diseaseGPS genetic disorder auxiliary diagnosis system

Manual 1.0

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Sample Patient and Information

Auxiliary Diagnosis System for Genetic disorders

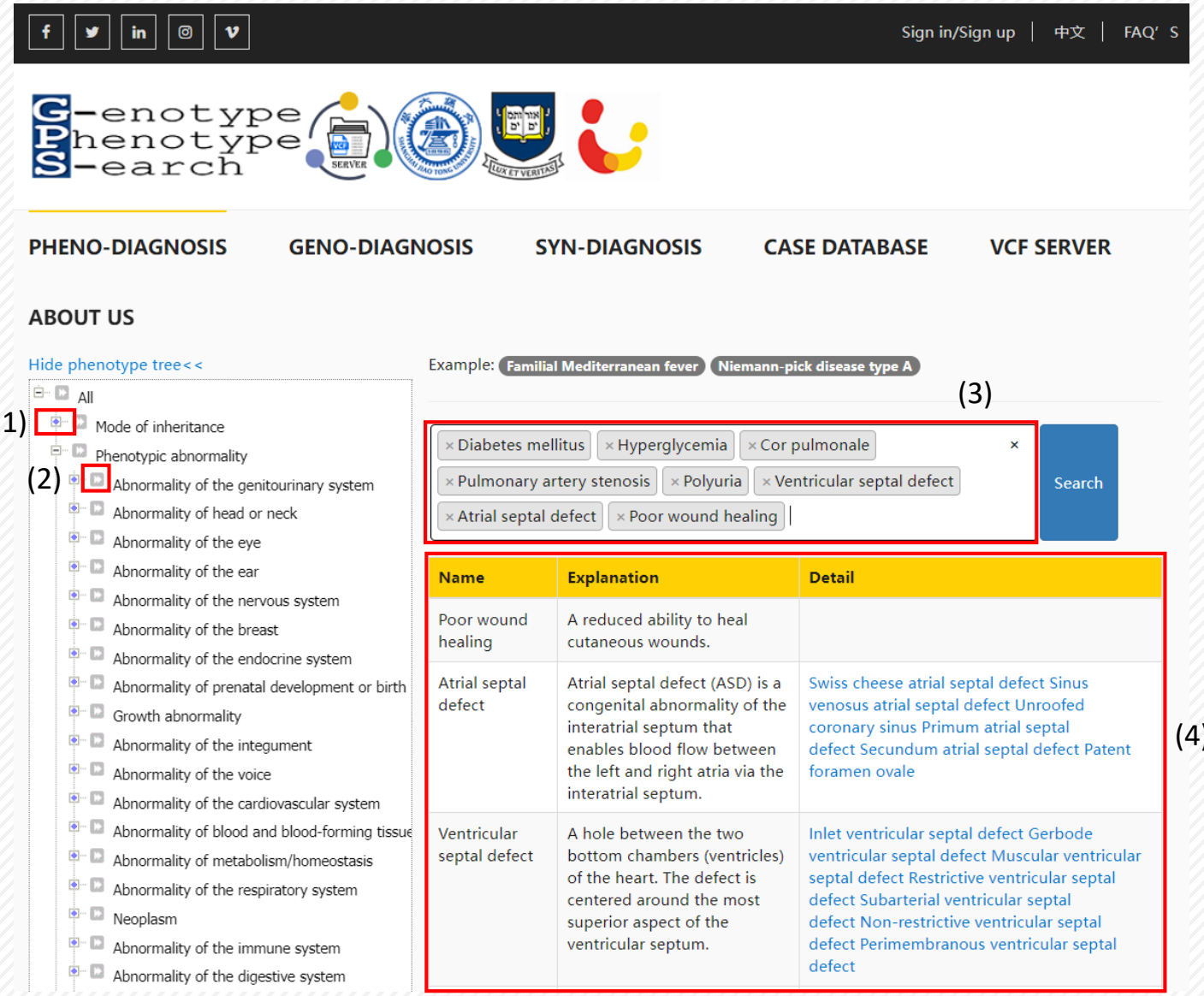
The subsequent process demonstrations have all used this sample patient

- Patient ID: example
- Phenotype: Diabetes mellitus, Hyperglycemia, Cor pulmonale, Pulmonary artery stenosis, Polyuria, Ventricular septal defect, Atrial septal defect, Poor wound healing
- HPO terms: HP:0000819,HP:0003074,HP:0001648,HP:0004415,HP:0000103,HP:0001629,HP:0001631,HP:0001058
- VCF file: example.vcf
- Pathogenic gene: GATA6
- Variants number: 65900→4217(After screening)

- ✓ After the integrated analysis by diseaseGPS, the phenotype score of OMIM:600001 is 0.75, ranking third; the genotype score in OMIM is 1.00, ranking fifth; the final comprehensive score is 0.87, ranking first.
- ✓ Confirmed by the clinical physician, the patient's pathogenic gene is GATA6, and the genetic disorder suffered is OMIM:600001
- ✓ OMIM:600001, HEART DEFECTS, CONGENITAL, AND OTHER CONGENITAL ANOMALIES; HDCA. For more details, please refer to the OMIM database link: https://www.omim.org/entry/600001?search=600001&highlight=600001

Phenotypic Diagnosis

Auxiliary Diagnosis System for Genetic disorders



STEP① Input Phenotype

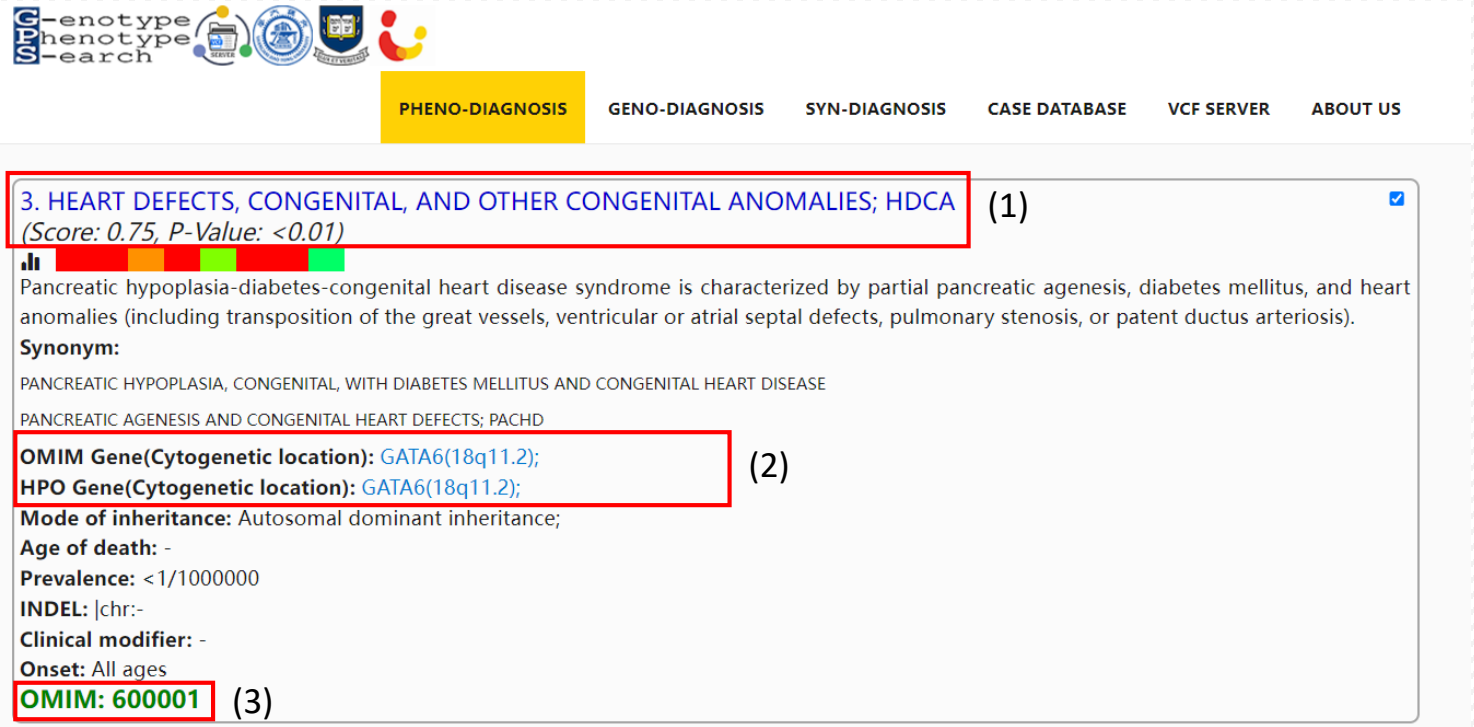
- (1) Click on the icon before the symptom to expand more detailed symptoms
- (2) Click on the icon before the symptom to add the symptom to the symptom input box
- (3) Phenotype input box
- (4) Phenotype information sheet

- After entering all the phenotypes of the patient, users can click the "Search" button to obtain the diagnosis results of phenotype-driven genetic disorders.

Phenotypic Diagnosis

Auxiliary Diagnosis System for Genetic disorders

STEP② View Phenotypic Diagnosis Results



- (1) Genetic disorder name and its predicted diseaseGPS score. The phenotype score for OMIM:600001 is 0.75, ranking third among all genetic disorders
- (2) Pathogenic gene
- (3) OMIM ID

- Users can click on the name of a genetic disorder to get more detailed information

Phenotypic Diagnosis

Auxiliary Diagnosis System for Genetic disorders

(1) Disease OMIM:600001 Home page

(2)

Seached phenotype	Disease phenotype	Similarity
Diabetes mellitus	Diabetes mellitus	100.00%
Hyperglycemia	Hyperglycemia	100.00%
Pulmonary artery stenosis	Pulmonary artery stenosis	100.00%
Ventricular septal defect	Ventricular septal defect	100.00%
Atrial septal defect	Atrial septal defect	100.00%
Cor pulmonale	Abnormal cardiac ventricle morphology	85.71%
Polyuria	Abnormality of the urinary system physiology	62.50%
Poor wound healing	Abnormality of head or neck	40.00%

(3)

Other phenotypes of this disease:

- Abnormality of the musculature
- Aplasia of the left hemidiaphragm
- Abnormal umbilical cord blood vessels
- Aplasia/Hypoplasia of the pancreas
- Abnormal heart valve physiology
- Abnormal ventriculoarterial connection
- Morphological central nervous system abnormality
- Colon perforation
- Abnormal umbilicus morphology
- Abnormal nervous system morphology

(4)

HEART DEFECTS, CONGENITAL, AND OTHER CONGENITAL ANOMALIES; HDCA

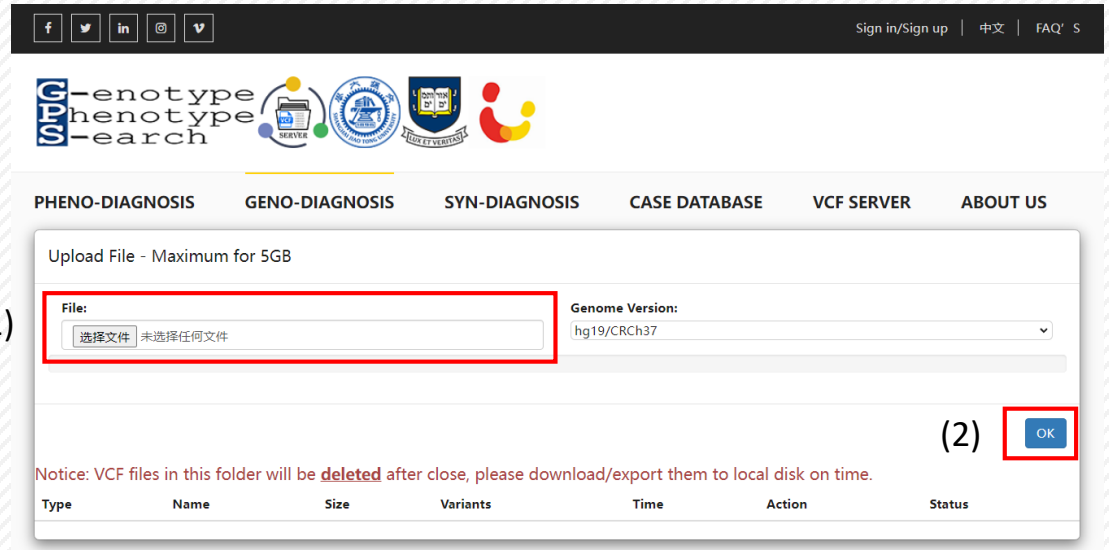
Text:Congenital heart defects and other congenital anomalies (HDCA) is caused by heterozygous mutation in the GATA6 gene ([601656]) on chromosome 18q11.Clinical Features:Yorifuji et al. (1994) described a nonconsanguineous Japanese family in which the mother had undergone cardiac surgery at 19 years of age for patent ductus arteriosus and atrial septal defect. She developed diabetes mellitus after her third pregnancy at the age of 28 years. After 2 offspring were found to have hypoplasia of the pancreas, she was reexamined; abdominal CT scan showed hypoplasia of the pancreas. Only the head and the uncus of the pancreas were present; most of the body and tail were absent. The first 2 offspring of this woman had died soon after birth from unknown causes. The third child had diabetes and cyanotic congenital heart disease and died at 2 years and 8 months. Necropsy showed severe hypoplasia of the pancreas. Cardiac anomalies consisted of transposition of the great vessels, ventricular septal defects, pulmonic stenosis, and atrial septal defect. The fourth-born child had tetralogy of Fallot which was corrected surgically at the age of 6 years. At the age of 14 years, a routine school urinalysis showed glucosuria. Ultrasonographic studies of the abdomen could not identify the body of the pancreas although the splenic vein was clearly visible. Only the head and the uncus of the pancreas were demonstrated.Balasubramanian et al. (2010) reported 3 unrelated children with pancreatic agenesis, confirmed by abdominal scan, and congenital heart defects. The first patient was a 4-year-old girl, born of nonconsanguineous parents, who developed hyperglycemia within the first 12 hours of life that required continuous insulin infusion and who also had exocrine pancreatic deficiency requiring replacement therapy. CT scan of the abdomen failed to show pancreatic tissue; on MRI, a small amount of

STEP③ View Detailed Information

- (1) OMIM ID
- (2) Similarities between searched phenotypes and disease phenotypes
- (3) Other phenotype of this genetic disorder
- (4) Textual description of this genetic disorder

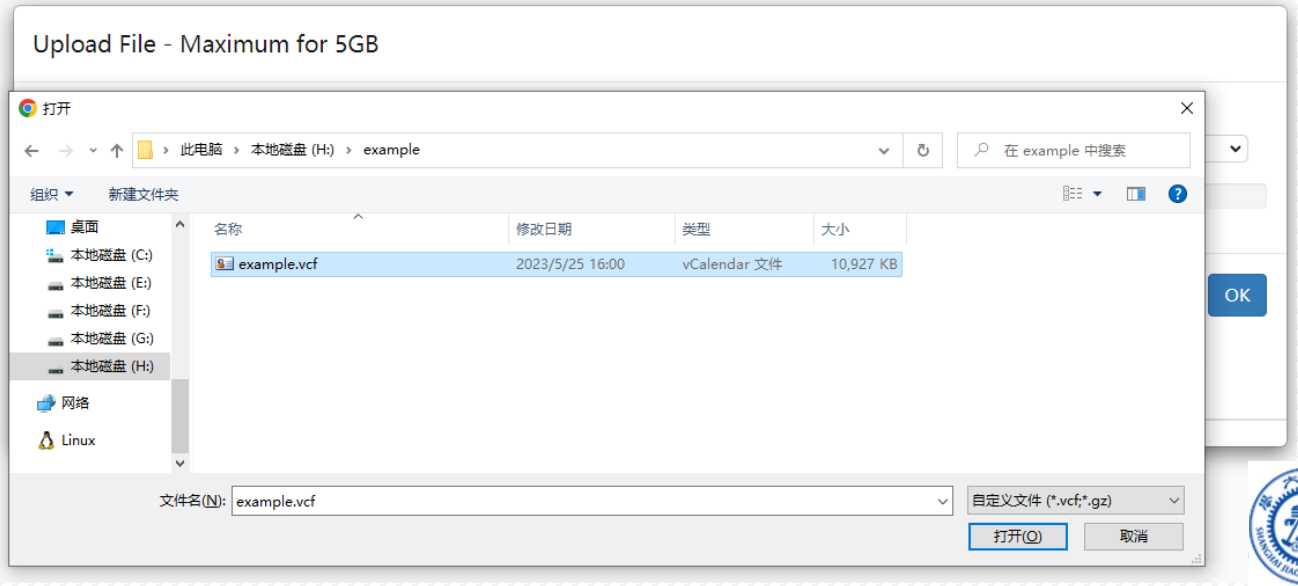
Genetic Diagnosis

Auxiliary Diagnosis System for Genetic disorders



STEP① Upload VCF file

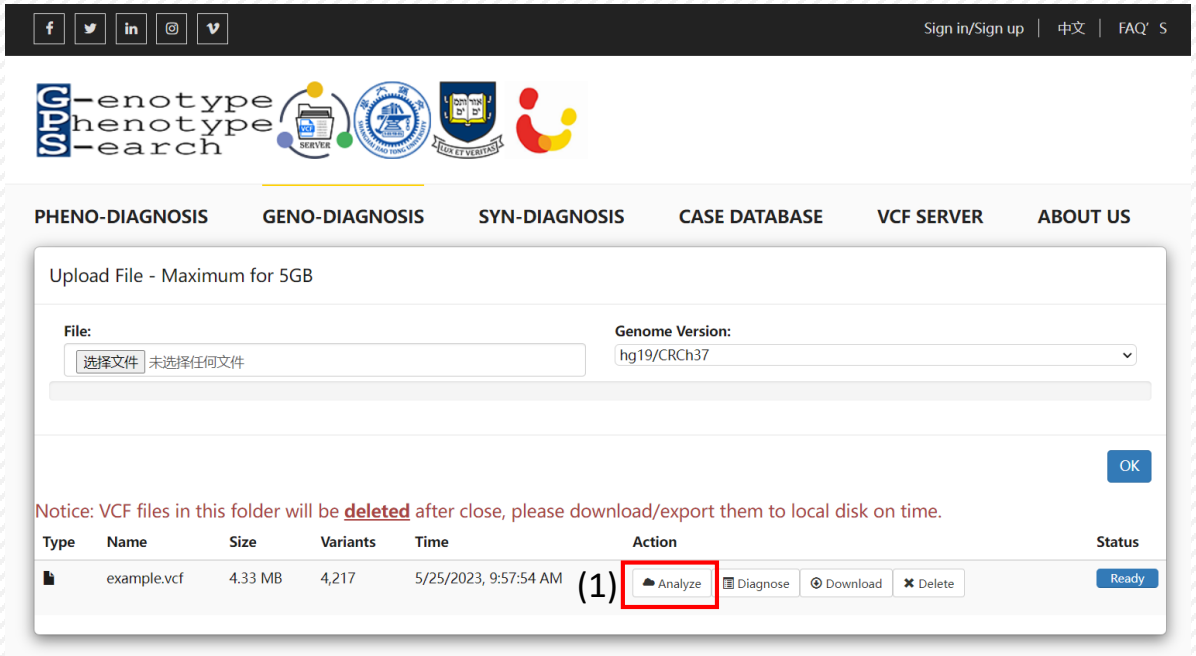
- (1) Click on the “Select File” button to upload VCF file from local disk
- (2) After the selection is complete, click the "OK" button to upload the file. At this time, the analysis will also be carried out synchronously. Please wait patiently

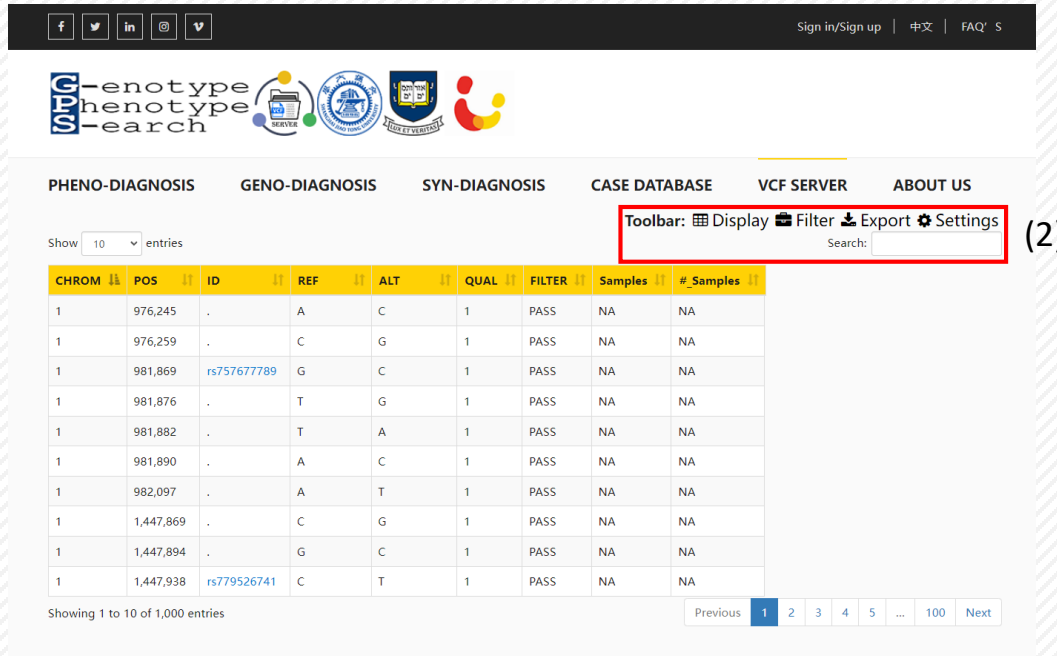


Genetic Diagnosis

Auxiliary Diagnosis System for Genetic disorders

STEP② Analyze VCF file



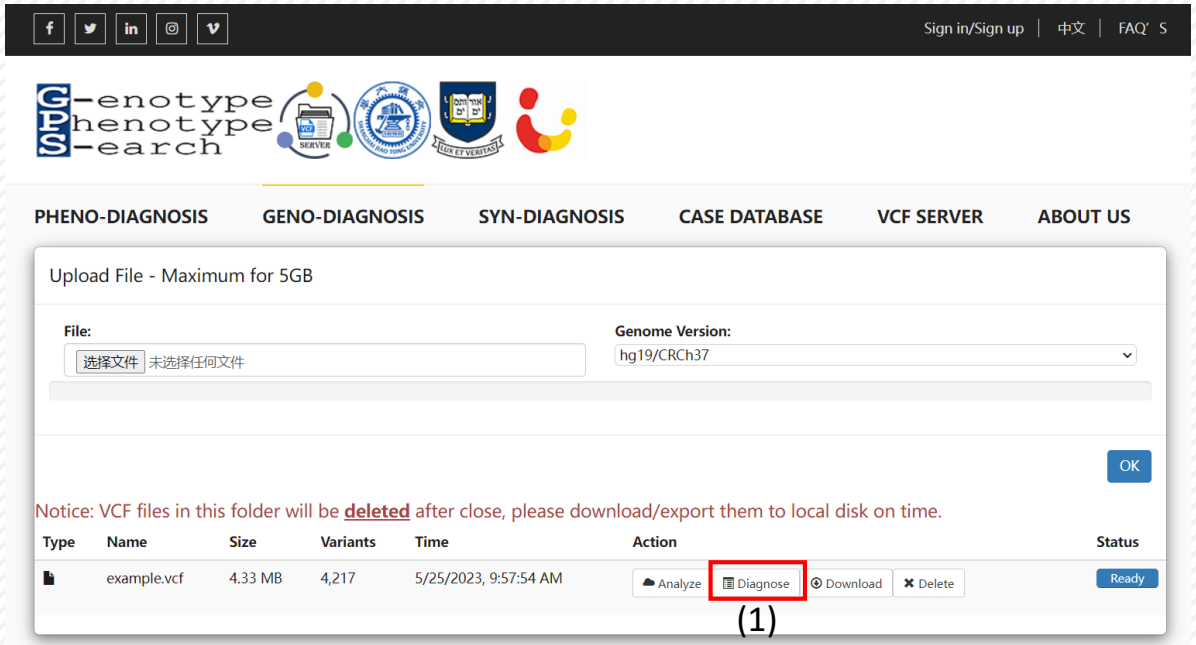


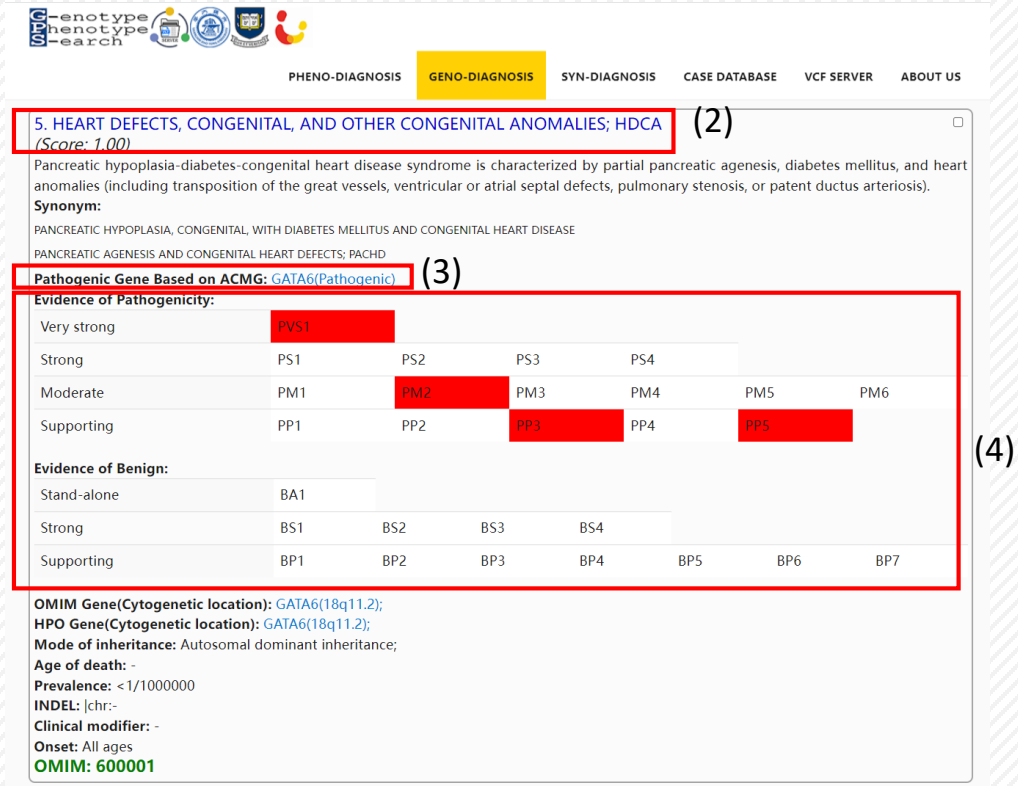
- (1) Click on the “Analyze” button to get detailed variant information
- (2) Perform personalized operations such as "Display", "Filter", "Export", "Settings" and "Search" in the "Toolbar" module.

Genetic Diagnosis

Auxiliary Diagnosis System for Genetic disorders

STEP③ Diagnosis VCF file





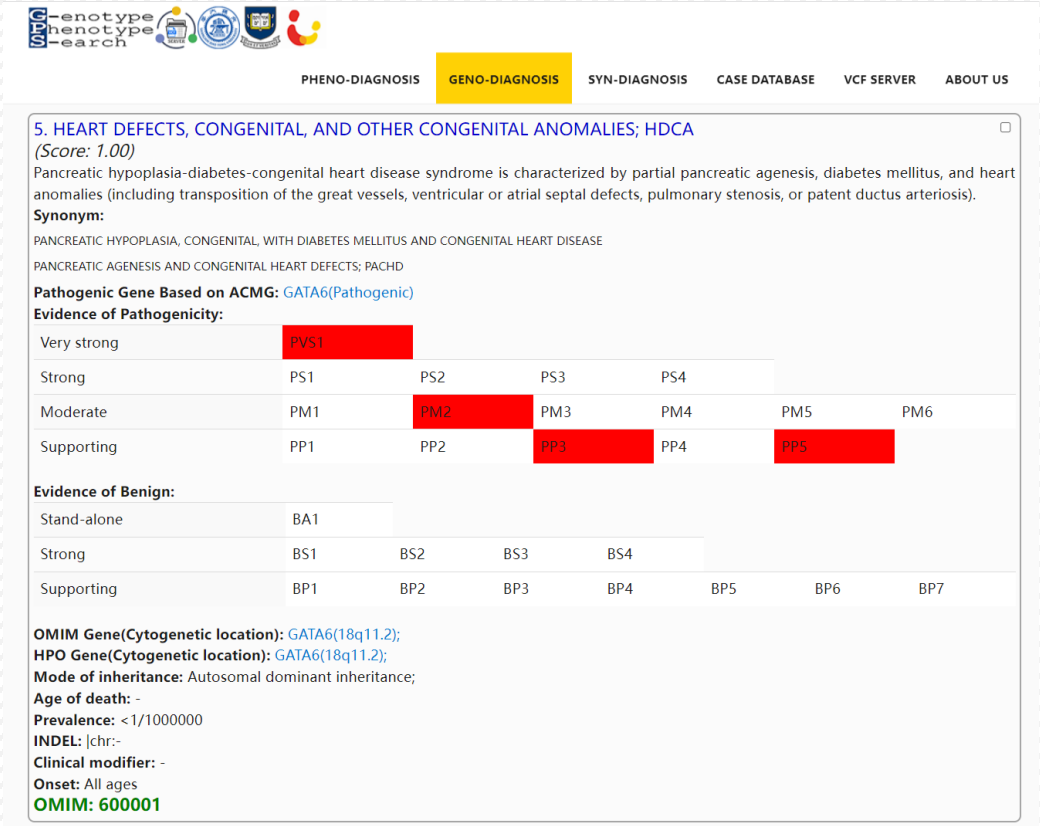
- (1) Click on the “Diagnose” button to predictive diagnosis of genetic disorders
- (2) The genotype score for OMIM:600001 is 1.00, ranking fifth among all genetic disorders
- (3) Pathogenic Gene. Click on the gene to get detailed information on the variants
- (4) Evidence of pathogenicity and benign based on ACMG-AMP guidelines

Genetic Diagnosis

Auxiliary Diagnosis System for Genetic disorders

ACMG-AMP Guidelines to Evidence of pathogenicity and benign

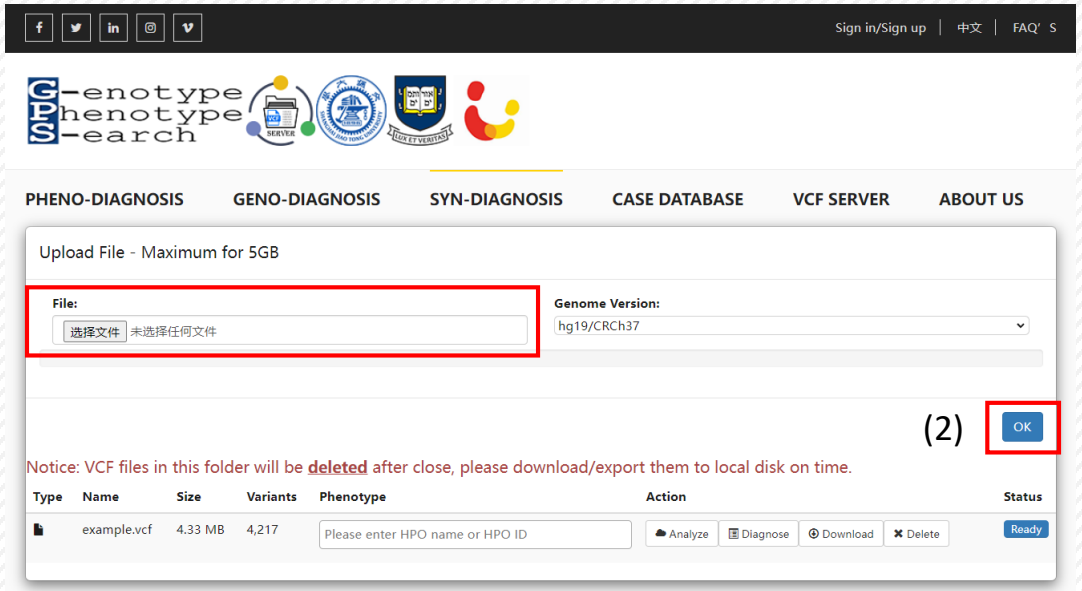
	Benign Evidence		Pathogenic Evidence			
	Strong	**Supporting**	**Supporting**	**Moderate**	**Strong**	**Very strong**
Population data(ESP/ExAC/1000 Genome)	Allele frequency > 5% BA1 Allele frequency > expected for disorder BS1 Inconsistent with observation in controls BS2			Absent in population databases or at extremely low frequency PM2	Prevalence in affecteds statistically increased over controls PS4	
Annotation and predictive data		Multiple computational studies show no impact on gene/gene product BP4 Missense in gene where only truncating cause disease BP1 Synonymous variant with non predicted splice impact BP7 In-frame indels in repeat	Multiple computational studies show deleterious impact on gene/gene product PP3	Novel missense change at the same position as another pathogenic missense change PM5 In-frame indels in non-repeat region or stop-loss PM4	Same amino acid change as another pathogenic missense change PS1	Predicted null variant in a gene where LOF is a known mechanism of disease(nonsense, frameshift, splice sites, initation codon, exon deletion) PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants PP2	Missense in functional domain/mutation hotspot PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1			
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in trans with a dominant variant BP2 Observed in cis with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			



Integrated Diagnosis

Auxiliary Diagnosis System for Genetic disorders

STEP① Upload VCF file

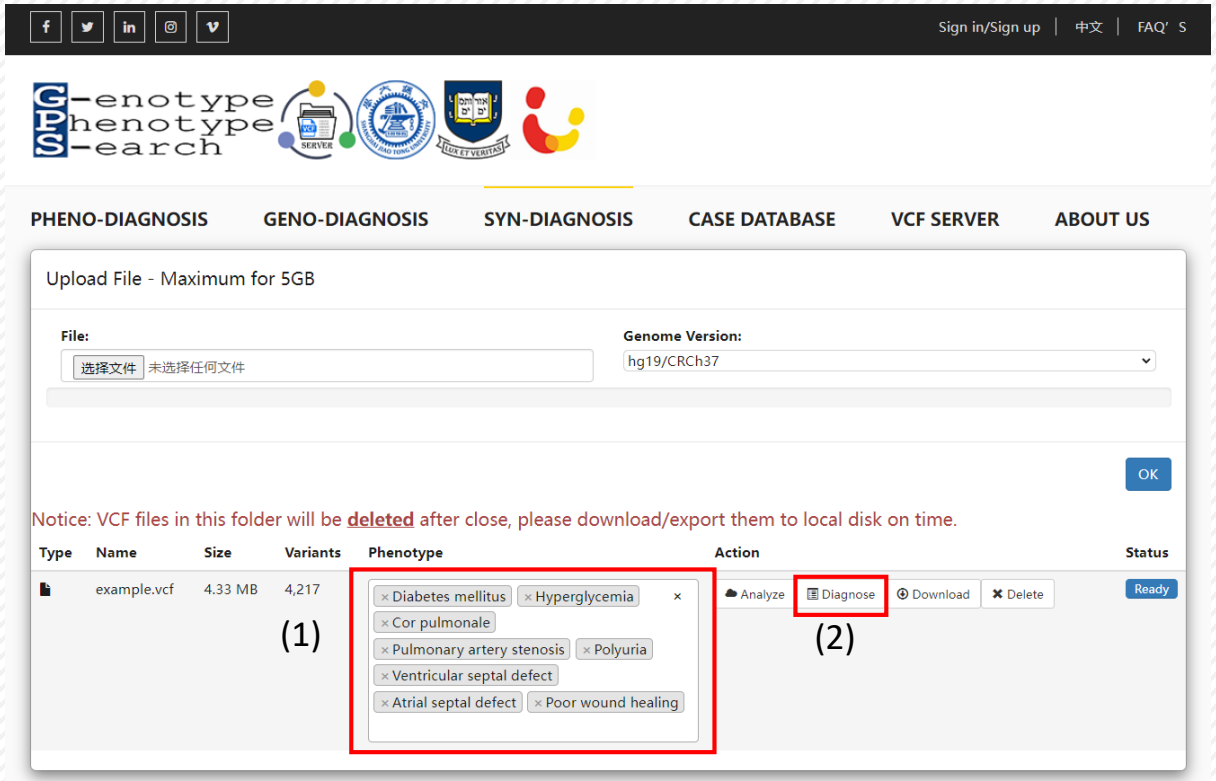


- (1) Click on the “Select File” button to upload VCF file from local disk
- (2) After the selection is complete, click the "OK" button to upload the file. At this time, the analysis will also be carried out synchronously. Please wait patiently

Integrated Diagnosis

Auxiliary Diagnosis System for Genetic disorders

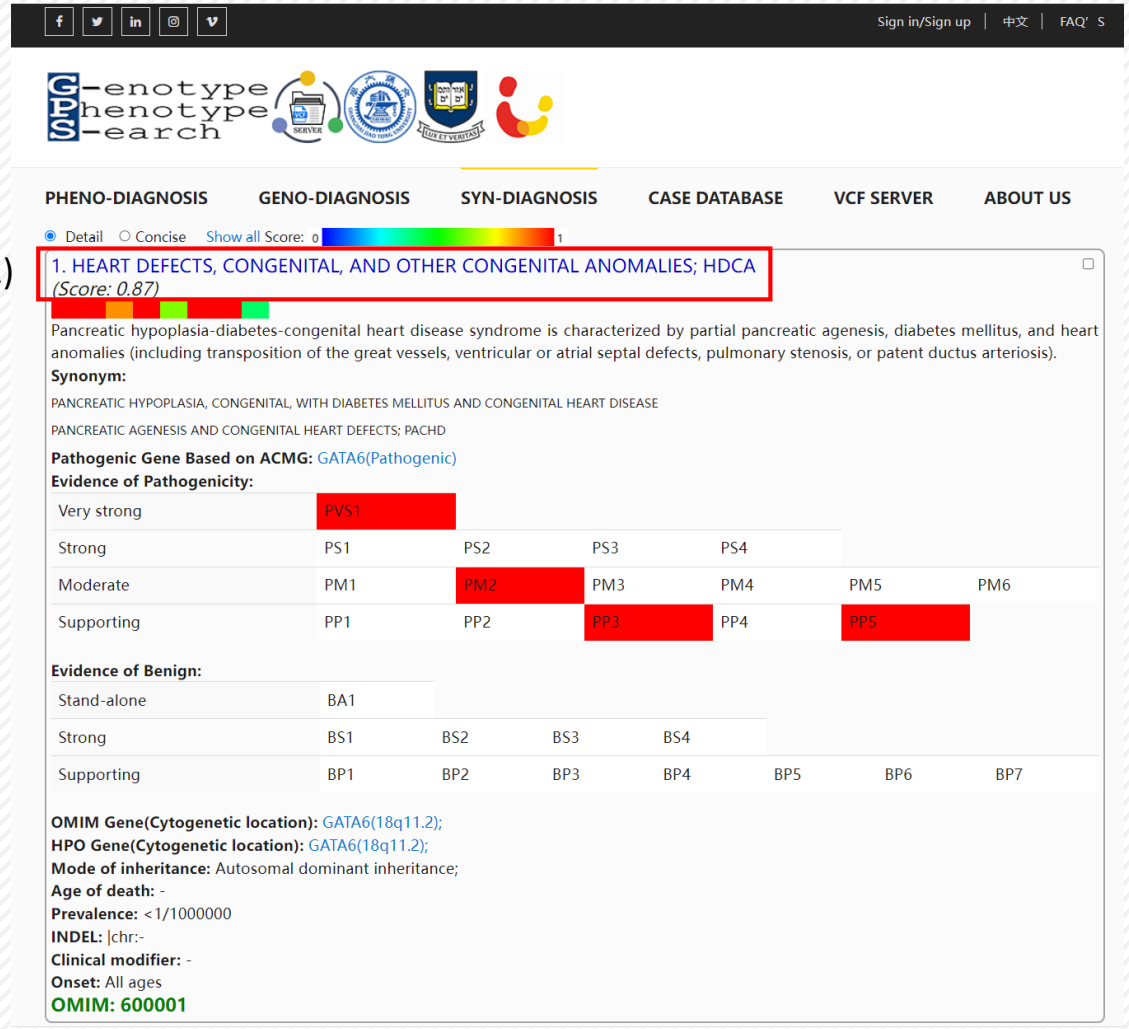
STEP② Input Phenotype



- (1) Input Phenotype
- (2) After inputting the phenotype, click the "Diagnose" button to perform an integrated diagnosis

Integrated Diagnosis

Auxiliary Diagnosis System for Genetic disorders



STEP③ View Integrated Diagnosis Results

- (1) The integrated score for OMIM:600001 is 0.87, ranking first among all genetic disorders
- The other detailed information is consistent with the phenotype analysis and genotype analysis. You can click on it to obtain more detailed information.

Welcome experts to use diseaseGPS!
Thank you for your suggestions and guidance!