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## Prevalence and Effect of Genetic Risk of Thrombo-embolic Disease in Inflammatory Bowel Disease

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### Abstract

**Background and Aims:** The largest cause of mortality in patients with inflammatory bowel disease (IBD) remains thrombo-embolic disease (TED). Recent reports have demonstrated that both monogenic and polygenic factors contribute to TED and 10% of ‘healthy’ subjects are genetically at high risk for TED. Our aim was to utilize whole exome sequencing (WES) and genome-wide genotyping to determine the proportion of IBD patients genetically at risk for TED and investigate the effect of genetic risk of TED in IBD.

**Methods:** The TED polygenic risk score (PRS) was calculated from genome-wide genotyping. Thrombophilia pathogenic variants (TPV) were extracted from WES. In total, 792 IBD patients

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Disclosure:

DPBM, TH, DL, and JB are faculty members at Cedars-Sinai Medical Center. TN, MK, GB, SH, LA, EM are employees at Cedars-Sinai. Cedars-Sinai has financial interests in Prometheus Biosciences, Inc., a company which has access to the data and specimens in Cedars-Sinai’s MIRIAD Biobank (including the data and specimens used in this study). Prometheus Biosciences, Inc. seeks to develop commercial products. DPBM and DL are paid consultants and shareholders of Prometheus Biosciences, Inc. DPBM: Consultant (Gilead Sciences, Boehringer-Ingelheim, Pfizer, Bridge Biotherapeutics, Qu Biologics, Prometheus Biosciences, Takeda, Palatin Technologies). Grant support (Janssen).

Date repository:

Our original data including raw genetic data and metadata is available at github (<https://github.com/mcgovernlab>).

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had both WES and genotyping data. We defined patients at genetically high risk for TED if they had a high TED PRS or carried at least one TPV.

**Results:** We identified 122 out of 792 IBD patients (15.4%) as genetically high risk for TED. Among 715 out of 792 subjects whose documented TED status were available, 63 of the 715 patients (8.8 %) had TED events. Genetic TED risk was significantly associated with increased TED event (OR = 2.5, P = 0.0036).

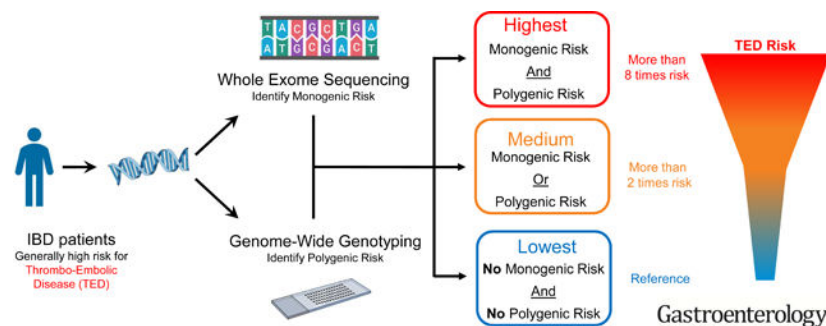
Additionally, we confirmed an additive effect of monogenic and polygenic risk on TED (P = 0.0048). Patients with high TED genetic risk more frequently had thrombosis at multiple sites (78 % vs 42 %, OR = 3.96, P = 0.048).

**Conclusions:** Genetic risk (both poly- and monogenic) was significantly associated with TED history. Our results suggest that genetic traits identify ~1 in 7 IBD patients who will experience 2.5-fold or greater risk for TED.

## LAY SUMMARY

Our analyses demonstrated that approximately 1 in 7 inflammatory bowel disease patients are at around 2.5 times higher risk of developing Thrombo-embolic disease.

## Graphical Abstract



## Keywords

Genetics; Inflammatory Bowel Diseases; Thrombosis

## Introduction:

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing inflammatory conditions of the gastrointestinal tract<sup>1</sup>. The incidence of IBD is increasing with a prevalence of over 1.3% in the US<sup>2</sup> and a global prevalence that surpasses 0.3%<sup>3</sup>. Patients with IBD are reported to have 3 – 4 fold increased risk of thrombo-embolic disease (TED) and the most significant cause of mortality in IBD remains TED<sup>4</sup>. This increased risk appears to be unique to IBD, as other chronic inflammatory diseases such as rheumatoid arthritis and celiac disease do not confer this risk<sup>5</sup>. More recently, TED also has been identified as a potential complication of JAK inhibition a mechanism of action recently approved for treating UC patients, which is now under FDA boxed warning for increased risk of thrombosis-associated morbidity and mortality. Due to

the impact of TED on IBD prognosis and therapeutic management, developing methods to identify IBD patients at high risk for TED is an urgent clinical issue.

A number of factors may influence increased TED risk, including disease activity, hospitalization, age, pregnancy, medications, surgery, and genetics<sup>6–10</sup>. Previous reports for genetic risks of TED in IBD patients have mainly focused on monogenic variants, such as Factor V Leiden deficiency<sup>10, 11</sup>. However, a recent study reported that risk of TED in the general population is influenced not only by monogenic risk, which classify individuals based on the presence or absence of discrete large effect variants, but also polygenic risk, which refers to the effect of numerous loci, often of small individual effect, across the genome. In a study containing two very large population cohorts, a combination of polygenic risk score (PRS, that aggregates multiple genetic TED risk variants) with two monogenic variants (Factor V Leiden deficiency and prothrombin G20210A mutation) delineated 10% of individuals with a ~2.5-fold increased likelihood of developing TED compared to non-high risk controls<sup>12</sup>. However, the prevalence and effects of polygenic and monogenic risk of TED in IBD patients has not previously been studied.

As the genetic etiology of TED becomes increasingly understood and the cost of genotyping/sequencing continues to decrease, the assessment of TED risk through genetics is becoming a viable clinical tool. If IBD patients with elevated risk of TED can be identified through genetic testing, there exists the potential to optimize drug therapy and the precise risks and benefits of anticoagulation prophylaxis can be considered on a personalized basis. To address this potential, the present study utilized whole exome sequencing (WES) to assess monogenic risk together with genome-wide genotyping to data to determine the proportion of IBD patients genetically at elevated risk for TED and investigate the effect of this risk on thrombotic events in IBD patients.

## Methods:

### Study design and subjects:

The study design is summarized in Figure 1. Samples were genotyped as part of the NIDDK IBDGC genotyping efforts. 11,584 samples were available following stringent quality control (details below), of which n=2,452 samples were recruited at Cedars-Sinai Medical Center (CSMC). The whole exome sequencing (WES) cohort consists of 3,198 subjects recruited at CSMC and 340 subjects provided to CSMC by the National Laboratory for the Genetics of Israeli Populations; all samples were sequenced at the BROAD Institute (see below). Admixture<sup>13</sup> analysis was used to calculate ethnicity proportion estimations for all individuals. Only subjects identified by admixture as European ancestry [EUR proportion 0.70] were included in the further analyses.

792 Cedars-Sinai European ancestry IBD cases had both whole genome genotyping and WES data available. IBD was defined on the basis of clinical symptoms as well as standard endoscopic, radiographic, and histological findings. Detailed clinical data, including patient gender, age at diagnosis, disease location and behavior (according to the Montreal Classification), surgical history, family history of IBD and thrombo-embolic disease (TED) history were available in 715 cases and was collected from the medical

records by two phenotypers (S.Y and L.A) who were blinded to the patients' genotype information. The Institutional Review Board of Cedars-Sinai Medical Center approved the study, and all patients provided written informed consent.

### **GSA genotyping, QC and imputation:**

Samples were genotyped on the Illumina Global Screening Array (GSA) at Feinstein Institute for Medical Research or at the Broad Institute in Massachusetts. Pre-imputation SNP QC metrics were applied for 700,078 SNPs including exclusion of non-autosomal markers and variants with MAF <1%, genotyping missingness >3% and deviation from Hardy-Weinberg equilibrium in controls  $P < 1 \times 10^{-6}$ . A total of 11,584 samples (8,984 IBD and 2,600 control) passed sample quality control, which included exclusion of samples with genotyping call rate <95%, gender discrepancies, duplicated samples, EUR proportion < 0.70, ambiguous disease information and sample permission use restrictions. Genotypes were phased using Eagle v2.3<sup>14</sup> and imputation was performed using the Michigan Imputation Server<sup>15</sup> per instructions and HRC r1.1<sup>16</sup> reference panel. Variants with estimated imputation accuracy (Rsq) <0.3 were excluded post-imputation prior to analyses. In total, 10,357,915 SNPs passed variant QC.

### **PRS calculation and normalization:**

Among 297 variants reported in the TED PRS<sup>12</sup>, 265 variants were available in our imputed GSA cohort. Using these 265 variants we generated the TED PRS using PLINK v2.00a software<sup>17</sup> for 2,600 controls and 8,984 IBD cases. We normalized PRS into Z-score and defined the top 5% normalized PRS among healthy control group as threshold.

### **Whole Exome-sequencing:**

Paired-end WES was performed based on Illumina platform with 20X reading depth in 3,538 subjects. Reads alignment to the human reference genome GRCh37 were performed using BWA and variant calling were performed based on GATK best practices. Individual variants with Genotyping Quality (GQ) < 65, depth (DP) < 20, Strand Odds Ratio (SOR) > 3 or call rate < 95% were removed. For SNPs, variants with ReadPosRankSum < - 4 or Fisher Strand filter (FS) > 60 were also removed. For indels, variants with ReadPosRankSum < - 20 or FS > 200 were also removed. In total, 3,349,656 variants passed QC. Samples with a mean genotype quality (GQ) < 65, a depth < 25, a genotype rate < 96.5%, or a transition/transversion (Ti/Tv) ratio < 2.5 were removed from further analysis. Individuals of ambiguous disease information were removed. Individuals of ambiguous imputed sex or imputed sex inconsistent with reported sex were also removed. A total of 3,309 samples (2590 IBD and 719 controls) passed QC.

### **Thrombophilia pathogenic variants extraction:**

Utilizing CLINVAR "Pathogenic" or "Likely Pathogenic" classification<sup>18</sup> we extracted variants located within 15 blood clotting related genes yielding a total of 7 different thrombophilia pathogenic variants (TPV) (Supplementary Table 1 and Table 2). All QC and variant annotation was performed using Hail (Hail Team. Hail 0.2.36-ed011219dd93 <https://github.com/hail-is/hail/releases/tag/0.2.36>).

**Definitions:**

We defined patients at high genetic risk for TED if they had a TED PRS more than the top 5% of the control population distribution or carried at least one TPV. This aligns with the report that individuals within the top 5% of the TED PRS have a ~2.5-fold increased risk of VTE relative to the rest of the population which is similar to the risk attributed to the presence of monogenic variants<sup>12</sup>. Disease activity at the time of TED for Crohn's Disease was measured by the Harvey-Bradshaw Index (HBI) and colonoscopy report at the time of clotting event (when available). Patients were considered to have active disease if they had HBI scores greater than or equal to 5 and/or endoscopy showed active disease, Disease activity at the time of TED for Ulcerative Colitis was evaluated by the full Mayo score. A full Mayo score above 2 was considered as active disease. Smoking status was defined as either currently smoking, past smoker, or never smoker as assessed at the most recent clinical visit. Patients who had history of IBD surgery were defined as having history of IBD related surgery (colectomy for UC and any bowel resection for CD) from their disease onset to last time of follow up. Hospitalization for any reason within 3 months before TED event and use of oral contraceptive pills (OCP) at the time of TED event was investigated. The use of any biologic therapy at the time of TED event were also investigated. Patients with TED were defined as patients who had a history of venous thrombosis at any site identified by ultrasonography or computed tomographic scanning. If patients had multiple episodes of TED events in their disease course, we considered the 1st time of TED in terms of time of TED event.

**Statistical Analysis:**

Fisher's exact test (two-sided) was used to explore associations of categorical data in Table 1 and Table 2. Unpaired t test was used to explore quantitative data between two groups in Table 1 and Table 2. For the multivariate model in Table 1 and Supplementary Table 4, logistic regression with all univariate risk factors with a p value < 0.05 were included together in the multivariable logistic regression model along with the first two principle components. Linear trend test in logistic regression with age at last visit, history of IBD surgery, and the first two principle components was performed for Figure 2. Logistic regression with age at last visit, history of IBD surgery, and the first two principle components was performed in Figure 3. Logistic regression was performed with the first two principle components in Supplementary Table 5 and Supplementary Table 6. A p value of <0.05 was considered statistically significant. All statistical analyses were performed with R software (version 3.6.1) [<http://www.rproject.org/>].

**Results:****Prevalence of IBD patients who are genetically high risk at TED;**

Among the 792 IBD subjects with both PRS and WES data, 49 subjects had a high PRS and 82 subjects carried at least one variant among the 7 identified TPVs, including Factor V Leiden, and the prothrombin G20210A mutation (Supplementary Table 2 for full list of TPVs). In total, 122 out of 792 IBD patients (15.4%) were identified as genetically 'high risk' for TED.

### **Difference of TED genetic risk among IBD and controls;**

There was no difference in: TED PRS distribution; frequency of Factor V Leiden mutation; and frequency of prothrombin G20210A mutation between 8,984 IBD cases and 2,600 controls ( $P = 0.84, 0.26, \text{ and } 0.94$  respectively; Supplementary Table 3).

### **Effect of genetic risk on TED event in multivariate model;**

Among the 792 subjects with WES and genotyping data, detailed longitudinal clinical information on TED events was available for 715 subjects (109 high risk and 606 non risk patients). In total, 63 of the 715 patients (8.8 %) had a documented TED event. TED patients had significantly longer disease duration (23.7 years vs 19.8 years,  $P = 0.034$ ), were older at IBD onset (30.1 years vs 23.7 years,  $P = 0.0075$ ) and were more likely to have had IBD surgery (OR = 2.36,  $P = 0.0045$ ). No other demographic or clinical factors were statistically associated with TED (Table 1). After adjustment for age, disease duration and history of IBD surgery, genetic TED risk was significantly associated with increased TED event (OR = 2.5,  $P = 0.0036$ , Table 1). Additionally, after adjusting multicollinearity between disease duration and age at disease onset, both high PRS and carriage of TPV were independently associated with TED, respectively (OR = 3.13,  $P = 0.0070$  and OR = 2.11,  $P = 0.042$ , Supplementary Table 5B).

### **Additive effect of genetic risk on TED event in IBD;**

We subsequently confirmed an additive effect of genetic risk on TED: patients with both a high PRS and carrying pathogenic variants are at the highest risk of TED; patients who have one risk factor (either high PRS OR carriage of a TPV) were medium risk: and patients without either of these genetic risk factors were at lowest risk (43 %, 15 % and 7 % respectively,  $P = 0.0048$ ; trend test) (Figure 2). Among patients with medium risk, patients with PRS had slightly higher risk than patients with TPV only (OR = 2.8 vs 1.8, respectively, Figure 3).

### **Characteristic of patients with genetic risk within TED cases;**

Patients with high TED genetic risk tended to have shorter time from IBD onset to TED event (11.62 years vs 18.91 years,  $P = 0.086$ ) and were more likely to have thrombosis documented at multiple sites (78 % vs 42 %, OR = 3.96,  $P = 0.048$ ) (Table 2). Among these 2 groups, disease activity at the time of TED, hospitalization within 3 months before TED and surgery before TED were not significantly different between the two 2 groups. Patients with high TED genetic risk were more likely to have received biologics (71% vs 37%, OR = 3.95,  $P = 0.024$ ). Biologics have previously been reported to have protective effect<sup>19, 20</sup> on TED.

### **Discussion:**

By aggregating whole genome genotyping and WES data, our analyses demonstrate that ~1 in 7 IBD patients have odds 2.5 times higher than non-genetically high risk IBD patients for experiencing TED. Higher genetic 'risk' was associated with TED events suggesting that these IBD patients may warrant more aggressive prophylaxis against TED and also might be subjects in whom JAK inhibitors may need to be used judiciously. TED PRS

and TPV were independently associated with TED and also have additive effects on TED events. Furthermore, our analysis within TED cases suggests genetic risk also affects disease severity of TED. Although the number of patients who 'carry' both PRS and TPV risks is small (7 patients), three developed TED at multiple sites and at a young age (mean 27.5 years).

The prevalence of TED in our IBD cohort was 8.8 %, consistent with previous findings<sup>21</sup>. The risk of TED in IBD patients is reported to be 3 to 4-fold higher compared to the general population<sup>6</sup>, which is attributed to risk factors including disease flare, extended disease location, and steroid use<sup>22</sup>. Our study confirmed long disease duration, older age at IBD onset and history of IBD-related surgery are risk factors for TED. Disease duration and age at onset are strongly associated with age at last visit to hospital (Supplementary Figure 1A and 1B). If we include all these 3 parameters into multivariate model, all of them became nonsignificant because of multicollinearity. Variance inflation factors (VIF) of age at last visit, disease duration and age at diagnosis in the model are 26.50, 13.65 and 17.11, respectively, which indicates strong multicollinearity among these variables (Supplementary Table 4A). If we combined disease duration or age at IBD onset with age at last visit, only age at last visit remains significant (Supplementary Table 4B and 4C). Age at last visit approximates current age, therefore, our study suggests older age, a well-established risk factor for TED, is the significant demographic risk factor for TED history<sup>23, 24</sup>. We also confirmed that history of IBD-related surgery was significantly associated with TED history (OR = 3.95 and 2.54 for colectomy history in UC and bowel resection for CD respectively). Importantly, this effect was independent from time-dependent parameters. IBD-related surgery has previously been reported to be one of the established risk factors of TED in multiple studies with a higher risk observed in UC cases requiring colectomy than CD-related surgeries<sup>25, 26, 27, 28</sup>. The elevated risk of UC-related surgeries probably reflects, in part, the higher inflammatory burden and perhaps this is a population in whom an increased understanding of genetic risk might have the largest impact. Importantly, genetic factors remained significant even after adjusting for age at last visit and history of IBD-related surgery, (Supplementary Table 5A and 5B).

In the within TED patients analyses (Table 2), we found that a high proportion of patients (74 %) had active disease at the time of TED event which is consistent with previous reports including in a single-center retrospective study, where 71% of IBD patients were found to have active disease at the time of the TED event<sup>29</sup>. Additionally, nearly half (47 %) of patients had experience of hospitalization within 3 months before TED event. These factors were not different between patients with or without genetic TED risk. Our results support prior evidence that active disease and hospitalization are risk factors of TED<sup>4, 6, 30</sup>, and demonstrate that these are independent from genetic risk. In our cohort, very few patients had undergone IBD-related surgery within 6 months before TED event, were taking OCPs at the time of TED (table 2) and no one was receiving prophylactic warfarin nor JAK inhibitor at the time of TED. Interestingly, patients with genetic risk of TED were receiving biologics more frequently than those without genetic risk at time of TED, whereas disease activity was not different between the 2 groups. Generally, biologics have been reported to have protective effect on TED<sup>19, 20</sup> suggesting that our findings may have underestimated the effect of genetic variation on TED risk. Finally, we found patients with genetic risk had



multiple site TED more frequently than those without genetic risk, which may indicate a more aggressive course of TED.

We did not find an elevated PRS TED distribution in IBD compared to controls. Additionally, the frequency of the two major TPVs (factor V Leiden and prothrombin G20210A mutation) were not elevated in IBD, consistent with previous studies<sup>21 10</sup>. Thus, elevated genetic burden of TED risk does not alone explain the increased risk of TED in IBD patients (Supplementary Table 3).

The relationship between TPVs and disease behavior or extent in IBD has not previously been studied and any relationship is important for interpreting our findings. We observed no association between elevated genetic burden (carriage of TPV and high PRS) and disease behavior and extent of disease (Supplementary Table 6 A and B).

In our analyses, access to WES enabled us to also include 'rare' TPVs beyond factor V Leiden and prothrombin G20210A mutation. As shown in Supplementary Table 2, we identified 5 out of 13 (38%) TED patients with 'other' TPVs suggesting that including only factor V Leiden and Prothrombin variants would miss over one third of 'monogenic' TPVs. Thus, looking at both common and rare TPVs is necessary for a more comprehensive estimate of monogenic TED risk. Furthermore, the additive effect we have shown here suggests that an accurate estimation of genetic risk requires both TPV and PRS assessment and that PRS may define a higher TED risk than TPVs alone.

With decreasing costs of sequencing and moves towards genomic medicine, it is likely that increasing numbers of people will have their genome sequenced making 'routine' integration of genetic risk assessment for various traits including TED possible. Our data suggest that ~1 in 7 IBD patients is at higher risk of TED and those IBD patients are at around 2.5 times increased risk of TED. Considering the relatively high prevalence of genetic risk and the fact that TED can lead to significant morbidity and even mortality, 'routine' screening of TED genetic risk for IBD patients may beneficially impact these poor outcomes. Further studies are warranted including, perhaps, randomized controlled trials of prophylactic anticoagulation in IBD patients at high risk of TED stratified by 'genetic risk.' With likely increasing availability of these types of data the IBD community requires the development of guidelines and strategies to determine whether these patients should be counseled about long term TED prophylaxis and also whether drugs such as JAK inhibitors should be used cautiously or avoided in this setting.

Our study has limitations. First, since our study is a retrospective study and there are some missing clinical information such as corticosteroid use, indwelling catheters, and family history of TED. Thus, it is difficult to estimate accurate effects of some clinical factors on TED. Second, since not all variants of TED PRS were available in our study, the result might be slightly different if all variants were included although if this has had an effect it is likely to have underestimated the true genetic contribution to TED. Third, since our study is a single centered analysis, the number of subjects is relatively small and additional cohorts will need to be studied. In addition, as is the case with the majority of genetic studies currently, our study is limited to European ancestry subjects and future studies will

be needed in other populations so that the benefits of Precision Medicine approaches such as the one described are available to all parts of society.

In conclusion, we have demonstrated that ~1 in 7 IBD patients are genetically at a higher risk for TED, and genetic risk is independently associated with TED events when adjusting for time-dependent parameters and IBD-related surgery. For comprehensive ‘prediction’ of genetic risk of TED both monogenic and polygenic approaches are needed. To our knowledge, this is the first report suggesting benefits for clinical decision making in IBD through combining both WES and whole genome genotyping. With increased interest in genomic sequencing/genotyping for clinical utility our findings suggest that strategies for managing patients at high risk of TED identified through genetic approaches should be developed.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## WHAT YOU NEED TO KNOW

### Background and Context:

Patients with inflammatory bowel disease (IBD) are at high risk of Thrombo-embolic disease (TED); however, prevalence and effect of genetic risk of TED in IBD remains unknown.

### New Findings:

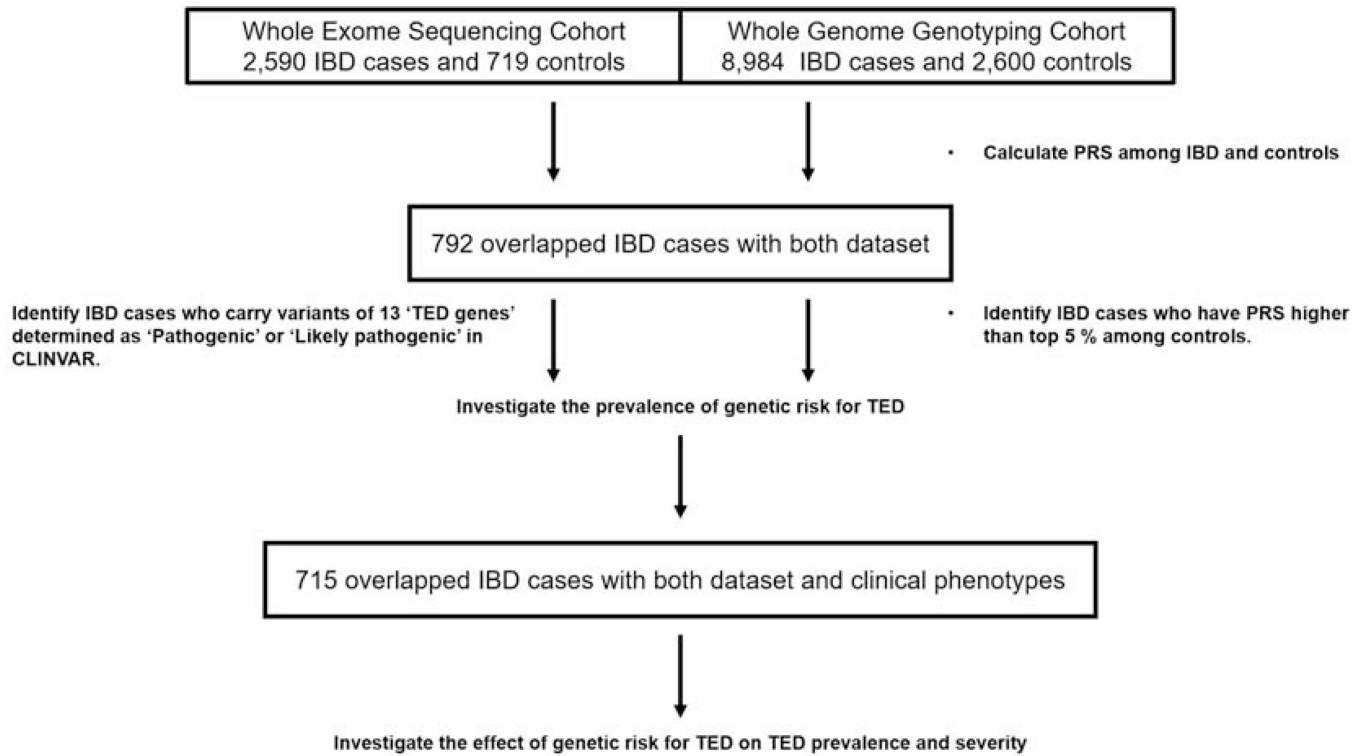
By aggregating whole exome sequencing (WES) and whole-genome genotyping data, we identified that ~1 in 7 IBD patients are genetically at around 2.5 times higher risk for TED. Genetic risk was significantly related with increased risk of TED events and there was an additive effect of monogenic and polygenic risks.

### Limitations:

Number of cases in our study was limited (N = 792). Thrombo-embolic events were determined retrospectively by chart review blinded to genetic status.

### Impact:

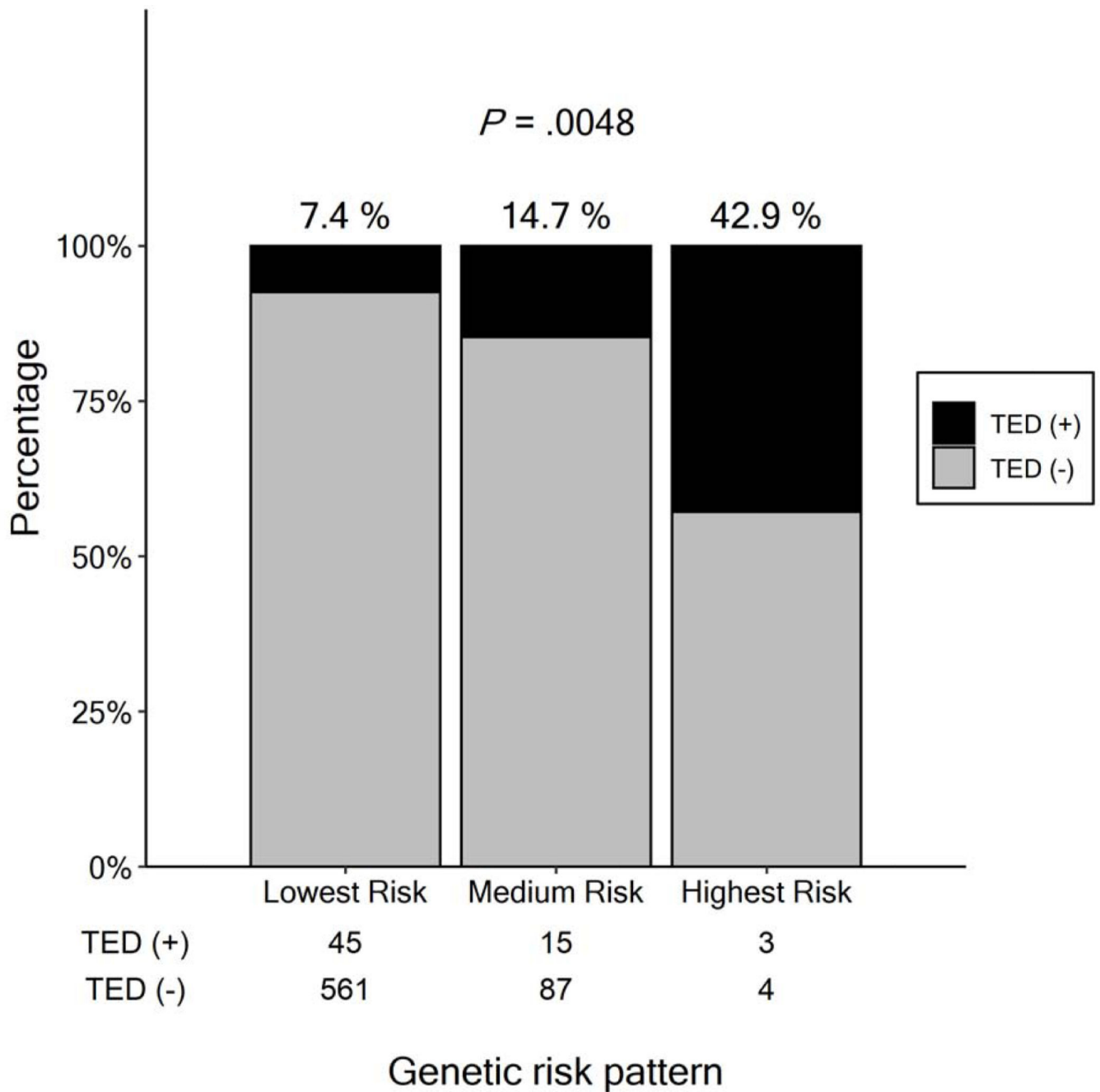
We found that more than 15 % of IBD patients are at higher risk of TED. Genetic test by combining monogenic and polygenic risk can identify IBD patients with higher risk of TED. WES provides a more comprehensive evaluation of genetic risk in IBD.



**Figure 1. Study design and cohorts.**

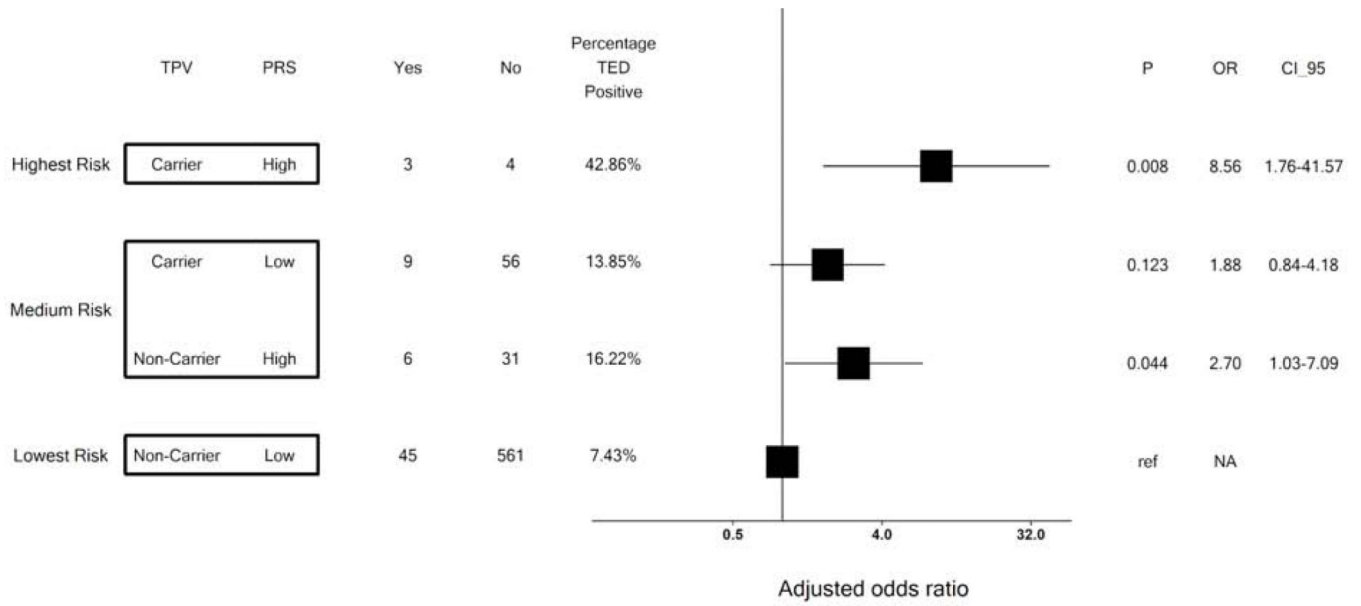
'Flow' of study and outline of study cohorts. Detailed information is described in the methods section.

IBD, Inflammatory bowel disease; PRS, Polygenic Risk Score; TED, thrombo-embolic disease



**Figure 2. Percentage of TED events in each Genetic Risk Group.**

The percentage of patients with thrombo-embolic disease (TED) in each group. X-axis shows classification of genetic risk for TED (“Lowest Risk”: patients without genetic risk; “Medium Risk”: patients who have one risk, either high PRS OR carriage of a TPV; “Highest Risk”: patients who both high PRS and a TPV). The numbers below each bar represents number of TED positive and negative cases in each group. P value was calculated by trend test.



**Figure 3. Risk of TED by monogenic and polygenic risk status.**

Patients were stratified into two groups according to their polygenic risk score (PRS) — high or low defined as more than the top 5% of the control population distribution or the other 95%, respectively. For carriers and non-carriers of thrombophilia pathogenic variant (TPV) in each PRS group, the p value and odds ratio (OR) for thrombo-embolic disease (TED) were calculated in a logistic regression model with age at last visit and the first two principal components as covariates. Non-carriers with low PRS served as the reference group. Each black square represents mean of OR in each group and horizontal line around each square represents the 95% confidence.



**Table 1.**

Univariate and multivariate models of associations of Thrombo-embolic Disease (TED) history.

	TED = No	TED = Yes	Univariate P value	Multivariate P value	OR	95%-CI
N	652	63				
Disease type						
CD	511 (78.37%)	46 (73.02%)	0.3408			
UC	129 (19.79%)	16 (25.4%)	0.3240			
IBDU	12 (1.84%)	1 (1.59%)	1.0000			
Gender						
Male	349 (53.53%)	32 (50.79%)	0.6935			
Female	303 (46.47%)	31 (49.21%)				
Age at IBD onset (year)	23.77 +- 12.74	30.11 +- 17.83	0.0075	0.0001	1.04	1.02–1.06
Disease duration (year)						
	19.83+-11.65	23.74+-13.87	0.0340	0.0083	1.03	1.01–1.05
A1	173 (34.06%)	12 (26.09%)	0.1515			
A2	287 (56.5%)	27 (58.7%)	0.6424			
A3	48 (9.45%)	7 (15.22%)	0.3119			
Subjects missing age at onset data	3	0				
Disease location						
L1	66 (13.15%)	2 (4.35%)	0.1015			
L2	61 (12.15%)	5 (10.87%)	1.0000			
L3	375 (74.7%)	39 (84.78%)	0.1121			
L4	85 (16.63%)	7 (15.22%)	1.0000			
Subjects missing disease location data	9	0				
Disease behavior						
B1	183 (36.31%)	12 (26.09%)	0.2008			
B2	253 (50.2%)	27 (58.7%)	0.2340			
B3	192 (38.1%)	25 (54.35%)	0.0600			
Subjects missing disease behavior data	7	0				
Perianal disease	296 (57.93%)	28 (60.87%)	0.7565			
Disease extent						
E1	12 (9.68%)	0 (0%)	0.3620			
E2	41 (33.06%)	4 (25%)	0.7762			
E3	71 (57.26%)	12 (75%)	0.1811			
Subjects missing disease extent data	5	0				
Extensive disease (E3 or L3)	446 (69.91%)	51 (80.95%)	0.1296			
Smoking status						
Current smoking	141 (22.63%)	16 (26.67%)	0.5203			
Past smoking	38 (6.1%)	5 (8.33%)	0.4148			
Never smoking	444 (71.27%)	39 (65%)	0.3024			
Subjects missing smoking data	29	3				

	TED = No	TED = Yes	Univariate P value	Multivariate P value	OR	95%-CI
IBD family history	200 (31.6%)	13 (21.67%)	0.1425			
Subjects missing IBD family history data	19	3				
Surgery history						
IBD-related bowel surgery	375 (57.52%)	48 (76.19%)	0.0045	0.0120	2.24	1.19–4.20
CD-related bowel surgery	333 (65.17%)	38 (82.61%)	0.0147			
Colectomy in UC	38 (29.46%)	10 (62.5%)	0.0116			
Genetic risk (high)	91 (13.96%)	18 (28.57%)	0.0050	0.0036	2.5	1.35–4.64

Data are presented as means  $\pm$  standard deviation (range), or n (%).

UC, ulcerative colitis; CD, Crohn's disease; IBDU, Inflammatory bowel disease undetermined;

**Table 2.**

Characteristics of IBD patients with TED events.

	Low risk	High risk	P value
N	45	18	
Female	21 (46.67%)	10 (55.56%)	0.5850
Male	24 (53.33%)	8 (44.44%)	
Interval from IBD onset to TED (year; mean $\pm$ SD)	18.91 $\pm$ 13.97	11.62 $\pm$ 14.21	0.0863
Age at TED (year; mean $\pm$ SD)	45.45 $\pm$ 17.24	50.58 $\pm$ 18.84	0.3441
Active disease at TED	25 (71.43%)	10 (83.33%)	0.7027
Subjects missing disease activity data	10	6	
Hospitalization within 3 months before TED	14 (41.18%)	8 (61.54%)	0.3279
Subjects missing hospitalizations data	11	5	
Current smoking	13 (30.95%)	3 (16.67%)	0.5224
Past smoking	4 (9.52%)	1 (5.56%)	1.0000
Never smoking	25 (59.52%)	14 (77.78%)	0.1516
Subjects missing smoking data	3	0	
IBD-related surgery within 6 months and prior to TED	2 (5.41%)	0 (0%)	1.0000
Subjects missing surgery data	8	3	
Women taking OCP at time of TED	4 (22.22%)	0 (0%)	0.2800
Subjects missing OCP data	3	1	
Biologic use at the time of TED	16 (37.21%)	12 (70.59%)	0.0244
Subjects missing biologic use data	2	1	
Multiple sites of TED	19 (45.24%)	14 (77.78%)	0.0447
Subjects missing multiple sites data	3	0	
Number of sites	2.15 $\pm$ 2.23	3.33 $\pm$ 3.44	0.2343

Data are presented as means  $\pm$  standard deviation (range), or n (%).

Percentage of OCP represents percentage within females.

TED, thrombo-embolic disease; High risk, genetically high risk for TED; Low risk, genetically low risk for TED; IBD, inflammatory bowel disease; OCP, oral contraceptive pills; Biologics, Infliximab, Adalimumab or Certolizumab.