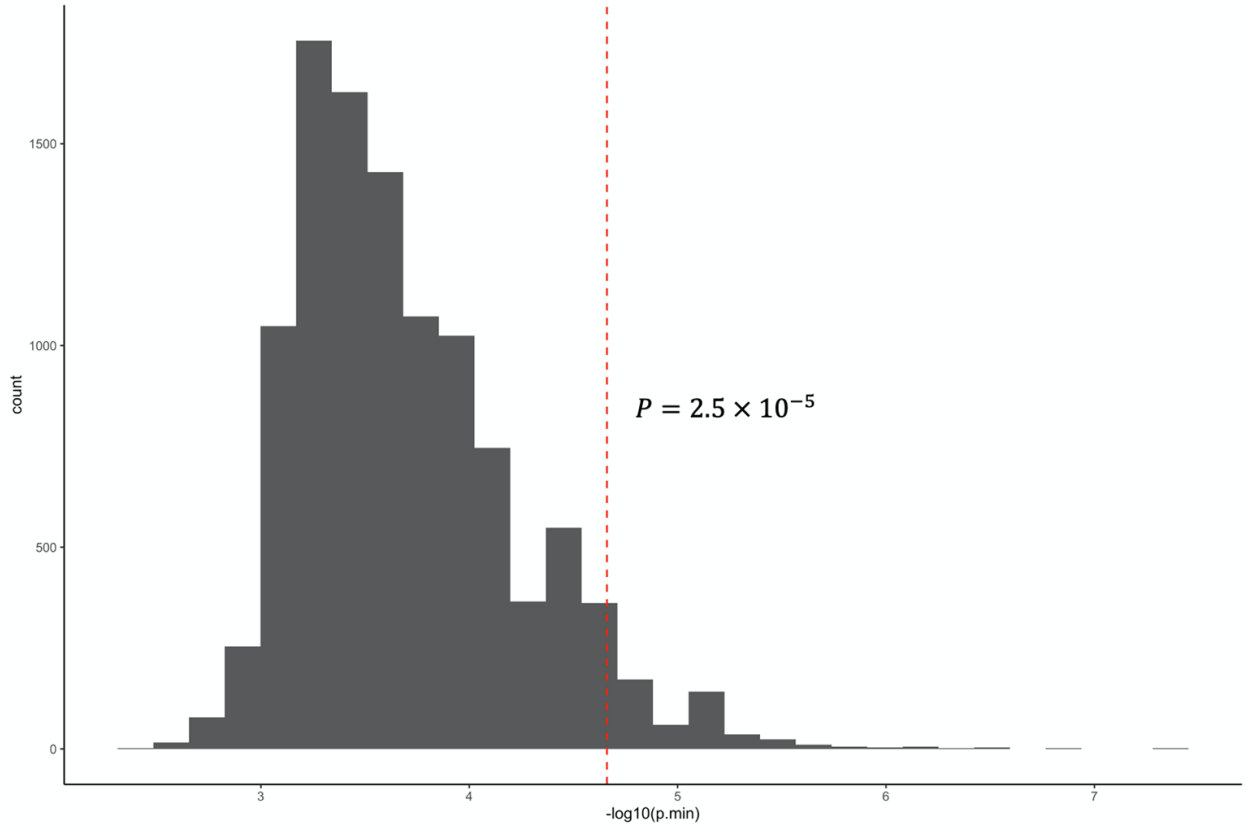
We conducted chart reviews to confirm the diagnoses of the PheWAS phenotypes and to study the relationships between new and known phenotypes. Specifically, for the PheWAS phenotype ovarian cysts, we reviewed all cases among *BRCA1/2* carriers in the HCR cohort (20 and 24 cases among carriers of *BRCA1* and *BRCA2*, respectively). We also reviewed a random subset of 54 cases among non-carriers of *BRCA1/2*. We tested the hypothesis that there was no difference in terms of the PheWAS phenotype capturing the actual diagnoses for ovarian cyst between carriers and non-carriers. Under this null hypothesis, P =1 for both genes.

Although we replicated all established gene-cancer associations defined by the ClinGen working groups,[24, 27] we reviewed all known phenotypes that were not replicated. Most of them were phenotypes that are not specifically collected in the current hospital systems in the US and/or phenotypes that UKB did not specifically collect data on. These phenotypes included diseases of teeth and supporting structures, malaise and fatigue, headache, mottled skin, disorders of skin pigmentation, seborrheic keratosis, constipation, dysphagia, tachycardia, myopia, cataract, and basal cell carcinoma. Data of these phenotypes were likely to be underdocumented in EHRs because of their relatively benign nature, lack of inclusion of dental records and their designated clinics. Most of these phenotypes were not specifically collected in the UKB cohort (eTable 4). After removing these phenotypes, only 20 known gene-phenotypes were not replicated, all of which was of a low or moderate penetrance according to literature.[28, 29]The probability of replicating these associations is expected to be lower compared to others with high penetrance. We also performed the same sensitivity analyses in European descendants only for these 20 known associations. No substantial differences were found, and these associations remained statistically insignificant.

eFigure 1. Number of Phenotypes Evaluated for Each Gene in the eMERGEseq, HCR, and UKB Data Sets



eFigure 2. Permutation Test to Estimate the Empirical Phenome-Wide Significant *P* Value Threshold to Control Type I Errors



We conducted 10,000 PheWASs of a random variable using firth logistic regression in the eMERGEseq data and analyzed the distributions of minimum P values (Pmin) for each PheWAS. The 95th percentile of Pmin was 2.5×10^{-5}, and we defined this P value as the empirical phenome-wide significance threshold at a significance level of $\alpha = 0.05$.

eTable 1. Full List of Genes Sequenced in the eMERGE Network

Gene	Original List
ACTA2	ACMG
ACTC1	ACMG
APC	ACMG
APOB	ACMG
BRCA1	ACMG
BRCA2	ACMG
BMPR1A	ACMG
CACNA1S	ACMG
COL3A1	ACMG
DSC2	ACMG
DSG2	ACMG
DSP	ACMG
FBN1	ACMG
GLA	ACMG
KCNH2	ACMG
KCNQ1	ACMG
LDLR	ACMG
LMNA	ACMG
MEN1	ACMG
MLH1	ACMG
MSH2	ACMG
MSH6	ACMG
MUTYH	ACMG
MYBPC3	ACMG
MYH11	ACMG
MYH7	ACMG
MYL2	ACMG
MYL3	ACMG
MYLK	ACMG
NF2	ACMG
PCSK9	ACMG
PKP2	ACMG
PMS2	ACMG
PRKAG2	ACMG

Gene	Original List
PTEN	ACMG
RB1	ACMG
RET	ACMG
RYR1	ACMG
RYR2	ACMG
SCN5A	ACMG
SDHAF2	ACMG
SDHB	ACMG
SDHC	ACMG
SDHD	ACMG
SMAD3	ACMG
SMAD4	ACMG
STK11	ACMG
TGFBR1	ACMG
TGFBR2	ACMG
TMEM43	ACMG
TNNI3	ACMG
TNNT2	ACMG
TP53	ACMG
TPM1	ACMG
TSC1	ACMG
TSC2	ACMG
VHL	ACMG
WT1	ACMG
ANGPTL3	SITE NOMINATED
ANGPTL4	SITE NOMINATED
ANK2	SITE NOMINATED
APOA5	SITE NOMINATED
APOC3	SITE NOMINATED
APOE	SITE NOMINATED
ATM	SITE NOMINATED
ATP1A2	SITE NOMINATED
BMPR2	SITE NOMINATED
CACNA1A	SITE NOMINATED
CACNA1B	SITE NOMINATED
CACNA1C	SITE NOMINATED
CFH	SITE NOMINATED
CFTR	SITE NOMINATED

Gene	Original List
CHEK2	SITE NOMINATED
COL5A1	SITE NOMINATED
CORIN	SITE NOMINATED
FLG	SITE NOMINATED
GRM1	SITE NOMINATED
GRM2	SITE NOMINATED
GRM5	SITE NOMINATED
GRM7	SITE NOMINATED
GRM8	SITE NOMINATED
HNF1A	SITE NOMINATED
HNF1B	SITE NOMINATED
IL33	SITE NOMINATED
IL4	SITE NOMINATED
KCNE1	SITE NOMINATED
KCNJ2	SITE NOMINATED
MC4R	SITE NOMINATED
MTHFR	SITE NOMINATED
NTRK1	SITE NOMINATED
OTC	SITE NOMINATED
PALB2	SITE NOMINATED
PLTP	SITE NOMINATED
POLD1	SITE NOMINATED
POLE	SITE NOMINATED
PON1	SITE NOMINATED
SCN1A	SITE NOMINATED
SCN9A	SITE NOMINATED
SERPINA1	SITE NOMINATED
SLC25A40	SITE NOMINATED
SLC2A10	SITE NOMINATED
TCF4	SITE NOMINATED
TCIRG1	SITE NOMINATED
TNF	SITE NOMINATED
TSLP	SITE NOMINATED
TTR	SITE NOMINATED
TYK2	SITE NOMINATED
UMOD	SITE NOMINATED
VDR	SITE NOMINATED

eTable 2. Population Characteristics of the eMERGEseq, HCR, and UKB Cohorts

	eMERGEseq (N=23,544)									HCR (N=3,242)	UBK (N= 187,234)
Site	**CCHMC**	**CHOP**	**Columbia**	**Geisinger**	**Harvard**	**KPW/UW**	**Mayo**	**Northwestern**	**VUMC**		
N	2936	2964	2314	2489	2472	2479	2439	2963	2431	3242	187,234
Ancestry*											
African	1100	1217	440	79	170	58	10	399	159	250	1580
Asian	31	83	190	19	75	934	17	145	19	71	9713
European	1810	1672	1676	2397	2233	1507	2417	2425	2262	2829	175941
Female (%)	1465 (50%)	923 (31%)	1238 (54%)	1688 (68%)	1404 (57%)	1517 (61%)	1409 (58%)	1828 (62%)	1139 (47%)	2851 (88%)	104055 (55.6%)
Age ranges (years)	0-80	0-22	0-89	0-90	0-91	7-89	0-73	0-90	9-90	0-99	38-85
Mean age (years)**	16.8	13.9	52.8	47.8	57.7	61.6	62.6	60.5	66.7	52.5	56.7
Mean (SD) EHR follow-up (years)	7.3 (3.1)	9.9 (4.0)	8.1(7.0)	13.1 (5.6)	11.9 (7.4)	18.1 (6.8)	22.1 (6.1)	13.0 (6.9)	11.7 (5.4)	8.8 (6.5)	12.4 (1.0)

SD: standard deviation; EHR: electronic health records; CCHMC: Cincinnati Children's Hospital Medical Center; CHOP: Children's Hospital of Philadelphia; KPW/UW Kaiser Permanente Washington/University of Washington; VUMC: Vanderbilt University Medical Center. The age range for each patient was determined by the first date and the last date of ICD codes in the record. Only CCHMC, CHOP, and HCR included children. * In the eMERGEseq cohort, the ancestry was determined by using common variants throughout the eMERGEseq panel that includes 214 ancestry informative markers, while the ancestry was self-reported in the HCR and UKB cohorts. **Mean age at recruitment for the UKB cohort; Mean of the last age documented in the electronic medical records for eMERGE and HCR.

eTable 3. Number and Percentage of Carriers by Each Gene in Each Ancestral Group Across 3 Cohorts

Genes	eMERGE			HCR			UKB		
	African	Asian	European	African	Asian	European	African	Asian	European
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
APC	5 (0.14)	1 (0.07)	8 (0.04)	2 (0.8)	1 (1.41)	18 (0.64)	0 (0)	5 (0.051)	23 (0.01)
ATM	6 (0.17)	3 (0.20)	73 (0.40)	0 (0)	0 (0)	29 (1.03)	8 (0.51)	69 (0.71)	1112 (0.63)
BRCA1	4 (0.11)	5 (0.33)	72 (0.39)	11 (4.4)	1 (1.41)	78 (2.75)	0 (0)	11 (0.11)	200 (0.11)
BRCA2	19 (0.52)	4 (0.26)	113 (0.61)	6 (2.4)	1 (1.41)	82 (2.89)	6 (0.38)	29 (0.30)	574 (0.33)
CHEK2	5 (0.14)	5 (0.33)	262 (1.42)	0 (0)	2 (2.82)	41 (1.45)	1 (0.06)	38 (0.39)	1682 (0.96)
MEN1	0 (0)	0 (0)	2 (0.01)	0 (0)	0 (0)	10 (0.35)	0 (0)	1 (0.01)	6 (0.003)
MLH1	4 (0.11)	1 (0.07)	8 (0.04)	2 (0.8)	0 (0)	12 (0.42)	0 (0)	7 (0.07)	71 (0.04)
MSH2	0 (0)	1 (0.07)	14 (0.08)	1 (0.4)	0 (0)	20 (0.71)	7 (0.44)	52 (0.54)	190 (0.11)
MSH6	2 (0.06)	2 (0.13)	46 (0.25)	1 (0.4)	2 (2.82)	14 (0.49)	1 (0.06)	10 (0.10)	191 (0.11)
MUTYH*	0 (0)	0 (0)	4 (0.02)	0 (0)	0 (0)	3 (0.11)	0 (0)	2 (0.02)	27 (0.02)
PALB2	5 (0.14)	1 (0.07)	22 (0.12)	2 (0.8)	0 (0)	26 (0.01)	1 (0.06)	14 (0.14)	352 (0.20)
PMS2	6 (0.17)	2 (0.13)	46 (0.25)	0 (0)	1 (1.41)	15 (0.53)	0 (0)	10 (0.10)	273 (0.16)
PTEN	0 (0)	1 (0.07)	12 (0.07)	0 (0)	0 (0)	3 (0.11)	1 (0.06)	0 (0)	25 (0.01)
RB1	2 (0.06)	0 (0)	0 (0)	3 (1.2)	0 (0)	3 (0.11)	0 (0)	0 (0)	8 (0.004)
RET	4 (0.11)	0 (0)	30 (0.16)	1 (0.4)	0 (0)	9 (0.32)	0 (0)	3 (0.03)	32 (0.02)
SDHB	1 (0.03)	1 (0.07)	4 (0.02)	0 (0)	0 (0)	4 (0.14)	0 (0)	1 (0.01)	21 (0.07)
SDHC	1 (0.03)	1 (0.07)	4 (0.02)	0 (0)	0 (0)	0 (0)	0 (0)	5 (0.05)	62 (0.04)
SDHD	0 (0)	2 (0.13)	2 (0.01)	0 (0)	0 (0)	5 (0.18)	0 (0)	1 (0.01)	20 (0.01)
TP53	0 (0)	1 (0.07)	10 (0.05)	1 (0.4)	1 (1.41)	2 (0.07)	1 (0.06)	24 (0.25)	73 (0.04)
TSC1	3 (0.08)	0 (0)	2 (0.01)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	33 (0.02)
TSC2	9 (0.25)	0 (0)	3 (0.02)	0 (0)	0 (0)	0 (0)	0 (0)	5 (0.05)	15 (0.009)
VHL	0 (0)	1 (0.07)	4 (0.02)	1 (0.4)	1 (1.41)	6 (0.21)	1 (0.06)	0 (0)	15 (0.009)
WT1	0 (0)	1 (0.07)	2 (0.01)	0 (0)	0 (0)	0 (0)	0 (0)	6 (0.06)	5 (0.003)

*Biallelic mutation carriers only. The number of participants in each ancestral group in each cohort is found in eTable 2.

eTable 4. Association Results of Known Gene-Phenotype Associations Documented in the OMIM Database

Gene	Phenotype	eMERGE	HCR	UKB	META	P	Phet	OMIM
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)			
APC	Benign neoplasm of stomach	7.88 (1.42-43.73)	17.97 (6.62-48.79)	15.87 (5.38-46.88)	15.07 (7.67-29.59)	3.32E-14	0.71	OMIM
APC	Benign neoplasm of the anus and anal canal	2.86 (0.62-13.24)	5.08 (1.58-16.36)	17.04 (2.74-105.9)	5.51 (2.41-12.61)	0.00029	0.34	OMIM
APC	Benign neoplasm of the colon and rectum	2.41 (0.84-6.94)	40.76 (13.76-120.78)	11.37 (5.13-25.22)	10.37 (5.99-17.96)	7.19E-16	0	Primary
APC	Benign neoplasm of the liver and intrahepatic bile ducts	61 (7.66-485.98)	26.47 (3.48-201.34)	144.8 (8.47-2475.59)	52.01 (14.29-189.29)	1.57E-08	0.62	
APC	Benign neoplasm of the small intestine	82.86 (13.58-505.54)	61.24 (15.95-235.17)	224.16 (32.56-1543.36)	90.58 (35.31-232.36)	8.22E-20	0.55	OMIM
APC	Dental caries	1.96 (0.31-12.37)	6.07 (1.13-32.63)		3.63 (1.05-12.58)	0.0419	0.37	OMIM
APC	Disorders of pigmentation	1.23 (0.3-4.95)	0.78 (0.16-3.95)		1.01 (0.35-2.91)	0.979	0.68	OMIM
APC	Gastritis and duodenitis	3.32 (0.98-11.25)	9.43 (3.66-24.31)	2.91 (1.16-7.29)	4.66 (2.61-8.33)	1.34E-06	0.18	
APC	Malignant neoplasm of other connective and soft tissue	14.36 (2.33-88.52)	2 (0.46-8.77)	22.61 (2.02-253.08)	5.93 (2.1-16.71)	0.00346	0.12	OMIM
APC	Malignant neoplasm of the colon and rectum	2.48 (0.37-16.55)	1.34 (0.47-3.84)	21.84 (7.13-66.9)	4.51 (2.22-9.2)	0.000182	0	Primary
APC	Other diseases of teeth and supporting structures	1.97 (0.31-12.49)		11.82 (1.23-113.3)	4.04 (0.97-16.87)	0.0557	0.23	OMIM
APC	Sebaceous cyst	0.88 (0.17-4.6)	1.24 (0.22-7.02)	7.91 (1.47-42.68)	2.05 (0.77-5.44)	0.355	0.15	OMIM
ATM	Abnormal findings in semen	15.72 (2.55-96.9)		2.9 (0.44-19.36)	7 (1.88-26.02)	0.00367	0.21	OMIM
ATM	Bronchiectasis	1.65 (0.42-6.45)		1.19 (0.73-1.94)	1.24 (0.78-1.96)	0.365	0.66	OMIM

ATM	Bronchitis	1.39 (0.86-2.27)	0.11 (0.02-0.73)	0.78 (0.47-1.31)	0.98 (0.69-1.39)	0.995	0.02	OMIM
ATM	Decreased white blood cell count	2.19 (1-4.83)	1.28 (0.45-3.62)	1.65 (1.09-2.49)	1.69 (1.2-2.39)	0.0109	0.7	OMIM
ATM	Diabetes mellitus	1.13 (0.67-1.91)	0.35 (0.09-1.4)	1.13 (0.93-1.39)	1.11 (0.92-1.34)	0.557	0.26	OMIM
ATM	Disease of capillaries	1.33 (0.43-4.08)	2.06 (0.33-12.95)	1.5 (0.56-4.05)	1.5 (0.75-2.99)	0.515	0.92	OMIM
ATM	Dysarthria	1.95 (0.32-11.7)		0.89 (0.18-4.3)	1.25 (0.38-4.09)	0.711	0.52	OMIM
ATM	Dystonia	0.49 (0.12-2.04)	2.68 (0.4-18)		0.9 (0.29-2.83)	0.858	0.16	OMIM
ATM	Elevated blood glucose level	0.95 (0.54-1.67)	0.55 (0.17-1.81)	0.72 (0.3-1.75)	0.82 (0.53-1.28)	0.691	0.68	OMIM
ATM	Epilepsy, recurrent seizures, convulsions	0.92 (0.42-2.03)	0.41 (0.04-4.62)	1.54 (1.03-2.3)	1.35 (0.95-1.92)	0.245	0.32	OMIM
ATM	Folate-deficiency anemia	31.13 (4.45-217.63)		1.66 (0.43-6.41)	4.31 (1.42-13.09)	0.00985	0.02	OMIM
ATM	Lack of coordination	4.24 (2.07-8.68)	0.86 (0.06-13.27)	1.85 (0.58-5.91)	3.16 (1.75-5.74)	0.000745	0.31	OMIM
ATM	Leukemia	1.7 (0.29-9.84)		2.46 (1.35-4.47)	2.37 (1.34-4.17)	0.00283	0.7	OMIM
ATM	Malignant neoplasm of stomach	4.62 (0.61-34.79)		4.24 (2.27-7.9)	4.27 (2.35-7.74)	1.8E-06	0.94	
ATM	Malignant neoplasm of the breast, female	2.57 (1.22-5.43)	1.17 (0.56-2.43)	2.69 (1.4-5.17)	2.05 (1.36-3.08)	0.00275	0.2	Primary
ATM	Malignant neoplasm of the pancreas	2.54 (0.39-16.39)	3.68 (0.77-17.52)	4.79 (2.72-8.43)	4.44 (2.66-7.4)	7.88E-08	0.79	
ATM	Megaloblastic anemia	5.53 (2.16-14.13)	0.6 (0.05-7.84)	0.96 (0.49-1.88)	1.66 (0.97-2.83)	0.18	0.01	OMIM
ATM	Non-Hodgkin lymphoma	3.84 (1.22-12.08)		1.62 (0.94-2.8)	1.9 (1.16-3.11)	0.0104	0.18	OMIM
ATM	Sinusitis	1.02 (0.64-1.63)	0.2 (0.05-0.71)	0.68 (0.43-1.1)	0.76 (0.55-1.05)	0.262	0.05	OMIM
ATM	Strabismus and disorders of binocular eye movements	1.51 (0.6-3.78)		0.73 (0.3-1.76)	1.03 (0.55-1.95)	0.917	0.26	OMIM
ATM	Tremor	1.1 (0.31-3.97)		0.56 (0.18-1.74)	0.76 (0.32-1.76)	0.516	0.44	OMIM
BRCA1	Benign neoplasms of the ovary	6.61 (2.35-18.6)	3.24 (1.45-7.23)		4.24 (2.25-7.99)	8.09E-06	0.29	OMIM

BRCA1	Gynecological benign neoplasms	2.84 (1.61-4.99)	1.51 (0.9-2.54)	0.98 (0.56-1.72)	1.61 (1.17-2.2)	0.0131	0.03	OMIM
BRCA1	Malignant neoplasm of retroperitoneum and peritoneum		3.29 (1.16-9.33)	25.69 (6.26-105.36)	6.8 (2.94-15.72)	7.46E-06	0.02	OMIM
BRCA1	Malignant neoplasm of the breast, female	7.79 (4.28-14.19)	0.8 (0.52-1.24)	32.78 (13-82.67)	2.55 (1.84-3.55)	1.8E-07	0	Primary
BRCA1	Malignant neoplasm of the fallopian tube and uterine adnexa	31.03 (4.42-217.96)	5.68 (2.29-14.11)	91.32 (18.6-448.41)	13 (6.25-27.03)	5.88E-11	0.01	Primary
BRCA1	Malignant neoplasm of the ovary	3.25 (0.72-14.61)	3.13 (1.73-5.66)	18.36 (8.01-42.1)	5.4 (3.41-8.54)	5.63E-12	0	Primary
BRCA1	Ovarian cyst	5.91 (3.4-10.29)	1.8 (1.05-3.07)	2.94 (1.3-6.64)	3.15 (2.22-4.46)	9.09E-10	0.01	
BRCA1	Vitamin D deficiency	0.51 (0.28-0.93)	0.17 (0.08-0.38)	0.58 (0.34-0.98)	0.44 (0.31-0.62)	2.66E-05	0.04	
BRCA2	Chromosomal anomalies	0.99 (0.2-4.96)	0.91 (0.06-14.97)	9.08 (1.67-49.42)	2.4 (0.82-7.04)	0.283	0.14	OMIM
BRCA2	Malignant neoplasm of kidney, except pelvis	1.1 (0.21-5.66)	0.96 (0.26-3.52)	0.49 (0.12-2)	0.79 (0.34-1.8)	0.851	0.71	OMIM
BRCA2	Malignant neoplasm of the breast, female	4.62 (2.72-7.84)	0.88 (0.56-1.38)	7.54 (3.75-15.13)	2.36 (1.73-3.21)	3.71E-07	0	Primary
BRCA2	Malignant neoplasm of the breast, male	31.16 (2.51-386.62)	3.18 (0.4-25.04)		7.95 (1.61-39.27)	0.0109	0.17	OMIM
BRCA2	Malignant neoplasm of the ovary	2.94 (0.84-10.31)	2.42 (1.28-4.6)	10.55 (6.23-17.86)	5.46 (3.71-8.05)	8.72E-17	0	Primary
BRCA2	Malignant neoplasm of the pancreas	4.7 (1.45-15.2)	3.43 (1.37-8.59)	3.56 (1.49-8.51)	3.74 (2.14-6.52)	2.12E-05	0.91	Primary
BRCA2	Ovarian cyst	4.07 (2.56-6.48)	2.64 (1.56-4.46)	2.72 (1.71-4.33)	3.12 (2.36-4.12)	1.29E-14	0.37	
CHEK2	Histocytoces		32.13 (2.35-439.03)	3.34 (0.48-23.17)	7.45 (1.57-35.31)	0.0114	0.17	OMIM
CHEK2	Leukemia	4.42 (2.18-8.94)	5.04 (1-25.41)	3.52 (2.26-5.47)	3.81 (2.64-5.48)	6.18E-12	0.81	
CHEK2	Malignant neoplasm of brain	1.03 (0.35-2.98)	1.41 (0.25-8.03)	0.85 (0.35-2.11)	0.98 (0.52-1.86)	0.998	0.88	OMIM

CHEK2	Malignant neoplasm of eye	2.36 (0.37-14.98)		1.81 (0.65-5.04)	1.93 (0.79-4.72)	0.151	0.8	OMIM
CHEK2	Malignant neoplasm of other connective and soft tissue	1.16 (0.45-3.04)	3.38 (1.06-10.79)	2.27 (1.09-4.7)	2.02 (1.2-3.4)	0.0294	0.35	OMIM
CHEK2	Malignant neoplasm of the breast	1.34 (0.84-2.16)	1.34 (0.72-2.48)	1.9 (1.58-2.3)	1.77 (1.5-2.1)	2.18E-10	0.27	Primary
CHEK2	Malignant neoplasm of the prostate	2.22 (1.25-3.96)	2.57 (0.33-19.95)	1.87 (1.47-2.4)	1.93 (1.54-2.42)	7.52E-08	0.84	OMIM
CHEK2	Malignant sarcoma-related cancers	1.25 (0.82-1.91)	2.35 (1.06-5.18)	1.6 (0.88-2.93)	1.48 (1.08-2.03)	0.0525	0.37	Primary
CHEK2	Multiple myeloma and malignant plasma cell neoplasms	2.66 (0.9-7.9)		3.28 (1.79-5.98)	3.12 (1.84-5.28)	0.000023	0.74	
MEN1	Acute pancreatitis	48.47 (3.07-765.51)	27.26 (4.68-158.68)	37.49 (2.86-490.91)	33.45 (9.25-121.02)	6.09E-07	0.94	
MEN1	Benign neoplasm of the pancreas	266.57 (12.16-5843.78)	18.97 (2.54-141.44)		41.64 (7.73-224.28)	1.42E-05	0.16	OMIM
MEN1	Benign neoplasm of the parathyroid gland	170.61 (8.48-3431.59)	37.21 (8.48-163.3)		50.11 (13.3-188.81)	7.34E-09	0.37	OMIM
MEN1	Benign neoplasm of the pituitary gland and craniopharyngeal duct	653.31 (42.56-10027.9)	54.06 (11.77-248.34)		97.73 (25.81-370.01)	1.52E-11	0.12	OMIM
MEN1	Benign neuroendocrine tumors	1392.98 (83.09-23351.94)	55.25 (14.43-211.51)		100.32 (29.85-337.12)	9.2E-14	0.04	Primary
MEN1	Diarrhea	2.82 (0.28-28.46)	0.45 (0.09-2.21)		0.81 (0.22-3.01)	0.755	0.2	OMIM
MEN1	Disorders of calcium metabolism	60.04 (4.86-741.21)	9.65 (2.59-36.04)	112.68 (12.31-1031.14)	22.41 (7.98-62.92)	2.68E-08	0.12	OMIM
MEN1	Disorders of the pituitary gland and its hypothalamic control	187.9 (13.94-2532.25)	47.11 (12.23-181.52)	64.42 (4.35-954.33)	63.37 (21.21-189.29)	1.02E-12	0.65	OMIM

MEN1	Hypercalcemia	110.96 (8.62-1428.34)	10.9 (2.61-45.56)		18.96 (5.44-66.03)	3.8E-06	0.12	OMIM
MEN1	Hypoparathyroidism	183.33 (8.99-3738.77)	41.95 (4.98-353.04)		68.54 (12.03-390.42)	1.91E-06	0.43	OMIM
MEN1	Malignant neoplasm of kidney, except pelvis		0.57 (0.04-8.24)	159.31 (8.64-2938.69)	7.47 (1.04-53.56)	0.0455	0.01	OMIM
MEN1	Malignant neoplasm of the adrenal gland		2.35 (0.33-16.65)	860.65 (33.67-21996.86)	11.39 (2.13-60.84)	0.00444	0	OMIM
MEN1	Malignant neoplasm of the endocrine glands		3.97 (1.06-14.82)	213.8 (29.15-1568.21)	13.35 (4.45-40.08)	3.83E-06	0	OMIM
MEN1	Malignant neoplasm of the pancreas	148.01 (7.56-2896.3)	21.31 (5.56-81.62)	172 (9.27-3191.69)	38.49 (12.45-119)	1.89E-09	0.28	OMIM
MEN1	Malignant neuroendocrine tumors	306.21 (13.6-6894.77)	53.31 (13.91-204.3)		70.14 (20.43-240.81)	1.44E-11	0.31	Primary
MEN1	Multiple endocrine neoplasia [MEN] type I	24879.04 (992.77-623473.77)	2334.9 (401.38-13582.37)		4024.03 (858.33-18865.46)	6.34E-26	0.21	OMIM
MEN1	Other specified diabetes*		40.14 (4.8-335.46)	347.53 (16.4-7362.77)	81.11 (14.19-463.6)	7.71E-07	0.26	OMIM
MEN1	Peptic ulcer	17.45 (1.33-228.23)	2.18 (0.31-15.18)		4.64 (0.98-21.83)	0.0523	0.21	OMIM
MEN1	Primary hyperparathyroidism	359.87 (25.02-5175.25)	380.91 (78.61-1845.63)	336.02 (29.67-3805.14)	365.56 (111.76-1195.71)	2.05E-21	1	OMIM
MEN1	Secondary hyperparathyroidism, non-renal	183.33 (8.99-3738.77)	27.09 (3.45-212.41)	355.21 (16.65-7575.97)	79.13 (17.9-349.89)	6.12E-08	0.32	OMIM
MLH1	Benign neoplasm of the skin	1.32 (0.42-4.13)	0.48 (0.1-2.23)	1.54 (0.49-4.84)	1.12 (0.55-2.3)	0.949	0.46	OMIM
MLH1	Diverticula of colon	1.51 (0.43-5.31)	0.65 (0.13-3.23)	1.42 (0.73-2.75)	1.31 (0.76-2.27)	0.626	0.66	OMIM
MLH1	Malignant neoplasm of the colon and rectum	34.79 (10.79-112.13)	4.92 (1.5-16.07)	13.67 (6.66-28.04)	13.48 (7.82-23.22)	8.43E-20	0.07	Primary
MLH1	Malignant neoplasm of the ovary		1.54 (0.25-9.54)	7.74 (1.45-41.31)	3.7 (1.08-12.69)	0.0376	0.2	OMIM
MLH1	Malignant sarcoma-related cancers	3.95 (1-15.67)	0.72 (0.14-3.71)	4.31 (0.59-31.66)	2.32 (0.91-5.89)	0.208	0.23	OMIM

MLH1	Other dyschromia	2.49 (0.67-9.3)	0.36 (0.03-3.95)	6.18 (0.77-49.83)	2.18 (0.79-5.99)	0.319	0.21	OMIM
MLH1	Other non-epithelial malignant neoplasm of skin	1.39 (0.24-8.13)	0.82 (0.16-4.26)	1.48 (0.66-3.31)	1.33 (0.68-2.6)	0.71	0.82	OMIM
MLH1	Ulceration of the lower GI tract	26.8 (5.15-139.47)	12.39 (1.98-77.46)		18.97 (5.57-64.67)	2.54E-06	0.54	
MSH2	Actinic keratosis	5.11 (1.71-15.29)	1.44 (0.36-5.78)	1.97 (0.69-5.56)	2.6 (1.34-5.04)	0.0186	0.3	OMIM
MSH2	Basal cell carcinoma	5.01 (0.98-25.51)	1.09 (0.2-5.95)		2.41 (0.75-7.82)	0.141	0.2	OMIM
MSH2	Benign neoplasm of the anus and anal canal	7.63 (2.29-25.4)	0.34 (0.03-3.67)	1.1 (0.21-5.62)	2.73 (1.11-6.69)	0.0896	0.03	OMIM
MSH2	Benign neoplasm of the colon and rectum	8.15 (2.95-22.51)	2.46 (1.06-5.68)	1.44 (0.99-2.1)	1.87 (1.35-2.59)	0.000892	0.01	OMIM
MSH2	Benign neoplasm of the skin	4.1 (1.51-11.1)	1.05 (0.37-2.98)	0.79 (0.35-1.78)	1.38 (0.8-2.37)	0.503	0.04	OMIM
MSH2	Benign neoplasm of the small intestine	46.41 (6.13-351.28)		7.24 (0.86-61.17)	19.25 (4.43-83.61)	7.88E-05	0.22	OMIM
MSH2	Diverticula of colon	3.98 (1.42-11.17)	1.01 (0.32-3.18)	1.02 (0.68-1.54)	1.21 (0.84-1.73)	0.596	0.05	OMIM
MSH2	Malignant neoplasm of stomach	26.14 (2.23-306.92)		1.83 (0.31-10.77)	4.53 (1.08-19.09)	0.0394	0.09	OMIM
MSH2	Malignant neoplasm of the breast, female	7.24 (1.87-27.98)	0.04 (0.01-0.23)	1.98 (0.33-11.97)	1.17 (0.47-2.9)	0.945	0	OMIM
MSH2	Malignant neoplasm of the colon and rectum	32.78 (10.93-98.3)	4.62 (1.81-11.76)	2.4 (1.22-4.73)	4.84 (2.97-7.91)	2.34E-09	0	Primary
MSH2	Malignant neoplasm of the eye, brain and other parts of central nervous system		2.77 (0.6-12.73)	3.27 (0.93-11.54)	3.06 (1.16-8.08)	0.0242	0.87	OMIM
MSH2	Malignant neoplasm of the prostate	17.98 (3.16-102.33)	1.26 (0.21-7.66)	1.51 (0.78-2.91)	1.95 (1.09-3.49)	0.0797	0.03	OMIM
MSH2	Malignant neoplasm of the skin	7.33 (2.66-20.21)	1.33 (0.53-3.35)	1.85 (1.22-2.82)	2.09 (1.46-2.99)	0.000288	0.03	OMIM

MSH2	Malignant neoplasm of the uterus	41.51 (8.82-195.37)	1.4 (0.24-8.21)	2.39 (0.71-8.03)	4.91 (2.12-11.37)	0.00103	0.01	Primary
MSH2	Malignant sarcoma-related cancers	10.57 (3.52-31.75)	1.07 (0.33-3.41)	1.34 (0.25-7.22)	2.99 (1.45-6.15)	0.0121	0.01	OMIM
MSH2	Other dyschromia	3.91 (1.25-12.23)	0.75 (0.15-3.7)	1.95 (0.33-11.62)	2.18 (0.96-4.96)	0.18	0.25	OMIM
MSH2	Other non-epithelial malignant neoplasm of skin	4.49 (1.29-15.56)	1.72 (0.57-5.16)	1.77 (1.12-2.82)	1.95 (1.3-2.91)	0.00515	0.38	OMIM
MSH2	Seborrheic keratosis	5.84 (2.14-15.96)	0.48 (0.11-2.12)	1.33 (0.44-4.01)	2.07 (1.06-4.03)	0.101	0.01	OMIM
MSH6	Basal cell carcinoma	2.53 (0.84-7.57)	0.55 (0.04-7.2)		2 (0.73-5.48)	0.179	0.28	OMIM
MSH6	Lymphoma	1.64 (0.28-9.47)		1.93 (0.6-6.24)	1.84 (0.69-4.87)	0.221	0.88	OMIM
MSH6	Malignant neoplasm of the bladder	8.3 (2.33-29.54)	18.98 (4.32-83.3)	2.28 (0.79-6.61)	5.63 (2.75-11.49)	1.33E-05	0.06	
MSH6	Malignant neoplasm of the colon and rectum	5.8 (2.56-13.12)	3.92 (1.23-12.49)	7.37 (4.41-12.31)	6.43 (4.28-9.65)	3.63E-18	0.6	Primary
MSH6	Malignant neoplasm of the ovary		4.68 (1.11-19.68)	6.74 (2.43-18.73)	5.96 (2.59-13.71)	2.63E-05	0.68	OMIM
MSH6	Malignant neoplasm of the uterus	13.81 (4.04-47.18)	18.88 (5.19-68.59)	19.89 (10.28-38.49)	18.42 (10.84-31.3)	6.33E-26	0.88	Primary
MSH6	Malignant sarcoma-related cancers	3.1 (1.44-6.67)	0.2 (0.02-1.77)	4.95 (1.53-16.02)	2.83 (1.53-5.24)	0.00402	0.04	OMIM
MSH6	Other dyschromia	0.75 (0.29-1.9)	1.08 (0.2-5.95)		0.81 (0.36-1.84)	0.619	0.71	OMIM
MUTYH	Benign neoplasm of stomach		52.8 (5.67-491.88)	6.22 (1.54-25.17)	11.36 (3.47-37.16)	5.82E-05	0.11	OMIM
MUTYH	Benign neoplasm of the colon and rectum	7.39 (1.21-45.06)	29.79 (3.16-281.06)	10.8 (4.92-23.7)	11.24 (5.66-22.33)	4.33E-11	0.62	Primary
MUTYH	Malignant neoplasm of kidney, except pelvis		84.13 (8.47-836.11)	12.57 (1.29-122.74)	32.28 (6.4-162.73)	2.55E-05	0.25	
MUTYH	Malignant neoplasm of the colon and rectum	9.59 (0.94-97.48)	21.97 (2.63-183.32)	34.52 (12.74-93.51)	27.17 (11.72-62.99)	1.35E-13	0.6	Primary

MUTYH	Polycystic ovarian syndrome	33.94 (2.3-501.28)	53.76 (5.76-502.08)		44.57 (7.99-248.73)	0.000015	0.8	
PALB2	Malignant neoplasm of the breast	3.34 (1.01-11.11)	1.94 (0.92-4.1)	3.68 (2.59-5.23)	3.28 (2.41-4.46)	3.8E-13	0.32	Primary
PALB2	Malignant neoplasm of the breast, female	1.97 (0.46-8.51)	1.62 (0.79-3.35)	1.8 (0.46-7.12)	1.71 (0.95-3.07)	0.203	0.97	OMIM
PALB2	Malignant neoplasm of the ovary		2.39 (0.86-6.68)	2.48 (0.85-7.24)	2.43 (1.16-5.11)	0.0187	0.96	OMIM
PALB2	Malignant neoplasm of the pancreas	12.86 (2.18-76.07)	5.23 (1.31-20.89)	5.16 (1.93-13.78)	6.04 (2.91-12.54)	8.81E-06	0.66	OMIM
PMS2	Basal cell carcinoma	1.82 (0.56-5.92)	0.49 (0.04-6.14)		1.44 (0.49-4.19)	0.507	0.36	OMIM
PMS2	Benign neoplasm of stomach	3.29 (1.06-10.21)	3.7 (0.75-18.19)	1.17 (0.58-2.36)	1.73 (0.99-3.03)	0.154	0.19	OMIM
PMS2	Benign neoplasm of the colon	2.06 (1.17-3.61)	1.76 (0.63-4.9)	0.84 (0.54-1.31)	1.23 (0.89-1.71)	0.461	0.04	OMIM
PMS2	Cannabis dependence	15.68 (2.57-95.76)	184.31 (8.31-4085.93)		29.34 (6.15-139.97)	2.24E-05	0.18	
PMS2	Leukemia	4.37 (0.92-20.8)		3.2 (1.05-9.69)	3.55 (1.44-8.77)	0.006	0.75	OMIM
PMS2	Lymphoma	1.56 (0.27-8.87)		1.79 (0.64-4.96)	1.73 (0.72-4.16)	0.224	0.89	OMIM
PMS2	Malignant neoplasm of the colon and rectum	5.91 (2.7-12.94)	3.89 (1.25-12.08)	2.65 (1.47-4.79)	3.6 (2.33-5.56)	6.4E-08	0.27	Primary
PMS2	Malignant neoplasm of the ovary	2.86 (0.43-19.23)	0.42 (0.04-5)		1.4 (0.31-6.35)	0.66	0.23	OMIM
PMS2	Malignant neoplasm of the uterus	5.96 (1.49-23.8)	1.82 (0.29-11.56)	2.41 (0.83-7.02)	3.03 (1.41-6.55)	0.0184	0.5	OMIM
PMS2	Malignant sarcoma-related cancers	1.04 (0.39-2.75)	0.62 (0.13-3.03)		0.9 (0.4-2.07)	0.813	0.58	OMIM
PMS2	Other dyschromia	1.36 (0.64-2.92)	1 (0.19-5.41)	1.59 (0.28-8.94)	1.33 (0.7-2.53)	0.684	0.93	OMIM
PMS2	Spermatocele	20.48 (4.14-101.22)	19.13 (1.51-242.84)		20.09 (5.19-77.7)	1.38E-05	0.96	
PTEN	Abnormality of gait and mobility	7.23 (2.14-24.39)		4.67 (0.6-36.19)	6.45 (2.27-18.35)	0.000473	0.72	OMIM

PTEN	Autistic disorder	9.37 (2.65-33.1)		109.39 (6.74-1775.77)	14.23 (4.51-44.94)	0.000006	0.12	OMIM
PTEN	Benign neoplasm of the colon and rectum	1.03 (0.31-3.45)	5.57 (0.7-44.48)	3.9 (1.49-10.2)	2.58 (1.27-5.24)	0.0319	0.18	OMIM
PTEN	Benign neoplasm of the genitourinary system		94.85 (5.27-1707.4)	40.91 (3.15-531.97)	59.25 (8.7-403.62)	3.05E-05	0.67	OMIM
PTEN	Benign neoplasm of the skin	0.39 (0.09-1.73)	7.92 (1.03-60.77)		1.12 (0.33-3.75)	0.856	0.02	OMIM
PTEN	Chronic gastritis	3.84 (0.51-28.68)	15.93 (1.3-194.97)	26.06 (7.75-87.58)	15.68 (6.01-40.92)	1.35E-07	0.28	
PTEN	Congenital deformities of skull, face, and jaw	35.22 (8.82-140.72)	94.27 (4.81-1847.2)		41.97 (11.96-147.34)	5.44E-09	0.56	OMIM
PTEN	Congenital malformation of the skin	7.14 (1.31-39)		93.06 (5.8-1492.69)	14.37 (3.38-61.15)	0.00031	0.12	OMIM
PTEN	Epilepsy, recurrent seizures, convulsions	3.33 (0.86-12.9)		3.78 (0.52-27.36)	3.47 (1.13-10.6)	0.0292	0.92	OMIM
PTEN	Goiter	3.03 (0.63-14.58)	17.41 (2.11-143.71)	24.68 (5.85-104.08)	10.71 (4.15-27.64)	0.000006	0.14	OMIM
PTEN	Hashimoto thyroiditis [Chronic lymphocytic thyroiditis]	15.59 (2.42-100.34)		76.87 (4.7-1258.15)	25.46 (5.41-119.89)	4.23E-05	0.35	OMIM
PTEN	Hearing impairment	2.97 (1-8.85)	5.5 (0.57-53.15)	5.22 (1.03-26.42)	3.76 (1.62-8.72)	0.00855	0.8	OMIM
PTEN	Hemangioma	2.1 (0.32-13.53)	8.73 (0.83-91.89)	19.05 (3-121.01)	6.87 (2.18-21.63)	0.00439	0.25	OMIM
PTEN	Hereditary ataxia	43.28 (3.26-573.85)		100.73 (6.16-1645.74)	63.9 (9.58-426.02)	1.75E-05	0.66	OMIM
PTEN	Hypoglycemia	4.53 (0.58-35.3)	42.22 (2.9-613.82)		10.36 (2.03-52.79)	0.00491	0.19	OMIM
PTEN	Hypothyroidism	1.51 (0.35-6.46)	0.7 (0.04-12.23)	4.74 (1.63-13.81)	2.8 (1.23-6.38)	0.0498	0.28	OMIM
PTEN	Lipoma	3.86 (0.79-18.94)	13.1 (1.11-154.2)	4.53 (0.93-22.09)	5.09 (1.83-14.13)	0.00762	0.7	OMIM
PTEN	Macrocephaly*	119.88 (18.44-779.54)	318.89 (13.28-7658.59)		154.23 (30.73-774.07)	9.26E-10	0.6	OMIM
PTEN	Malignant neoplasm of the endocrine glands	12.11 (2.01-72.9)	10.05 (0.93-109.11)		11.32 (2.7-47.5)	0.000912	0.9	OMIM
PTEN	Malignant neoplasm of the kidney		12.64 (0.98-163.72)	12.94 (1.31-128.05)	12.81 (2.32-70.67)	0.00343	0.99	OMIM

PTEN	Malignant neoplasm of the thyroid	20.92 (3.15-139.01)	17.24 (1.43-207.96)		19.49 (4.32-87.99)	0.000113	0.9	Primary
PTEN	Myopia	1.16 (0.29-4.69)		9.16 (1.01-82.74)	2.1 (0.65-6.81)	0.217	0.12	OMIM
PTEN	Obesity	1.29 (0.41-4.05)	1.89 (0.23-15.4)	1.41 (0.36-5.53)	1.41 (0.63-3.16)	0.708	0.95	OMIM
PTEN	Other congenital malformations of circulatory system	14.84 (2.38-92.33)		54.52 (3.9-762.4)	22.63 (5.04-101.71)	4.73E-05	0.43	OMIM
PTEN	Phakomatosis	493.07 (115.64-2102.41)	744.3 (64.79-8550.79)	445.78 (38.81-5120.18)	525.83 (173.23-1596.13)	2.77E-27	0.95	OMIM
PTEN	Postprocedural hypothyroidism	12.93 (2.1-79.74)		23.66 (3.49-160.42)	17.22 (4.61-64.39)	2.33E-05	0.65	OMIM
PTEN	Respiratory failure	2.17 (0.33-14.12)		5.28 (0.66-42.08)	3.23 (0.8-12.99)	0.0982	0.53	OMIM
PTEN	Strabismus and disorders of binocular eye movements	4.5 (0.89-22.63)		12.97 (1.32-127.2)	6.41 (1.71-23.95)	0.00578	0.46	OMIM
PTEN	Thyroiditis	9.81 (1.66-58.06)		39.79 (3.09-512.2)	15.49 (3.6-66.66)	0.000233	0.38	OMIM
RB1	Blindness and low vision	130.16 (9.96-1700.53)	19.08 (2.58-140.81)	68.94 (4.63-1026.69)	45.38 (11.62-177.23)	2.88E-07	0.48	OMIM
RB1	Hemo onc - by cell of origin		4.26 (0.51-35.97)	17.84 (2.69-118.37)	9.5 (2.31-39.11)	0.00183	0.33	OMIM
RB1	Malignant neoplasm of retina	2883.69 (84.16-98806.94)	451.34 (64.2-3172.91)	15416.25 (334.9-709639.53)	1163.2 (244.56-5532.5)	8.09E-18	0.23	Primary
RET	Benign neoplasm of the adrenal gland	4.85 (0.63-37.22)	0.42 (0.03-5.3)		1.86 (0.38-9.12)	0.445	0.14	OMIM
RET	Constipation	0.62 (0.26-1.47)	0.18 (0.02-1.55)	1.64 (0.5-5.35)	0.75 (0.39-1.46)	0.694	0.17	OMIM
RET	Diarrhea	0.77 (0.33-1.76)	0.81 (0.2-3.28)		0.78 (0.38-1.59)	0.495	0.94	OMIM
RET	Diplopia	9.9 (3.04-32.23)	7.99 (0.82-77.72)		9.46 (3.32-26.97)	2.61E-05	0.87	
RET	Disorders of parathyroid gland	4.18 (1.43-12.27)	6.72 (1.88-23.99)		5.1 (2.24-11.59)	0.000103	0.58	OMIM
RET	Diverticula of colon	1.2 (0.53-2.74)	0.22 (0.02-2.14)	1.02 (0.38-2.78)	1 (0.54-1.85)	1	0.39	OMIM

RET	Elevated blood pressure reading without diagnosis of hypertension	0.97 (0.32-2.92)	0.52 (0.04-6.95)	10.76 (1.89-61.26)	1.66 (0.69-3.99)	0.522	0.05	OMIM
RET	Fever of unknown origin	0.26 (0.09-0.74)	0.2 (0.02-1.85)		0.25 (0.09-0.64)	0.00392	0.84	OMIM
RET	Goiter	4.71 (2.04-10.88)	3.91 (1.15-13.32)		4.44 (2.22-8.86)	2.36E-05	0.8	OMIM
RET	Heart failure	2.2 (0.91-5.28)	0.61 (0.04-8.76)	2.56 (0.58-11.31)	2.07 (1-4.28)	0.145	0.64	OMIM
RET	Hemangioma	0.74 (0.16-3.53)	1.56 (0.25-9.84)		1.01 (0.31-3.33)	0.987	0.55	OMIM
RET	Hyperparathyroidism	1.07 (0.2-5.59)	5.44 (1.42-20.79)		2.85 (1.01-8.09)	0.0485	0.13	OMIM
RET	Hypertension	1.24 (0.64-2.41)	1.38 (0.43-4.44)	0.48 (0.22-1.05)	0.9 (0.57-1.44)	0.914	0.14	OMIM
RET	Hypocalcemia	7.01 (2.01-24.49)	1.69 (0.26-10.87)		4.51 (1.59-12.73)	0.0045	0.21	OMIM
RET	Hypoparathyroidism	36.09 (8.25-157.84)	6.75 (0.71-64.41)		21.84 (6.35-75.07)	9.89E-07	0.22	OMIM
RET	Hypothyroidism	3.61 (1.71-7.63)	7.63 (2.29-25.49)	1.3 (0.41-4.16)	3.35 (1.92-5.85)	0.000118	0.11	OMIM
RET	Malignant neoplasm of brain	3.66 (0.51-26.15)	0.7 (0.05-10.89)		2.09 (0.42-10.33)	0.366	0.34	OMIM
RET	Malignant neoplasm of the adrenal gland	23.99 (3.62-158.94)	1.6 (0.25-10.48)		6.14 (1.62-23.26)	0.00758	0.05	OMIM
RET	Malignant neoplasm of the endocrine glands	27.37 (11.19-66.97)	7.72 (2.33-25.59)		17.4 (8.5-35.64)	5.77E-15	0.1	Primary
RET	Malignant neoplasm of the thyroid	39.92 (15.32-104.07)	15.77 (4.64-53.6)		28.05 (13.19-59.63)	4.58E-18	0.24	Primary
RET	Multiple endocrine neoplasia [MEN] type IIA	2471.2 (481.35-12686.93)	843.16 (165.12-4305.41)		1440.91 (454.05-4572.67)	5.25E-35	0.36	OMIM
RET	Postprocedural hypothyroidism	22.79 (9.07-57.25)	11.77 (3.46-40.07)	7.92 (0.91-69.01)	16.49 (8.21-33.11)	3.23E-14	0.55	OMIM
RET	Tachycardia	1.24 (0.45-3.43)	2.07 (0.45-9.59)	3.29 (0.47-22.84)	1.65 (0.76-3.6)	0.447	0.65	OMIM
SDHB	Benign neoplasm of the adrenal gland	30.15 (2.4-378.87)	64.94 (8.57-492.31)	30.89 (6.07-157.21)	38.8 (12.48-120.61)	2.09E-09	0.83	Primary
SDHB	Benign neoplasm of the salivary glands		64.12 (3.7-1110.6)	7.55 (0.89-63.92)	16.29 (2.95-90.01)	0.00138	0.24	OMIM

SDHB	Disorders of pigmentation	1.87 (0.27-12.85)	3.95 (0.46-34.03)		2.61 (0.62-10.96)	0.192	0.61	OMIM
SDHB	Dysphagia	2.05 (0.29-14.25)		2.04 (0.9-4.62)	2.04 (0.96-4.33)	0.0643	1	OMIM
SDHB	Heart failure	2.09 (0.3-14.64)		1.6 (0.58-4.44)	1.69 (0.69-4.19)	0.254	0.81	OMIM
SDHB	Malignant neoplam of the bone and/or cartilage		13.15 (1.16-149.19)	20.3 (3.21-128.6)	17.32 (3.98-75.29)	0.000143	0.78	OMIM
SDHB	Malignant neoplasm of kidney, except pelvis		5.51 (0.55-55.54)	5.87 (1.5-22.92)	5.77 (1.78-18.67)	0.00342	0.96	OMIM
SDHB	Malignant neoplasm of retroperitoneum and peritoneum		21.44 (1.72-267.51)	11.52 (1.22-108.54)	15.15 (2.83-81.03)	0.00149	0.72	OMIM
SDHB	Malignant neoplasm of stomach	67.37 (4.49-1010.56)		6.61 (1.29-33.86)	12.28 (3.03-49.74)	0.000441	0.15	Primary
SDHB	Malignant neoplasm of the adrenal gland		25.34 (3.15-204.02)	61.42 (7.75-486.79)	39.58 (9.11-172.04)	9.26E-07	0.55	OMIM
SDHB	Malignant neoplasm of the aortic body and other paraganglia		1047.17 (101.81-10771.02)	354.34 (71.59-1753.81)	501.26 (134.08-1873.99)	2.45E-20	0.45	OMIM
SDHB	Malignant neoplasm of the endocrine glands		66.59 (8.38-529.49)	13.84 (4.17-45.92)	20.52 (7.26-57.96)	1.18E-08	0.2	OMIM
SDHB	Malignant neoplasm of the kidney		11.69 (1.56-87.91)	5.46 (1.41-21.08)	6.91 (2.25-21.23)	0.000739	0.54	OMIM
SDHB	Malignant neoplasm of the oral cavity		35.49 (2.54-496.17)	4.36 (0.59-32.06)	9.35 (1.9-45.93)	0.00591	0.21	OMIM
SDHB	Malignant neoplasm of the uterus	57.87 (3.54-945.32)	7.07 (0.69-72.24)	4.67 (1.23-17.68)	7.36 (2.53-21.41)	0.00121	0.28	OMIM
SDHB	Migraine with aura	27.96 (4.68-166.96)	11.58 (1.06-126.82)		20.39 (4.87-85.38)	3.68E-05	0.56	OMIM
SDHB	Palpitations	1.51 (0.23-9.99)	0.87 (0.05-15.38)	3.97 (1.62-9.68)	3.01 (1.39-6.56)	0.0208	0.45	OMIM
SDHB	Secondary hypertension	8.18 (0.87-76.77)	23.08 (2.88-184.99)	26.97 (2.32-312.93)	17.04 (4.67-62.19)	9.95E-05	0.73	OMIM

SDHC	Benign neoplasm of the eye, brain and other parts of central nervous system	9.72 (1-94.81)		4.85 (0.64-36.85)	6.59 (1.45-29.99)	0.0146	0.66	Primary
SDHC	Constipation	0.84 (0.14-4.98)		0.89 (0.31-2.58)	0.88 (0.35-2.18)	0.779	0.96	OMIM
SDHC	Disorders of pigmentation	1.53 (0.23-10.09)		4.83 (0.64-36.62)	2.61 (0.66-10.38)	0.173	0.42	OMIM
SDHC	Dysphagia	1.86 (0.27-12.73)		1.18 (0.32-4.3)	1.36 (0.46-3.98)	0.577	0.7	OMIM
SDHC	Intestinal obstruction	8.07 (0.86-75.47)		1.99 (0.33-12.04)	3.45 (0.85-14.02)	0.0833	0.34	OMIM
SDHC	Palpitations	2.41 (0.47-12.41)		3.27 (0.92-11.66)	2.92 (1.07-7.96)	0.0366	0.77	OMIM
SDHD	Benign neoplasm of the carotid body	3009.81 (86.46-104773.23)	154.24 (5.24-4539.2)	5736.3 (150.04-219304.93)	1258.09 (164.84-9601.68)	5.15E-11	0.3	OMIM
SDHD	Chromosomal anomalies	41.3 (2.97-574.25)	20.48 (1.53-273.71)		28.93 (4.56-183.45)	0.000356	0.71	OMIM
SDHD	Heart failure	3.8 (0.45-32.25)	3.83 (0.45-32.59)	3.92 (0.53-29.26)	3.86 (1.15-12.91)	0.0911	1	OMIM
SDHD	Hemangioma	6.75 (0.71-63.89)	0.93 (0.05-16.85)		3.21 (0.54-18.95)	0.199	0.29	OMIM
SDHD	Left heart failure	26.52 (2.08-338.88)		6.05 (0.73-50.09)	11.05 (2.17-56.24)	0.0038	0.38	OMIM
SDHD	Malaise and fatigue	1.58 (0.27-9.32)	0.17 (0.02-1.64)	4.07 (0.55-30.21)	1.22 (0.39-3.87)	0.942	0.11	OMIM
SDHD	Malignant neoplasm of the aortic body and other paraganglia	3668.82 (223.86-60127.13)	461.89 (57.38-3718.02)	548.31 (24.27-12389.75)	853.09 (195.48-3722.93)	3.15E-18	0.48	Primary
SDHD	Malignant neoplasm of the carotid body		447.61 (52.24-3835.18)	4280.06 (541.63-33821.5)	1445.41 (325.93-6410.04)	1.02E-21	0.14	OMIM
SDHD	Malignant neoplasm of the endocrine glands	41.91 (5.01-350.16)	73.87 (10.32-528.59)	90.92 (21.24-389.11)	71.77 (25.77-199.87)	3.01E-15	0.84	Primary
SDHD	Palpitations	1.93 (0.26-14.52)	0.8 (0.05-13.81)	4.18 (0.56-31.28)	2.21 (0.62-7.89)	0.477	0.64	OMIM
SDHD	Tremor		14.1 (1.18-168.22)	22.05 (1.96-247.49)	17.73 (3.14-100.11)	0.00113	0.8	OMIM
TP53	Acute leukemia		147.26 (14.41-1504.88)	19.75 (4.15-93.98)	36.86 (10.09-134.61)	4.82E-08	0.16	OMIM
TP53	Acute lymphoid leukemia		151.09 (8-2855.03)	47.84 (3.59-636.92)	79.07 (11.33-551.65)	1.04E-05	0.56	OMIM

TP53	Acute myeloid leukemia		198.83 (18.5-2136.95)	17 (2.77-104.44)	42.11 (9.96-178.13)	3.71E-07	0.11	OMIM
TP53	Benign neoplasm of other connective and soft tissue	6.13 (0.73-51.57)	19.88 (1.66-237.77)	7.3 (0.87-61.38)	8.97 (2.47-32.49)	0.00379	0.76	OMIM
TP53	Epilepsy, recurrent seizures, convulsions	8.99 (2.54-31.87)		0.96 (0.19-4.75)	3.8 (1.41-10.26)	0.00837	0.03	OMIM
TP53	Malignant neoplasm of brain		19.88 (1.66-237.77)	8.36 (1.56-44.82)	10.97 (2.73-44.09)	0.000734	0.57	OMIM
TP53	Malignant neoplasm of other connective and soft tissue	18.54 (2.84-120.93)		5.98 (0.75-47.79)	11.16 (2.77-44.9)	0.000685	0.43	Primary
TP53	Malignant neoplasm of stomach		55.85 (3.71-840.22)	4.11 (0.57-29.96)	10.23 (2.06-50.74)	0.00444	0.13	OMIM
TP53	Malignant neoplasm of the breast, female	10.66 (2.09-54.36)	1.18 (0.2-6.83)	7.62 (1.42-40.86)	4.84 (1.83-12.82)	0.00642	0.16	Primary
TP53	Malignant neoplasm of the colon and rectum	3.21 (0.44-23.14)	6.34 (0.68-59.4)	2.51 (0.94-6.73)	2.97 (1.31-6.74)	0.0342	0.76	OMIM
TP53	Malignant neoplasm of the eye, brain and other parts of central nervous system		15.08 (1.34-169.84)	5.28 (1.08-25.84)	7.24 (1.92-27.32)	0.0035	0.48	OMIM
TP53	Malignant neoplasm of the of bronchus and lung	14.12 (2.27-87.83)		2.22 (0.54-9.19)	4.46 (1.45-13.68)	0.00899	0.12	OMIM
TP53	Malignant neoplasm of the prostate	4.28 (0.51-35.68)		0.84 (0.29-2.46)	1.17 (0.45-3.06)	0.745	0.18	OMIM
TP53	Malignant neoplasm of the skin	5.91 (1.82-19.19)	1.76 (0.24-12.99)	0.91 (0.43-1.92)	1.57 (0.86-2.88)	0.336	0.03	OMIM
TP53	Malignant sarcoma-related cancers	7.23 (1.9-27.49)		3.18 (0.47-21.61)	5.53 (1.85-16.53)	0.00223	0.49	Primary

TSC1/2	Benign neoplasm of the skin	2.17 (0.7-6.78)		4.78 (0.96-23.78)	2.83 (1.12-7.16)	0.0281	0.43	OMIM
TSC1/2	Cyst of kidney	9.52 (2.71-33.44)		7.24 (0.83-62.74)	8.88 (3-26.31)	8.12E-05	0.83	OMIM
TSC1/2	Hypothyroidism	0.68 (0.13-3.53)		1.61 (0.38-6.74)	1.11 (0.38-3.27)	0.85	0.44	OMIM
TSC1/2	Other disorders of the kidney and ureters	8.19 (2.63-25.56)		3.53 (0.49-25.47)	6.64 (2.48-17.81)	0.000168	0.47	OMIM
VHL	Benign neoplasm of brain	59.62 (4.04-880.71)	18.65 (1.54-225.95)		31.9 (5.12-198.84)	0.000208	0.53	OMIM
VHL	Benign neoplasm of the adrenal gland	75.76 (8.63-664.98)	9.39 (1.95-45.12)		19.22 (5.38-68.6)	5.28E-06	0.13	OMIM
VHL	Benign neoplasm of the endocrine glands	23.88 (3.25-175.58)	6.07 (1.37-26.78)	16.58 (1.58-174.53)	10.99 (3.8-31.8)	5.72E-05	0.52	OMIM
VHL	Benign neoplasm of the eye, brain and other parts of central nervous system	25.75 (3.47-191.25)	21.59 (5.4-86.3)		22.85 (7.31-71.45)	7.45E-08	0.89	Primary
VHL	Benign neoplasm of the pancreas	95.44 (5.84-1561.16)	17.15 (1.4-210.54)		36.88 (5.7-238.43)	0.000151	0.37	OMIM
VHL	Benign neoplasms of external female genital organs and cervix		7.93 (0.83-75.61)	8.15 (0.89-74.15)	8.04 (1.66-38.95)	0.00961	0.99	OMIM
VHL	Congenital malformations of pancreas	188.04 (9.94-3557.09)	33.23 (2.43-454.26)		71.45 (10.12-504.26)	1.85E-05	0.39	OMIM
VHL	Congenital malformations of spleen	111.4 (6.6-1880.13)	131.16 (4.97-3463.79)		119.45 (14.07-1014.39)	1.17E-05	0.94	
VHL	Cyst and pseudocyst of pancreas	112.32 (16.05-785.91)	13.95 (2.15-90.52)		37.99 (9.87-146.28)	1.24E-07	0.13	OMIM
VHL	Cyst of kidney	20.07 (3.48-115.78)	5.2 (1.2-22.54)	21.82 (3.28-144.93)	11.4 (4.34-29.99)	5.18E-06	0.38	OMIM

VHL	Elevated blood pressure reading without diagnosis of hypertension	5.96 (0.99-35.77)	2.26 (0.33-15.36)		3.79 (1.02-14.04)	0.0461	0.47	OMIM
VHL	Headache	2.06 (0.4-10.57)	0.5 (0.1-2.47)	2.13 (0.49-9.33)	1.33 (0.54-3.27)	0.828	0.35	OMIM
VHL	Hemangioma	5.22 (0.6-45.31)	9.14 (2.53-33.08)	16.78 (1.59-176.71)	9.05 (3.33-24.6)	9.06E-05	0.77	OMIM
VHL	Hypotension	6.55 (1.08-39.82)	1.75 (0.39-7.85)	3.6 (0.49-26.53)	3.14 (1.16-8.53)	0.0801	0.54	OMIM
VHL	Malignant neoplasm of brain	111.14 (15.91-776.08)	6.73 (1.17-38.59)	37.2 (2.93-472.68)	25.89 (8.14-82.33)	2.51E-07	0.1	Primary
VHL	Malignant neoplasm of kidney, except pelvis	158.88 (21.7-1163.37)	4.18 (0.96-18.28)	43.06 (5.76-322.23)	19.85 (7.15-55.13)	7.19E-08	0.01	OMIM
VHL	Malignant neoplasm of other connective and soft tissue	48.7 (5.94-399.02)	1.74 (0.27-11.44)		7.65 (1.88-31.1)	0.00444	0.02	OMIM
VHL	Malignant neoplasm of spinal cord	1176.59 (87.28-15860.83)	94.66 (9.3-964.02)	484.55 (21.5-10919.67)	326.7 (71.91-1484.2)	6.27E-13	0.35	Primary
VHL	Malignant neoplasm of the adrenal gland	98.53 (5.99-1620.78)	19.15 (4.78-76.79)		26.46 (7.63-91.82)	2.46E-07	0.3	Primary
VHL	Malignant neoplasm of the pancreas	48.75 (3.45-689.2)	3.6 (0.71-18.2)	32.34 (2.62-399.76)	10.33 (3.08-34.7)	0.000793	0.15	OMIM
VHL	Medulloadrenal hyperfunction	802.95 (31.31-20590.13)	4.91 (0.57-42.63)		23.53 (3.89-142.19)	0.00058	0.01	OMIM
VHL	Other diseases of spinal cord	39.69 (6.41-245.92)	7.14 (0.79-64.78)	13.38 (1.33-134.14)	17.79 (5.36-59.06)	1.59E-05	0.48	OMIM
VHL	Other disorders of the brain and CNS	32.05 (5.3-193.83)	7.03 (1.54-32.04)		13.2 (4.14-42.1)	1.29E-05	0.21	OMIM
VHL	Phakomatosis	489.93 (58.57-4098.08)	171.15 (44.13-663.79)	429.18 (19.96-9229.13)	250.08 (85.71-729.65)	6.56E-23	0.67	OMIM
VHL	Stroke	3.66 (0.45-29.53)	0.62 (0.04-8.95)		1.87 (0.36-9.66)	0.456	0.3	OMIM
VHL	Syringomyelia and syringobulbia	122.77 (7.12-2117.3)	117.52 (5.75-2400.14)	667.73 (28.42-15690.28)	201.42 (35.66-1137.82)	1.47E-08	0.67	OMIM

VHL	Tachycardia	2.67 (0.35-20.24)	1.02 (0.18-5.75)		1.53 (0.41-5.71)	0.525	0.48	OMIM
WT1	Cataract	2.53 (0.3-21.39)		1.41 (0.3-6.56)	1.72 (0.5-5.99)	0.392	0.66	OMIM
WT1	Hypertension	8.16 (0.76-87.66)		0.76 (0.2-2.79)	1.31 (0.42-4.13)	0.641	0.09	OMIM
WT1	Malignant neoplasms (excluding BCC)	0.36 (0.03-4.88)		1.76 (0.46-6.76)	1.26 (0.38-4.17)	0.708	0.29	OMIM

OR: odds ratio; CI: confidence interval; OMIM: online Mendelian Inheritance in Man
*We defined gene-cancer associations with definitive evidence according to ClinGen as the primary gene-cancer association. We did not include WT1 with Wilms tumors as we did not find carriers in our pediatric cohorts. All odds ratio and *P* values were estimated by firth logistic regression models as described in the Methods section. Blank cells indicate no phenotype was found among carriers for the gene in the cohort and thus we were not able to evaluate the association.

eTable 5. Sensitivity Analyses With Analyses Restricted to European Descendants for All Newly Identified Associations

Genes	Phenotype	eMERGE	HCR	UKB	Meta	P summary	Phet
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)		
Neoplastic diseases							
ATM	Gastric cancer	5.8 (0.65-21.77)	-	3.95 (2.17-6.54)	4.09 (2.18-7.68)	1.19E-05	0.73
ATM	Pancreatic cancer	-	3.61 (0.71-11.53)	5.04 (3.09-7.74)	4.85 (2.84-8.27)	7.02E-09	0.69
MUTYH	Kidney cancer	-	84.13 (10.92-93.63)	12.96 (1.44-50.69)	4.05 (1.53-10.73)	4.98E-03	0.27
MSH6	Bladder cancer	7.65 (2.44-18.64)	17.45 (4.02-60.23)	2.41 (0.8-5.54)	5.28 (2.54-10.97)	4.94E-05	0.11
CHEK2	Leukemia	4.36 (2.31-7.51)	5.95 (1.17-19.40)	3.57 (2.41-5.07)	3.86 (2.68-5.56)	4.23E-12	0.78
CHEK2	Plasma cell neoplasms	2.64 (0.87-6.08)	-	3.13 (1.77-5.09)	3 (1.75-5.14)	6.17E-05	0.79
APC	Benign liver/IHBD tumor	109.71 (19.75-442.34)	30.86 (5-141.81)	169.54 (18.48-691.83)	70.68 (18.7-267.12)	2.77E-09	0.57
Non-neoplastic diseases							
APC	Gastritis/duodenitis	4.68 (1.08-17.67)	7.99 (2.92-20.59)	3.18 (1.19-7.52)	4.83 (2.51-9.32)	1.59E-05	0.47
BRCA1	Ovarian cyst	6.22 (3.56-10.94)	1.80 (1.01-3.07)	3.06 (1.39-5.87)	3.28 (2.27-4.73)	1.96E-09	0.01
BRCA2	Ovarian cyst	4.79 (3.01-7.59)	2.3 (1.33-3.84)	2.87 (1.86-4.23)	3.24 (2.42-4.33)	1.84E-14	0.12
BRCA1	Vitamin D deficiency	0.47 (0.21-0.92)	0.20 (0.05-0.50)	0.66 (0.38-1.07)	0.48 (0.34-0.68)	2.67E-04	0.05
PTEN	Chronic gastritis	4.1 (0.44-17.34)	17.29 (1.48-139.62)	3.82 (1.52-8.67)	4.52 (1.99-10.25)	1.46E-03	0.55
MEN1	Acute pancreatitis	52.85 (4.28-652.99)	24.16 (4.95-101.83)	41.82 (4.26-211.98)	32.68 (9.03-118.36)	7.50E-07	0.88
MUTYH	Polycystic ovaries	33.44 (2.71-412.65)	2.76 (0.96-6.16)	-	3.84 (1.44-10.19)	6.99E-03	0.09
PMS2	Cannabis dependence	17.64 (3.57-54.09)	176.69 (12.29-2407.33)	-	32.21 (6.66-155.87)	1.58E-05	0.21
RET	Diplopia	10.26 (3.63-24.09)	9.8 (0.93-58.11)	-	10.16 (3.52-29.32)	1.80E-05	0.97
MLH1	Lower GI ulcer	47.63 (11-179.71)	17.95 (3.25-68.13)	-	30.29 (8.31-110.45)	2.37E-07	0.46
PMS2	Spermatocele	19.88 (5.08-59.25)	5.68 (0.04-70.57)	-	16.34 (3.76-71.01)	1.93E-04	0.54
VHL	Splenic anomalies	132.91 (12.73-824.27)	168.19 (6.32-35114.78)	-	146.66 (16.33-1316.83)	8.42E-06	0.92

OR: odds ratios, CI: confidence interval. GI: gastrointestinal. IHBD: intrahepatic bile duct. Plasma cell neoplasms also include multiple myeloma. We utilized firth logistic regression in this PheWAS assuming a dominant model except MUTYH, which assumed a recessive model. Due to the scarceness of carriers of VHL and APC and a low prevalence of cannabis use in HCR, wide CIs were observed, and caution should be exercised when interpretating these results. Cells with dashes indicate no phenotype was found among carriers for the gene in the cohort and thus we were not able to evaluate the association.

eTable 6. Sensitivity Analyses That Removed Participants With Prior Cancer Diagnoses in New Associations With Noncancer Phenotypes in the UKB Cohort

Genes	Phenotypes	Carriers with the phenotype	Cases	Carriers without phenotypes	Controls	OR (95% CI)	P
BRCA1	Ovarian cyst	7	2685	204	184549	2.89 (1.29-5.76)	0.02
BRCA2	Ovarian cyst	18	2685	591	184549	2.21 (1.31-3.39)	0.003
MEN1	Acute pancreatitis	1	1421	6	185813	39.81 (4.12-190.12)	0.005
PTEN	Chronic gastritis	5	2570	21	184664	20.62 (7.13-50.41)	4E-06

eTable 7. Sensitivity Analyses for *CHEK2* in the UKB Cohort

Gene	Phenotypes	Carriers in Cases	Cases	Carriers in controls	Controls	OR (95% CI)	P
Remove all participants with cancer diagnoses before blood sampling							
CHEK2	Leukemia	17	751	1704	186483	2.60 (1.63-4.12)	0.0005
CHEK2	Malignant plasma cell neoplasms	12	462	1709	186772	3.12 (1.73-5.24)	0.0009
Remove all participants with prior cancer diagnoses and those diagnosed with cancer within 3 years after blood sampling							
CHEK2	Leukemia	15	666	1413	164654	2.82 (1.71-4.50)	0.0006
CHEK2	Malignant plasma cell neoplasms	10	426	1418	164894	2.97 (1.50-5.21)	0.003

eTable 8. Associations of Pathogenic/Likely Pathogenic Variants in *CHEK2* With Subtypes of Leukemia

Subtypes of leukemia	eMERGE	HCR	UKB	Meta	P summary	Phet
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)		
Acute leukemia	5.80 (2.40-14.01)	4.47 (0.58-34.59)	4.18 (2.09-8.36)	4.72 (2.79-7.99)	5.68E-08	0.85
Acute lymphoid leukemia	7.83 (2.51-24.41)	-	3.08 (0.46-20.79)	6.13 (2.31-16.29)	2.75E-04	0.41
Acute myeloid leukemia	4.80 (1.48-15.62)	5.87 (0.71-48.86)	5.09 (2.50-10.36)	5.07 (2.82-9.11)	3.78E-07	0.99
Chronic leukemia	5.38 (2.12-13.64)	5.74 (0.69-47.81)	3.37 (1.91-5.96)	3.91 (2.44-6.27)	1.19E-07	0.66
Chronic lymphoid leukemia	5.25 (1.78-15.49)	7.32 (0.82-65.49)	3.22 (1.69-6.13)	3.82 (2.23-6.53)	6.20E-06	0.63

eTable 9. Associations of *BRCA1* and *BRCA2* With Phenotypes With Phenome-Wide Significance in PheWAS

Phenotype	*BRCA1*		*BRCA2*		P het
	OR (95% CI)	*P*	OR (95% CI)	*P*	
Malignant neoplasm of the breast	3.69 (2.81-4.85)	6.19E-20	4.4 (3.6-5.38)	1.94E-46	0.32
Malignant neoplasms (excluding BCC)	2.20 (1.78-2.73)	3.66E-12	2.7 (2.34-3.12)	3.27E-40	0.14
Sequelae of cancer	5.04 (3.78-6.72)	5.09E-27	4.08 (3.19-5.22)	7.54E-28	0.29
Secondary malignant neoplasm	1.99 (1.47-2.68)	4.15E-05	3.2 (2.6-3.94)	6.03E-27	0.02
Malignant neoplasm of the ovary	5.4 (3.41-8.54)	5.63E-12	5.46 (3.71-8.05)	8.72E-17	0.97
Malignant neoplasm of other and ill-defined sites	1.58 (1.16-2.15)	1.57E-02	2.37 (1.94-2.89)	2.79E-16	0.06
Ovarian cyst	3.15 (2.22-4.46)	9.09E-10	3.12 (2.36-4.12)	1.29E-14	0.97
Gynecological malignant neoplasms	3.18 (2.21-4.57)	3.43E-09	2.91 (2.2-3.85)	6.48E-13	0.73
Secondary malignancy of lymph nodes	1.96 (1.37-2.81)	1.20E-03	2.65 (2.02-3.47)	1.38E-11	0.23
Secondary malignant neoplasm of digestive systems	3.21 (1.96-5.26)	2.31E-05	3.83 (2.63-5.58)	2.15E-11	0.60
Secondary malignancy of bone	1.25 (0.63-2.47)	8.10E-01	3.56 (2.45-5.17)	2.03E-10	0.28
Corpus luteum cyst or hematoma	3.3 (1.79-6.08)	6.79E-04	3.24 (2.14-4.91)	2.07E-07	0.97
Malignant neoplasm of the prostate	1.45 (0.83-2.55)	4.32E-01	2.49 (1.8-3.44)	2.50E-07	0.29
Secondary malignant neoplasm of liver	1.87 (1.06-3.31)	9.71E-02	2.8 (1.94-4.04)	2.94E-07	0.35
Malignant neoplasm of male genitalia	1.34 (0.77-2.33)	5.95E-01	2.39 (1.74-3.28)	4.79E-07	0.31
Pelvic peritoneal adhesions, female (postoperative infection)	2.62 (1.41-4.86)	9.72E-03	3.14 (2.02-4.89)	2.77E-06	0.68
Follicular cyst of ovary	4.22 (1.8-9.9)	4.13E-03	4.99 (2.62-9.49)	6.13E-06	0.79
Secondary malignancy of respiratory organs	2.72 (1.63-4.52)	6.16E-04	2.61 (1.76-3.89)	1.23E-05	0.92
Noninflammatory disorders of ovary, fallopian tube, and broad ligament	2.97 (1.84-4.77)	4.26E-05	2.56 (1.72-3.82)	2.09E-05	0.67
Malignant neoplasm of the pancreas	0.83 (0.21-3.36)	7.99E-01	3.74 (2.14-6.52)	2.12E-05	0.05
Elevated cancer antigen 125 [CA 125]	8.6 (4.10-18.03)	1.20E-08	6.74 (2.77-16.4)	2.63E-05	0.68
Malignant neoplasm of the fallopian tube and uterine adnexa	13 (6.25-27.03)	5.88E-11	6.13 (2.51-14.98)	3.73E-04	0.24

Benign mammary dysplasia	2.38 (1.7-3.32)	2.28E-06	1.78 (1.32-2.39)	7.78E-04	0.24
Benign neoplasms of the ovary	4.24 (2.25-7.99)	8.09E-06	2.69 (1.57-4.58)	1.39E-03	0.31
Malignant neoplasm of retroperitoneum and peritoneum	6.80 (2.94-15.72)	7.46E-06	4.07 (1.89-8.73)	1.53E-03	0.40
Abnormal tumor markers	4.05 (2.15-7.64)	1.53E-05	2.52 (1.24-5.13)	1.05E-02	0.33
Other nonmalignant breast conditions	2.37 (1.72-3.26)	9.09E-07	1.53 (1.13-2.05)	2.05E-02	0.08
Other and nonspecific abnormal cytological, histological and immunological findings	3.83 (2.08-7.05)	1.58E-05	2.09 (1.05-4.16)	3.60E-02	0.20
Vitamin D deficiency	0.43 (0.30-0.62)	2.5E-05	0.83 (0.61-1.14)	5.28E-01	0.05

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