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Scheme 5B - Interpretive: HFE Genotype and Hereditary Haemochromatosis

Clinical Scenario 3/2025

GP Surgery: Dr Greet, Park Avenue Practice, Stirling, FK8 2AU

Patient Name: Rebecca Weeks (female)
DOB: 01/09/1980
NHS Number/Patient ID: 578 357 1342
Address: 271 Bellfield Road, Stirling FK8 3KU

Clinical Details/Reason for testing: Rebecca's husband has been identified as compound heterozygous for C282Y p.(Cys282Tyr) and H63D p.(His63Asp), she has requested testing and wishes to know the risk to their offspring.

Serum ferritin 450µg/L

HFE genotyping results: p.Cys282Tyr not detected, p.His63Asp not detected

Please prepare an interpretive report with appropriate advice for the requesting GP.

The report should contain sufficient information for the GP to determine what further action is required.

Clinical Scenario 4/2025

GP Surgery: Dr Mustard, Trevithick Surgery, Camborne, Cornwall, TR14 8TT
Patient Name: Charu Shah (female)
DOB: 04/08/1968
NHS Number/Patient ID: 984 757 8560
Address: 59 Barlowena, Camborne, Cornwall, TR14 7RP

Clinical Details/Reason for testing: Charu has been diagnosed with diabetes and has had both hips replaced. Her serum ferritin is 5000mg/l. The GP wanted to eliminate haemochromatosis as a possible explanation. The GP wants to know whether there is any further action required to rule out other forms of inherited iron overload.

HFE genotyping results: The HFE genotype came back as normal. The C282Y p.(Cys282Tyr) mutation was not detected.

The report should contain sufficient information for the GP to determine what further action is required.

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General feedback/comments from the assessors:

We have had a number of queries over the last few returns regarding terminology and more specifically the accurate use of HGVS nomenclature. HGVS guidelines clearly state that "all variants should be described at the most basic level, the DNA level." "c." for coding, "g." for genomic, etc., with RNA or protein-level descriptions optional and supplementary. However, we are sympathetic to the fact that we have a range of genomic and biochemistry laboratories partaking in the scheme and that this is interpretative side of the scheme. In the UK, NHS labs often use the protein-level notation e.g., p.(Cys282Tyr) in reports for several reasons:

- Haemochromatosis has been widely discussed in terms of "C282Y" and "H63D" for decades in clinical guidelines and patient literature and these shorthand names derive from the protein-level change.
- When communicating results to family members or in patient letters, protein-level names are simpler and less technical than full DNA HGVS codes.
- Clinicians (especially non-genetic specialists) find amino acid changes easier to interpret than nucleotide changes.
- Seeing "Cys282Tyr" immediately conveys the functional impact on the protein, which is what matters for disease risk.

To this end we would like to see the appropriate protein nomenclature used in the report when referring to the variants. This is as follows: the p.(Cys282Tyr) variant (also known as C282Y) and the p.(His63Asp) variant (also known as H63D). It is up to the participants should they wish to include the previous shorthand names in their report.

A note on parenthesises.
When variants affect how the transcript (RNA) is produced and subsequently translated into protein, and only DNA has been analysed, the impact on RNA and protein can only be predicted. The HGVS nomenclature demands predicted consequences to be reported in parentheses. In our case the predicted consequence of the NM_000410.4 c.845G>A change on the protein level is described as p.(Cys282Tyr).

No penalty points for deviation from this have been issued from the scheme for this return but will be reinstated for the next distribution.

HGVS Recommendations for the Description of Sequence Variants: 2016 Update.
den Dunnen JT, Dalgleish R, Maglott DR, Hart RK, Greenblatt MS, McGowan-Jordan J, Roux AF, Smith T, Antonarakis SE, Taschner PEM,
On behalf of the Human Genome Variation Society (HGVS), the Human Variome Project (HVP), and the Human Genome Organisation (HUGO)
Hum Mutat 37(6):564-9 (2016). doi:10.1002/humu.22981

HGVS Nomenclature 2024: Improvements to community engagement, usability, and computability.
Hart RK, Fokkema IFAC, DiStefano M, Hastings R, Laros JFJ, Taylor R, Wagner A, den Dunnen JT
On behalf of the HGVS Variant Nomenclature Committee (HVNC)
Genome Med **16**, 149 (2024) doi:10.1186/s13073-024-01421-5