Potential Impact of Excess Weight on Clinical Outcomes in Wolfram Syndrome

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Background and Aims

- **Wolfram syndrome 1 (WS1)** is a rare autosomal recessive disorder of endoplasmic reticulum (ER) stress: loss of wolframin function causes insulin-deficient diabetes, progressive optic atrophy and multisystem involvement.[1]
- Marked heterogeneity limits genotype–phenotype correlation and the search for disease modifiers.[2]
- In Israel, one common variant, **WFS1 p.R558C**, dominates and is linked to a milder phenotype,[3] giving a more homogeneous cohort.

Aim To define genotype–phenotype correlations and the role of body weight in a nationwide WS1 cohort.

Methods

42 genetically confirmed WS1 → **−2** asymptomatic minors → **40** analyzed, 32 families

- **Design:** nationwide, multicenter, registry-based cross-sectional study (STROBE); age at onset reconstructed retrospectively; enrollment 2021–2026.
- **Genetics:** gene panel, exome or Sanger sequencing; ACMG variant classification.
- **Exposures:** genotype (p.R558C vs other) and BMI ≥ 25 kg/m² (WHO; adults).
- **Outcomes:** age at diagnosis of diabetes, optic atrophy, hearing impairment and urinary symptoms.
- **Statistics:** Fisher's exact and Mann–Whitney U tests; Kaplan–Meier with log-rank test; exploratory, unadjusted (SPSS 29).
- **Ethics:** IRB-approved; informed consent signed by participants or guardians.

Cohort and clinical spectrum

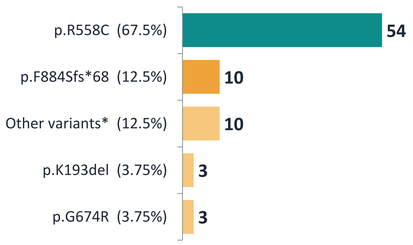
40 participants from 32 unrelated families

33 y median age (IQR 24–46); 70% female

73% carry ≥ 1 p.R558C allele (n = 29)

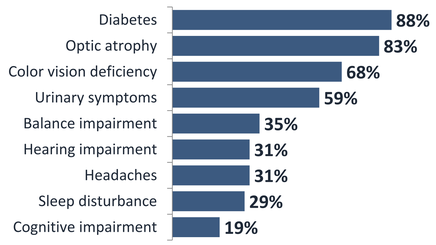
9 y median delay from diabetes onset to WS1 diagnosis

Pathogenic variant alleles (n = 80)



*Six variants, each in < 3 alleles. p.F884Sfs*68 is a founder variant in the Druze Arab community.[5]

Manifestations (% of participants)



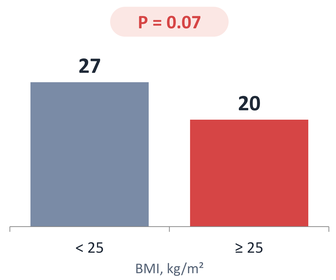
n = 36–40 per item. Urinary = lower urinary tract symptoms.

Excess weight

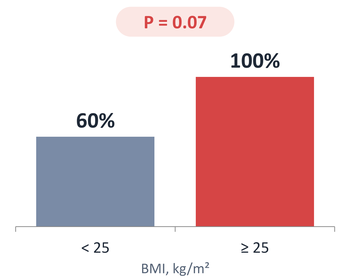
Adults carrying ≥ 1 p.R558C allele (n = 28)

BMI < 25 (n = 21) BMI ≥ 25 (n = 7)

Median age at diabetes diagnosis, years



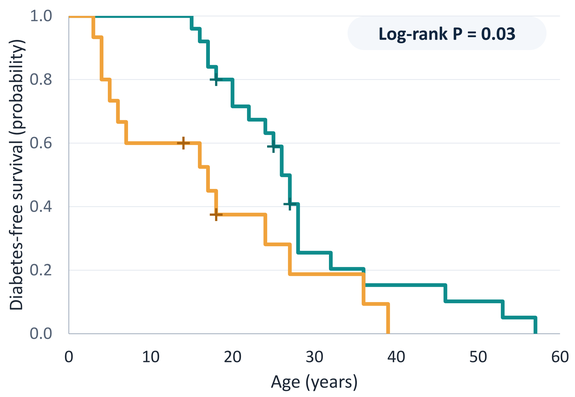
Color vision deficiency, % of participants



Trends, not statistically significant. IQR 18–33 vs 16–25 y; 12/20 vs 7/7. Same direction in p.R558C homozygotes alone.

Genotype shapes phenotype

p.R558C homozygous (n = 25) Other genotypes (n = 15)



No. at risk

p.R558C	25	25	19	5	3	2	0
Other	15	9	4	2	0	0	0

Median age at diabetes diagnosis, years
26 vs 16
P = 0.01 IQR 20–29 vs 5–26

Hearing impairment
5% vs 64%
P < 0.001 n = 22 vs 14

Adult BMI, kg/m²
22.5 vs 25.2
P = 0.005 n = 24 vs 10

Insulin pump use
9% vs 46%
P = 0.03 n = 22 vs 13

p.R558C homozygosity: later diabetes onset, less hearing impairment, lower BMI

A possible double hit

HYPOTHESIS

1 Genetic
Reduced wolframin function (p.R558C)

2 Metabolic
Adiposity adds ER stress (high-fat diet, mice)[4]

→ **Earlier disease expression**
Earlier diabetes onset
More color vision deficiency

Conclusions

- **WFS1 p.R558C** defines an attenuated WS1 phenotype with later-onset diabetes.
- In p.R558C carriers, excess weight showed trends toward earlier diabetes and more color vision deficiency.
- Weight management is a potentially modifiable target; prospective studies are needed.

Excess weight may exacerbate Wolfram syndrome manifestations
Hypothesis-generating: small, cross-sectional, unadjusted

References

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