

A fast AI-based variant prioritization system for NGS data in the context of inherited disease analysis

### Introduction

There are about 480 million people who suffered from inherited diseases. The incidence of inherited diseases is 6%. The number of newborn babies is about 120 million every year, indicating 7.2 million rare disease patients increased every year. A total of 6,172 known rare diseases have been identified and 85% of rare diseases are caused by altered genes.

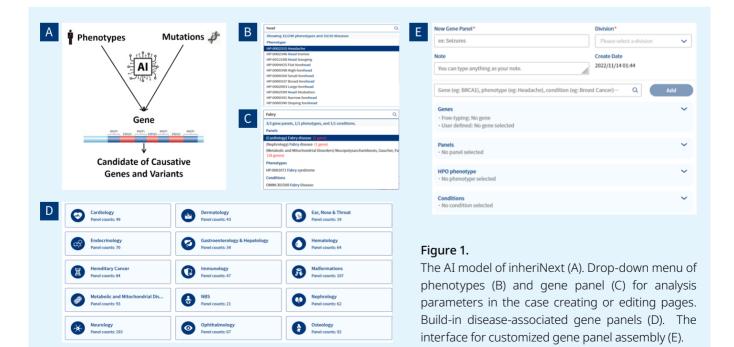
The declining cost of next-generation sequencing brings genetic testing to a mainstream approach for rare disease diagnosis. However, the interpretation of genetic testing results is time-consuming, which takes about 3.5 hours for geneticists or doctors to study a case. InheriNext saves 70% of the time and extremely reduces the cost of such resources. InherNext will be your good partner in healthcare institutes and genetic test companies.



## Leverage AI to inherited diseases

InheriNext is an AI-based variant prioritization system for NGS data (VCF or FASTO files). InheriNext provides accurate candidates and diverse functionalities for inherited disease analysis in a few minutes and extremely reduces the burdens for geneticists. InheriNext brings two AI-based variant prioritization approaches. Users could use either HPO-based phenotypes or gene panels to obtain candidates for SNPs and INDELs (Figure 1A-D). A customized panel designer allows users to assemble frequently used phenotypes or genes into a customized panel (Figure 1E).

InheriNext dedicatedly designed a user-friendly interface. Users could quickly learn to use and interpret analysis results in a short time. The analysis parameters are shown at the top of the case page to bring a quick review of parameters (Figure 2A). The phenotype analysis results show in Figure 2B and provide several annotations, such as HGVS, conditions, phenotype network, ClinVar, automated ACMG and dbSNP. For the prediction scores and population databases, inheriNext provides up to 14 and 11 annotations, respectively (Figure 2C and D). The phenotype network shows the distance of phenotype similarity between sample phenotypes and disease-associated phenotypes. ClinVar plays a

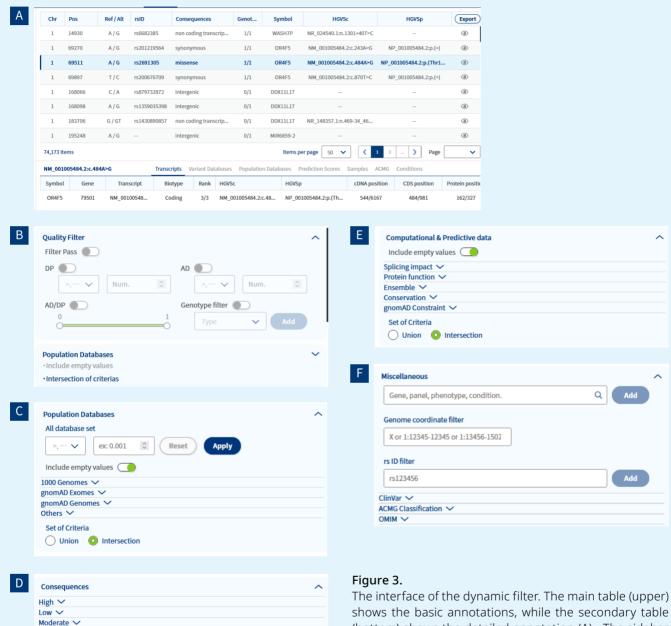


critical reference during the analysis. InheriNext not only provides interpretation, review status, condition and conflict from ClinVar but also tabulates metrics between consequences and interpretation for each gene (Figure 2E). This could tremendously assist users to infer the pathogenicity according to consequences. The American College of Medical Genetics and Genomics (ACMG) published a guideline to classify variants based on 28 criteria (2015). However, the determination of these criteria is a labor burden. InheriNext implements up to 17 ACMG automated criteria and elaborates reasons for those criteria to save time for users (Figure 2F). In addition, the Proactive analysis is implemented and automatically filters pathogenic, null, carrier and ACMG secondary findings variants (Figure 2A). In summary, users could adopt these comprehensive annotations to determine the likely causative variants.

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Functional Data       BS3 ①       PP4 ①       PP3 ②       Cutoffs (A). Interface of candid genes (B). User could fur click the prediction score, point click the prediction score	Functional Data       B53 ①       PP4 ①         Other       BP6 ①       PP4 ①         Automated criteria       Explanation         BP1: Supporting       The pathogenicity of the gene region influenced by the missense variant was known to be caused by primarily truncation.       Cutoffs (A). Interface of candid genes (B). User could fur click the prediction score, prolation database (1K EAS/gnore EAS), ClinVar and ACMG colution         PP2: Supporting       RVR1 was reported to have a low rate of benign missense variants are a common mechanism of the disease.       EAS), ClinVar and ACMG colution to obtain details in the poly pages (C-F).         PP3: Supporting       MetaSVM score and GERP++RS support a deleterious effect on the gene or gene product.       to obtain details in the poly pages (C-F).	NM_000540.3:c.14 Reset Strength of Evid Population D Allelic Evidenc Cosegration I	217 42046>A 40046>A 40046>A 40046>A 40046>A 40046>A 40046A 4004004A 40046A 40040040000000000	137 Ber Strong	nign Criteria Suppor	ting ( ① ( ① ( ①)	Uncerta Supporting	In significance Path Moderate PM2 ( PM2 ( PM3 ( PM3 ( PM6 ( PM1 (	iogenic C	riteria Strong PS4 ①		1,127 Rules	Fi Th re te	ne interf sults. Ca rs are sh ages, suc	ase ana Iown at h as phe	alysis p the top enotype	oara o of es, g
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Other       Image: PP6 (C)        Image: PP6 (C)	Other       Image: PP4 (I) (Image: PP4	NM_000540.3::.14 Reset Strength of Evid Population D Allelic Evidenc Cosegrgation I	217 42046>A 42046A 420604A 4206A 42046A 4206A 42046A 4206A 4206A 4206A 4206A 4206A 4206A 420604A 4206A 4206A 42064A 420604A 420604A 42060404A 42066A 42066A 4200	137 Ber Strong	nign Criteria Suppor	ting 2 ① 3 ① 4 ① 4 ①	Uncerta Supporting	Pati Moderate PH2 ( PH2 ( PH2 ( PH3 ( PH4 ( 2 PH4 ( 2 PH4 ( 2 PH4 (	iogenic C	riteria Strong PS4 ①		1,127 Rules	Fi Th re te pa pa	ne interf sults. Ca rs are sh ages, suc anels, alla	ase ana Iown at h as phe ele freq	alysis p the top enotype juency	oara o of es, <u>c</u> cut
Automated criteria         Explanation         Click the prediction score, por lation database (1K EAS/gnor PP2: Supporting           PP2: Supporting         The pathogenicity of the gene region influenced by the missense variant was known to be caused by primarily truncation.         Iation database (1K EAS/gnor EAS), ClinVar and ACMG colu to obtain details in the pop	Automated citeria         Explanation           BP1: Supporting         The pathogenicity of the gene region influenced by the missense variant was known to be caused by primarily truncation.         click the prediction score, por lation database (1K EAS/gnor EAS), ClinVar and ACMG colu to obtain details in the por pages (C-F).	NM_000540.3:c.14 Rest Strength of Evid Population D Allelic Evidenc Cosegration f	217 4204G>A 5 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	137 Bet Strong ≥ BA1 ① ≥ BS1 ① ≥ BS2 ① BS4 ①	nign Criteria Suppor	ting 2 ① 3 ① 4 ① 4 ①	Uncerta Supporting	Pati Moderate PH2 ( PH2 ( PH2 ( PH3 ( PH4 ( 2 PH4 ( 2 PH4 ( 2 PH4 (	iogenic C	riteria Strong P54 () P52 () × P51 ()		1,127 Rules	Fi Th re te pa ar	ne interf sults. Ca rs are sh ages, suc anels, alla nd phen	ase ana Iown at h as phe ele freq Iotype/V	alysis p the top enotype juency variants	oara o of es, <u>c</u> cut s s
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PP2: Supporting         RVR1 was reported to have a low rate of benign missense variation and missense variants are a common mechanism of the disease.         EAS), ClinVar and ACMG colu           PP3: Supporting         MetaSVM score and GERP++RS support a deleterious effect on the gene or gene product.         EAS)	PP2: Supporting       RYR1 was reported to have a low rate of benign missense variation and missense variants are a common mechanism of the disease.       EAS), ClinVar and ACMG colu         PP3: Supporting       MetaSVM score and GERP++RS support a deleterious effect on the gene or gene product.       to obtain details in the pop         PM2: Medecate       Absent from controls or at extremely low frequency (<0.5%) in the following database(s): gnomAD AF (7.95539e-06) and ExAC AF	NM_000540.3:c.1 Reset Strength of Evid Population D Allelic Evidenc Cosegrgation I Computation Predictive Da Functional D: Other	217 42046>A 5 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	137 Strong 2 84 () 2 851 () 2 852 () 854 () 853 ()	nign Criteria Suppor BP2 BP2 SBP3 SBP4 SBP4 SBP4	1 (ing) 2 (i) 3 (i) 4 (i) 4 (i) 4 (i) 5 (i) 6 (i) 7 (i)	Uncerta Supporting PP2 () PP3 ()	Pati Moderate PH2 ( PH2 ( PH2 ( PH3 ( PH4 ( 2 PH4 ( 2 PH4 ( 2 PH4 (	iogenic C	riteria Strong P54 () P52 () × P51 ()		1,127 Rules	Fi Th re te pa ar cu ge	ne interf sults. Ca ages, suc anels, alla nd phen atoffs (A). enes (B).	ase ana own at h as phe ele freq ootype/v Interfao User	alysis p the top enotype uency variants ce of ca could	oara o of es, g cut s s andi fur
PP3: Supporting MetaSVM score and GERP++RS support a deleterious effect on the gene or gene product. to obtain details in the pop	PP3: Supporting         Meta5VM score and GERP++RS support a deleterious effect on the gene or gene product.         to obtain details in the pop           PM7: Moderate         Absent from controls or at extremely low frequency (< 0.5%) in the following database(s): gnomAD AF (7.95539e-06) and ExAC AF	NM_000540.3:c.14 Reset Strength of Evid Population D Allelic Evidenc Cosegration I Computation Predictive Da Functional Da Other Automated crit	217 242045-A 5 dence 5	137 Bec Strong S BA1 () S BS1 () BS2 () BS4 () BS3 () xplanation	nign Criteria Suppor BP2 BP5 SBP4 SBP4 SBP4 SBP4 SBP6		Uncerta Supporting PP2 () PP3 () PP3 () PP4 () X PP5 ()	In significance Pati Moderate PM2 ( PM2 ( PM3 (	r contraction of the second seco	riteria Strong P54 () P52 () × P51 () P53 ()		1,127 Rules iry Strong	Fi Th re te pa ar cu ge cli	ne interf sults. Ca rs are sh ages, suct anels, allo nd phen itoffs (A). enes (B). ck the pl	ase ana own at h as phe ele freq notype/v Interfao User redictio	alysis p the top enotype Juency variants ce of ca could n score	oara o of es, <u>o</u> cut s s andia fur e, po
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2 Explore the human genome

InheriNext brings a fully manual filtering function for seasoned users, the dynamic filter (Figure 3). Multiple filtering criteria can be applied, such as variants quality, allele frequency, consequence, chromosome coordinate, gene panel, ClinVar, dbSNP, ACMG classification and mode of inheritance. User-defined filter configurations can be saved, allowing quick adoption of filters for one other analysis.



shows the basic annotations, while the secondary table (bottom) shows the detailed annotation (A). The sidebar allows customized variant filtering with the variant quality (B), population database (C), consequence (D), prediction scores(E) and miscellaneous criteria (F).

Modifier 🗸

Exact match

3 The report system

As long as the preliminary analysis is finished, users could add the likely-causative variants or any variants of interest to the Monitor (Figure 4A). The listed variants in the Monitor can be deleted or changed position with another variant accordingly. To report variants, users could add the "add to report" button in the Monitor. The added variants will be shown in the Report system. The Report system provides several chapters allowing users to choose which chapter is needed to be published (Figure 4B). These chapters include Diagnosis (phenotype and gene filter), Proactive (pathogenic, null, carrier, ACMG SF variants), Pharmacogenetics and Appendix, etc... The report can be reviewed and edited with its descriptions as well (Figure 4C).

H CYP27A1 -	Position (HG38)	Exon/Intron location	HGVSc	HGVSp	Zygosity	Consequence	Prediction scores	1K EAS / gnomAD EAS	Taiwan Biobank	Clinvar	ACMG	
E D Gene Panel Pathogenic Variants Null Variants	Carrier chr2:218 814696G × >C	* 8/9	NM_0007 84.4:c.14 15G>C	NP_0007 75.1:p.Gl y472Ala	het	missense variant	9   15	0.00194175 / 0.0015224	0.003	Conflicting interpretati ons of pathogenic ity	Likely pathogenic	r
	chr2:2188 13095C>T	5/9	NM_0007 84.4:c.10 16C>T	NP_0007 75.1:p.Th r339Met	het	missense variant , splice region variant	12   17	0.000970874 / 0.000108873	N/A	Pathogenic Likely pathogenic	Uncertain significanc e	r
Conditions												
Cerebrotendinous xanthomatosis   AR 🔻												
Edit Section	Report Preview &	Editing									-	•
Patient Information	C									Report	t Date: 2024/08/1	3
Patient Information	S Inheri	iNext.								Sample ID: I	IHN22080103239	5
Diagnosis 🦲	👳 Diagno	osis										
Result Summary			date causative-va	riants. The analy	rsis is based on	the phenotypes of the pa	tient or specific genes.					
Interpretation	The result is	only for clinical refe	rences, and it has	to be interpreted	d by medical p	rofessionals.						
Interpretation	The result is Phenotype :	only for clinical refe Myocarditis; Incre	rences, and it has ased circulating to			rofessionals.						
	The result is Phenotype Gene Panels Gene :	only for clinical refe Myocarditis; Incre Comprehensive	rences, and it has ased circulating to cardiology openicity and corro	roponin I concerr elation has been	ntration	ed on phenotypes, gene p		I genes to disease cand	idates (CPT1A \ C	PT18 × CPT1C × C	PT2), which	
✓ Interpretation CYP27A1 chr2:218814696G>C ●	The result is Phenotype Gene Panels Gene :	only for clinical refe Myocarditis; Incre Comprehensive	rences, and it has ased circulating to cardiology openicity and corro	roponin I concerr elation has been	ntration	ed on phenotypes, gene p		f genes to disease cand	idates (CPT1A 丶 C	PT1B - CPT1C - C	PT2). which	
✓ Interpretation CYP27A1 chr2:218814696G>C ●	The result is Phenotype Gene Panels Gene :	only for clinical refe Myocarditis; Incre Comprehensive	rences, and it has ased circulating to cardiology openicity and corro	roponin I concerr elation has been	ntration	ed on phenotypes, gene p		f genes to disease cand	idates (CPT1A 丶 C	PT1B \ CPT1C \ C	PT2). which	
Interpretation CYP27A1 chr2:218814696G>C CYP27A1 chr2:218813095C>T	Gene ?	only for clinical refe Myocarditis; Incre c Comprehensive he analysis of pathni cludes 1016 gene(s)	rences, and it has ased circulating to cardiology openicity and corro	roponin I concerr elation has been	ntration	ed on phenotypes, gene p		d genes to disease cand	idates (CPT1A × C	PT1B、CPT1C、C	PT2). which	
Interpretation CYP27A1 chr2:2188146966>C CYP27A1 chr2:218813095C>T Proactive Test	The result is Phenotype Gene 1 and Result Surr	only for clinical refe Myocarditis; Incre c Comprehensive he analysis of patho cludes 1016 gene(s) mmary :	rences, and it has ased circulating to cardiology openicity and corro	roponin I concerr elation has been	ntration	ed on phenotypes, gene p		d genes to disease cand	idates (CPT1A、C	PT18、CPT1C、C	PT2]. which	
Interpretation CYP27A1 chr2:2188146966>C CYP27A1 chr2:218813095C>T Proactive Test Result Summary Interpretation	Gene ?	only for clinical refe Myocarditis; Incre c Comprehensive he analysis of patho cludes 1016 gene(s) mmary :	rences, and it has ased circulating to cardiology openicity and corro	roponin I concerr elation has been	ntration	ed on phenotypes, gene p		d genes to disease cand	idates (CPT1A 、 C	PT1B - CPT1C - C	PT2). which	
<ul> <li>Interpretation</li> <li>CYP27A1 chr2:2188146966&gt;C C</li> <li>CYP27A1 chr2:218813095C&gt;T C</li> <li>Proactive Test</li> <li>Result Summary</li> <li>Interpretation</li> <li>No variants have been added yet.</li> </ul>	The result is Phenotype Gene 1 and Gene 1 The Result Sum CYPP2	only for clinical refe : Myocarditis; Incre s: Comprehensive he analysis of pathon cludes 1016 gene(s) mmary : 7A1 sitien	rences, and it has ased circulating to cardiology openicity and corro	roponin I concerr elation has been	ntration executed base of Genes for Dise	ed on phenotypes, gene p	anels, related gene, and	genes to disease cand	idates (CPT1A 、 C rs ID	P	arental	
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<ul> <li>Interpretation</li> <li>CYP27A1 chr2:2188146966&gt;C C</li> <li>CYP2TA1 chr2:218813095C&gt;T C</li> <li>Proactive Test</li> <li>Result Summary</li> <li>Interpretation</li> <li>No variants have been added yet.</li> </ul>	The result is Phenotype Gene 1 and Gene 1 The Result Sur CYP2:	only for clinical refe : Myocarditis; Incre : Comprehensive he analysis of pathon cludes 1016 gene(s) mmary : 7A1 ition G38)	rences, and it has ased circulating to cardiology genicity and corr The full list is in A Exon/Intron	roponin I concen elation has been (ppendix - List of	tration executed base f Genes for Dise VSc VSc Acc1415G> 1	ed on phenotypes, gene p and biagnosis.	Zygosity	Consequence	rs ID	PI	arental Prigin Iknown	
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#### Figure 4.

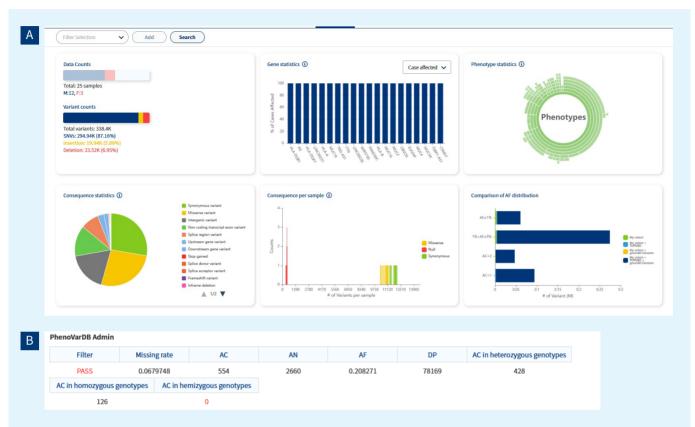
The interface of the Monitor and the Report system. The Monitor section (A). The chapter selection tool in the Report system (B). Preview page of the Report system (C).



The population databases play very important role regarding to the inherited disease analysis. Sometimes, we could find the highly recurrent variants in our dataset which exhibit extremely low AF in public databases. This may suggest that possible artifacts (sequencing or library preparation) or

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population stratifications. Hence, a customized population database is essential. InheriNext implements the PhenoVarDB system to allow users to create their own population databases and annotate to their own cases (Figure 5A and B). The PhenoVarDB is also embedded with community and sharing system destined for creating a huge population database with other cooperators or community users.

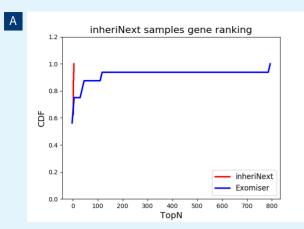


#### Figure 5.

The statistic summary of customized population database (A). The statistic includes sex, variant count, affected case (%), affected gene(%), phenotype distributions, consequences proportion(%), variant counts per sample by consequences and AF distribution against TOPMED and gnomAD databases. A case was annotated by the customized population database which was shown in the pop-up page of population database annotation (B).

# D Performance

To evaluate the overall performance of InheriNext, we compared it with Exomiser using 16 samples. The data demonstrated that inheriNext pinpointed the positives within 10 top-ranked variants for each sample. However, Exomiser exhibited lower performance that some positives were found in hundreds-ranked variants (Figure 6A). This data suggested that InheriNext exhibits higher accuracy compare to the Exomiser. We further compared the performance and functionalities with a commercial product, competitor M. The data demonstrated that inheriNext outperforms competitor M in several functionalities, such as supported file format, independent analysis, gene panel prioritization, proactive analysis, automated ACMG annotations, number of allele frequency annotations, Dynamic filter, custom population database and genomic browser (Figure 6B). For analysis duration, even competitor M declares WES for 2-5 minutes and WGS for 10-15 minutes. However, it takes 1~2 hr for queuing. Therefore, it's hard to judge the analysis duration for inheriNext and competitor M. For the accuracy performance, inheriNext found the positives in the 4 and 1 samples with 1st and 2nd rank, respectively. While competitor M found the positives in the 4 samples with 1st rank but left 1 positive sample without answering. In conclusion, it's hard to judge which one outperforms one other owing to the sample size.



В

	InheriNext	Competitor M
Input file format	Fastq, VCF	VCF
Analysis duration (VCF)	WES : 5~10 min WGS : 15~20 min	WES : 2~5 min WGS : 10~15 min
Variant prioritization performance	1 <sup>st</sup> :4; 2 <sup>nd</sup> :1	1 <sup>st</sup> :4; No result:1
Trio analysis	No (Developing)	Yes
Independent analysis results	3	1
Gene panel prioritization	Yes	No
Proactive analysis	Yes (Pathogenic, Null, Carrier, ACMG IF)	Yes (Carrier, ACMG IF)
Automated ACMG annotation	Yes	No (Manual)
Prediction score annotations	14	17
Allele frequency annotations	11	1
Report	Yes	Yes
Dynamic Filter	Yes	Yes (AF ≥ 2% variants were not showed)
Custom population database	Yes (Summary charts, Community sharing)	Yes
CNV	TXT file download(fastq)	CNV interface
QC metrics	TXT file download(fastq)	QC interface
Genomic browser	8 tracks	5 tracks

#### Figure 6.

The performance comparison of InheriNext. Cumulative distribution of top rank for inheriNext and Exsomiser (A). Comparison table of functionalities and performance between inherNext and competitor M (B).



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