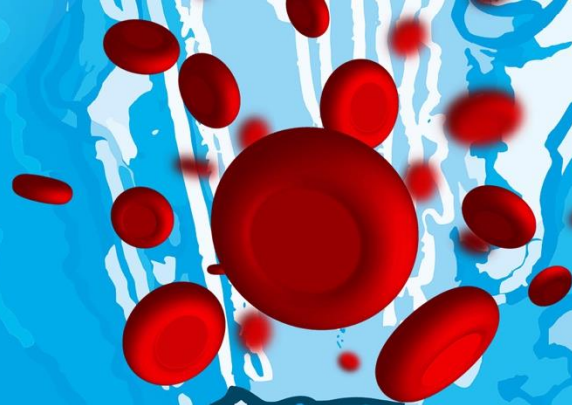




*Ampliamento dello spettro mutazionale del deficit di G6PD:
nuove varianti associate a CNSHA
e implicazioni diagnostiche*

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Meeting del CLUB DEL

**Globulo
Rosso** 2026

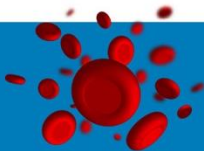
NAPOLI

28-29 SETTEMBRE 2026

Complesso dei SS. Marcellino e Festo

Disclosures

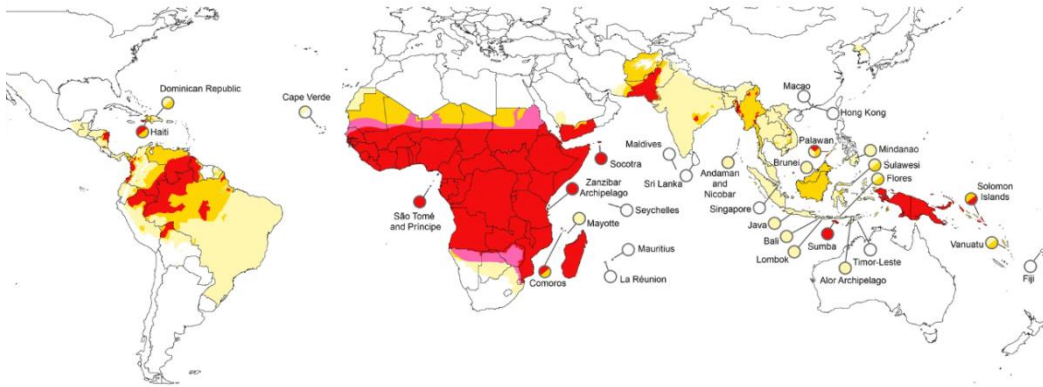
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other



G6PD deficiency: beyond a “well-defined” disorder

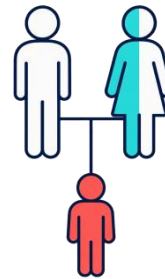
DISTRIBUTION

Enriched in malaria-endemic regions



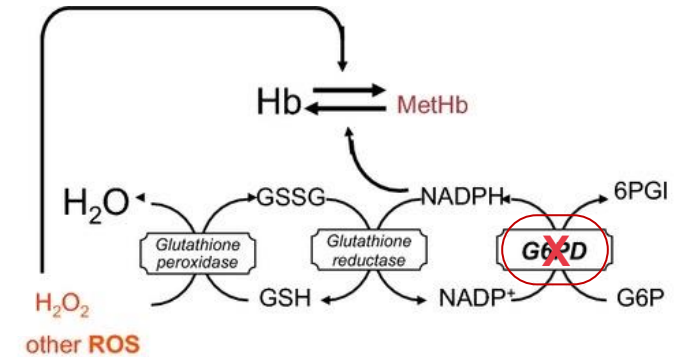
INHERITANCE

X-linked recessive



MECHANISM

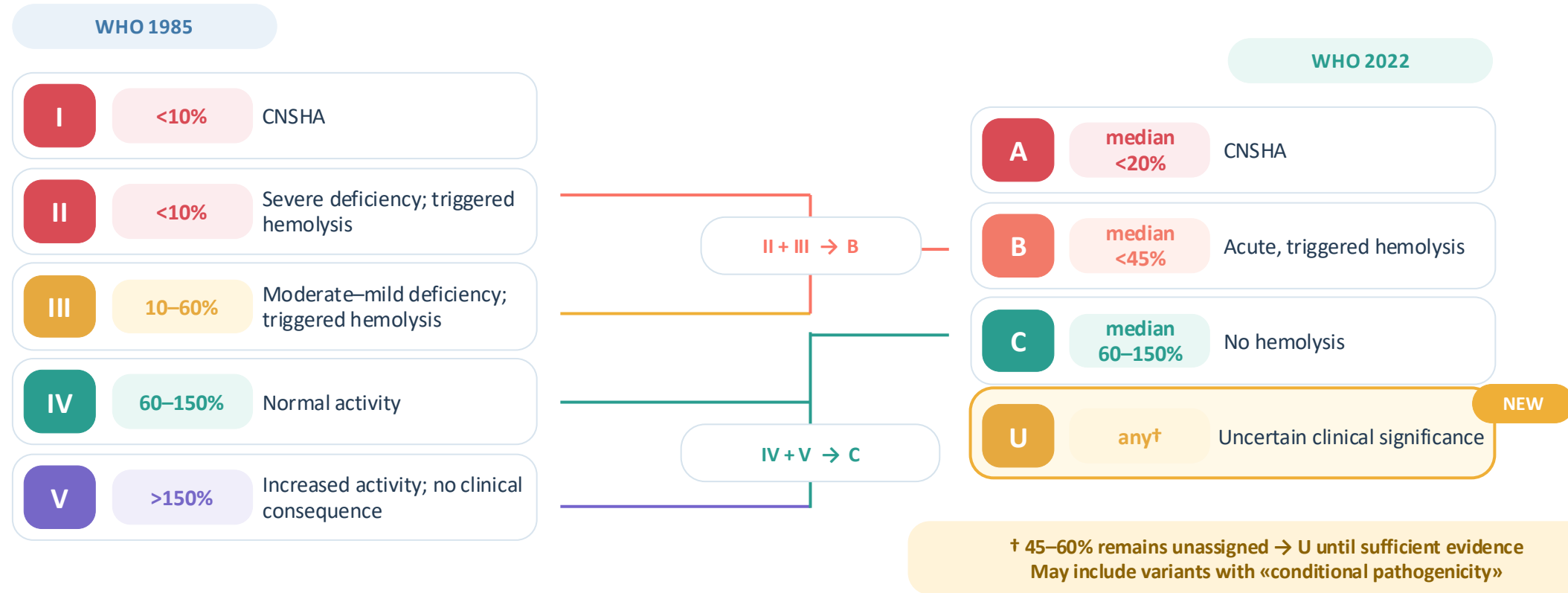
oxidative vulnerability



More than 400 variants in the G6PD gene have been reported, contributing to broad phenotypic heterogeneity

WHO classification of G6PD variants: what changed?

The 2022 consultation, consolidated in 2024, replaces five historical classes with A–B–C–U



The diagnosis is straightforward, the interpretation often is not



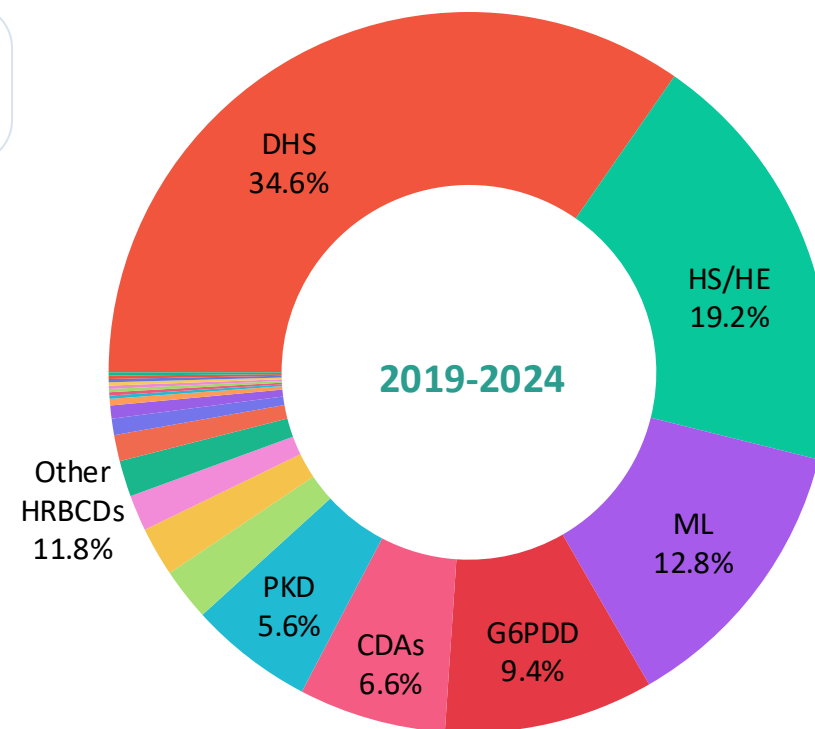
Molecular characterization of G6PDD within our HRBCD cohort

1

MOLECULAR SCREENING FOR HRBCDs (2019-2024)



t-NGS/WES of 1240 patients | 548 families



Percentages were calculated on 681 diagnosed patients; undiagnosed or partially diagnosed patients were excluded.

G6PDD accounts for 9.4% of diagnosed HRBCDs

1



MOLECULAR SCREENING FOR HRBCDs (2019-2024)

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2

G6PDD COHORT

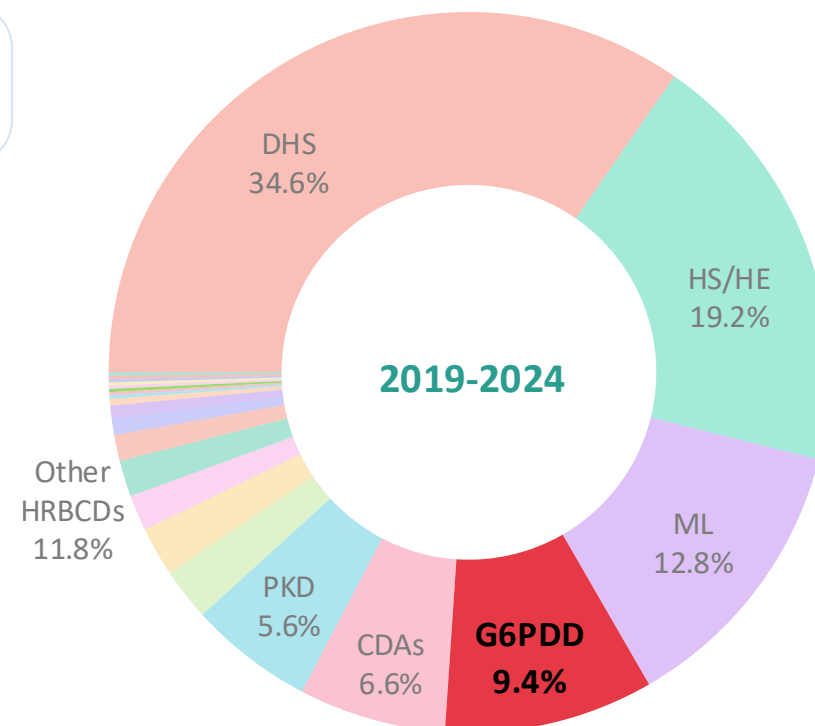
62 patients | 59 unrelated families

54%

Clinical suspicion
of G6PD

36%

Clinical suspicion
of HRBCDs



Percentages were calculated on 681 diagnosed patients; undiagnosed or partially diagnosed patients were excluded.

Expanding the spectrum of *G6PD* variants

1



MOLECULAR SCREENING FOR HRBCDs (2019-2024)

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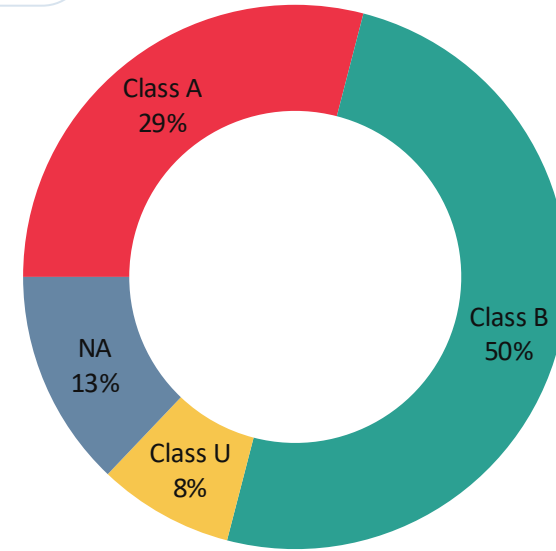
G6PDD COHORT

62 patients | 59 unrelated families

3

MOLECULAR OUTPUT

17 causative *G6PD* variants



■ Class A ■ Class B ■ Class U ■ NA



ACMG
guidelines



WHO 2022
classification



G6PD variant
repository



Geck et al.,
AJHG, 2023

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ACMG
guidelines



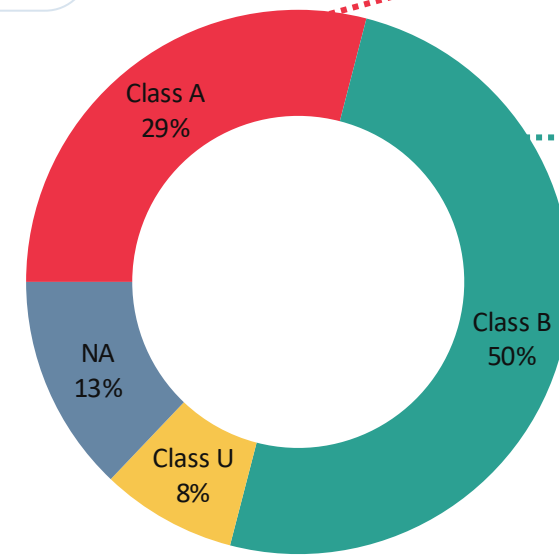
WHO 2022
classification



G6PD variant
repository



Geck et al.,
AJHG, 2023



■ Class A ■ Class B ■ Class U ■ NA

94% CLASS A-II

p.Ser188Phe
Mediterranea

19% CLASS B-III

p.Asp282His
Seattle

Expanding the spectrum of *G6PD* variants

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MOLECULAR OUTPUT

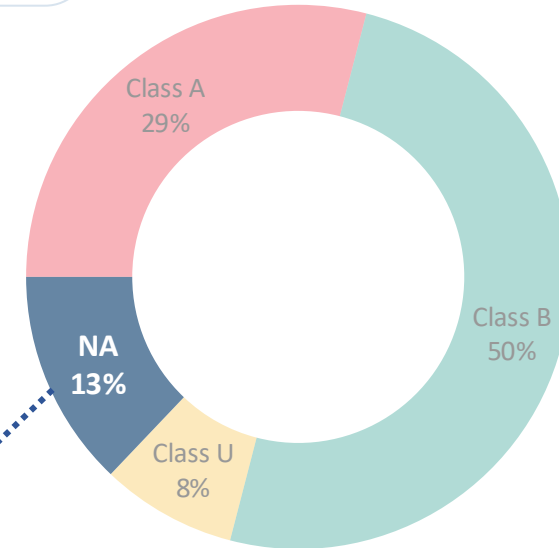
17 causative *G6PD* variants



ACMG
guidelines



WHO 2022
classification



5 NOVEL VARIANTS

Patient	Gender	Genotype
P6	Male	c.1456A>G; p.Ser486Gly (Hem)
P44	Male	c.320A>G; p.Tyr107Cys (Hem)
P48	Male	c.542A>G, p.Asp181Gly; c.376A>G, p.Asn126Asp (Hem)
P60	Male	c.1307 C>T, p.Ala436Val (Hem)
P61	Female	c.202G>A, p.Val68Met; c.376A>G, p.Asn126Asp; c.1115A>G, p.Gln372Pro (Het)

■ Class A ■ Class B ■ Class U ■ NA

Genotype-phenotype correlation of novel variants

1



MOLECULAR SCREENING FOR HRBCDs (2019-2024)

t-NGS/WES of 1240 patients | 548 families

2

G6PDD COHORT

62 patients | 59 unrelated families

3

MOLECULAR OUTPUT

17 causative *G6PD* variants

4

GENOTYPE-PHENOTYPE CORRELATION

Integrated interpretation

5 NOVEL VARIANTS

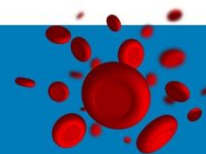


Structural
Prediction



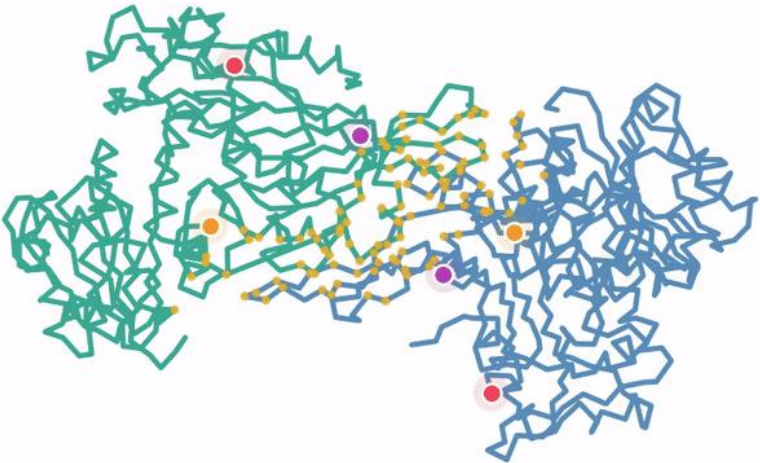
Clinical
data

Patient	Gender	Genotype
P6	Male	c.1456A>G; p.Ser486Gly (Hem)
P44	Male	c.320A>G; p.Tyr107Cys (Hem)
P48	Male	c.542A>G, p.Asp181Gly; c.376A>G, p.Asn126Asp (Hem)
P60	Male	c.1307 C>T, p.Ala436Val (Hem)
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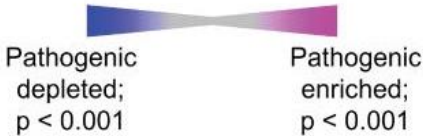


Structural mapping of novel G6PD variants (I)

Patient	Gender	Genotype	Spatial Scan Statistic (<i>p</i> -value)	Genotype Classificaton°
P6	Male	c.1456A>G; p.Ser486Gly (Hem)	24.6, Class I (0.01)	A (I) ←
P44	Male	c.320A>G; p.Tyr107Cys (Hem)	2.3, Class III (0.13)	B (III) ↗
P48	Male	c.542A>G, p.Asp181Gly; c.376A>G, p.Asn126Asp (Hem)	4.6, Class II (0.07)	B (II) ↗ tetramer interface
P60	Male	c.1307 C>T, p.Ala436Val (Hem)	854.2, Class I (0.001)	A (I) ←
P61	Female	c.202G>A, p.Val68Met; c.376A>G, p.Asn126Asp; c.1115A>G, p.Gln372Pro (Het)	15.4, Class I (0.01)	A (I) ← dimer interface



- Chain A
- Chain B
- Dimer interface
- Gln372
- Ala436
- Ser486



Three out of five variants localize near structurally critical regions of the dimer

Cunningham AD, Mochly-Rosen D. Matters (Zur). 2017 Sep 14;2017:10.19185/matters.201705000008;
PDB DOI: <https://doi.org/10.2210/pdb7snf/pdb>

Genotype-phenotype correlation of novel variants

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17 causative *G6PD* variants

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GENOTYPE-PHENOTYPE CORRELATION

Integrated interpretation

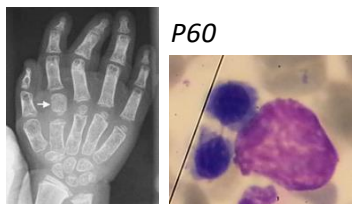
5 NOVEL VARIANTS

✓ Structural
Prediction

✓ Clinical
data

Patient	Gender	Genotype
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P44	Male	c.320A>G; p.Tyr107Cys (Hem)
P48	Male	c.542A>G, p.Asp181Gly; c.376A>G, p.Asn126Asp (Hem)
P60	Male	c.1307 C>T, p.Ala436Val (Hem)
P61	Female	c.202G>A, p.Val68Met; c.376A>G, p.Asn126Asp; c.1115A>G, p.Gln372Pro (Het)

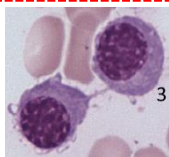
Clinical reassessment of patients with novel variants (II)



Skeletal dysmorphisms
Internuclear bridges

G6PDD mimics CDA I

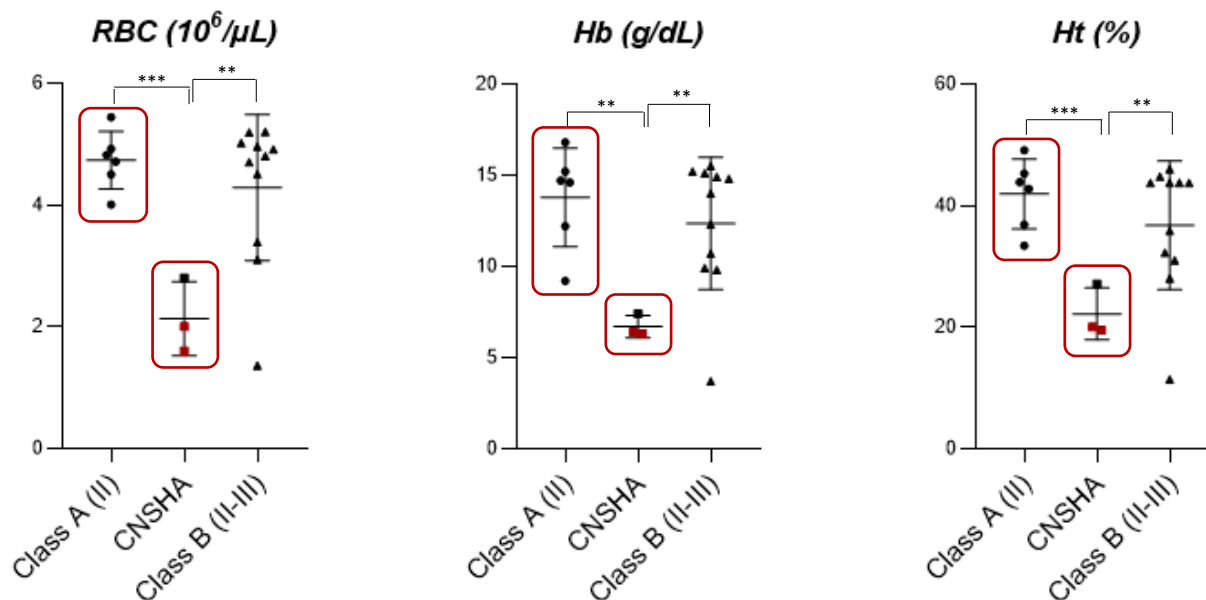
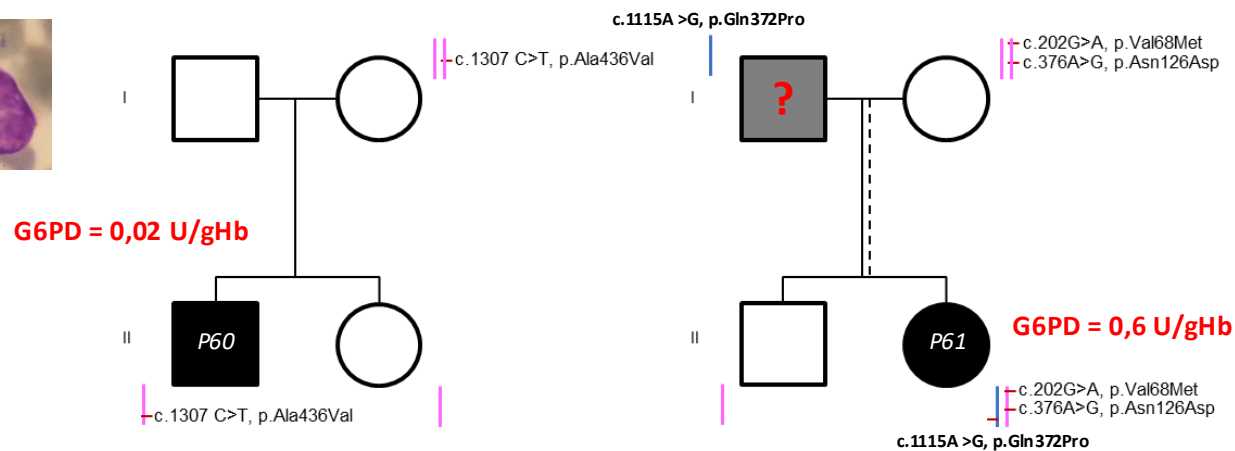
Hypercellularity
Intercytoplasmic bridges



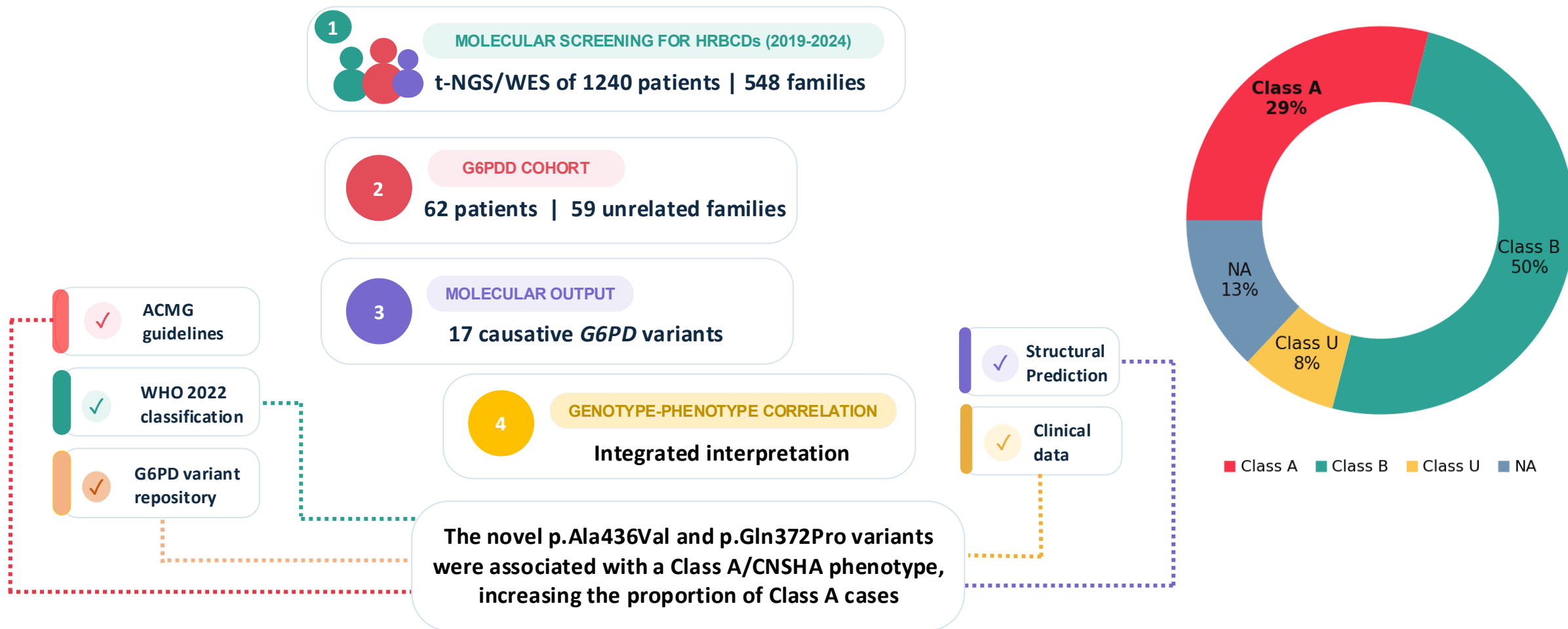
P62 variant: p.Pro409Arg (CNSHA-Suwalki) ■

P60 variant: p.Ala436Val ■

P61 variant: p.Gln372Pro ■



Integrated evidence supports reclassification as Class A



G6PD deficiency: beyond a familiar diagnosis



G6PD deficiency can cause chronic hemolysis and mimic other inherited anemias



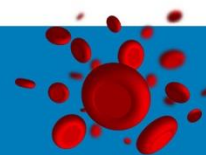
Five previously unreported variants expand the mutational spectrum of G6PD



Clinical, biochemical and structural evidence supports a Class A/CNSHA phenotype for p.Ala436Val and p.Gln372Pro

NEXT STEP

Molecular Dynamic Simulation (MDS) to refine structural modelling of novel variants



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