

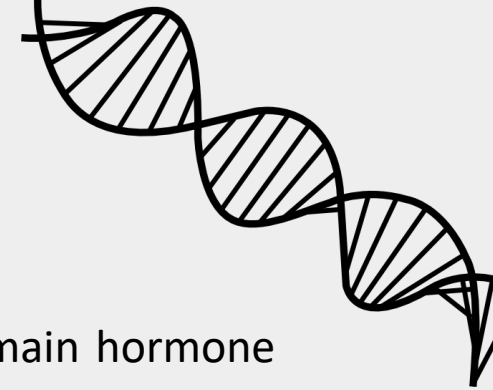
Widening the spectrum of *TMPRSS6* gene pathogenic variants related with hereditary iron deficiency

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BACKGROUND



- ❖ *TMPRSS6* encodes Matriptase-2, a negative regulator of hepcidin expression (**Figure 1**), the main hormone regulator of iron absorption [1].
- ❖ Iron-Refractory Iron-Deficiency Anemia (IRIDA) is a rare autosomal recessive hypochromic microcytic anemia derived from loss-of-function mutations in the *TMPRSS6* gene [2].
- ❖ Several *TMPRSS6* genetic variants are known to influence iron homeostasis and erythropoiesis, giving rise to lower levels of serum iron biomarkers and abnormal hematological parameters [2].

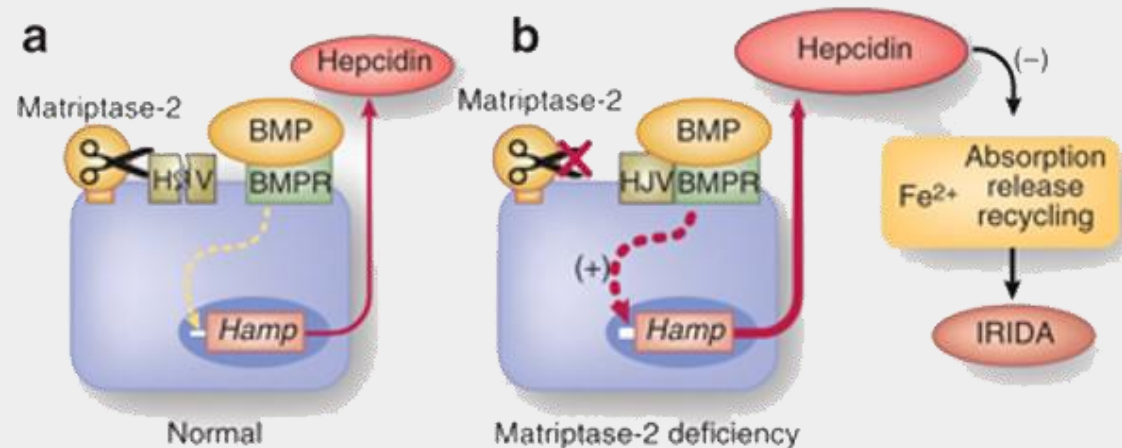
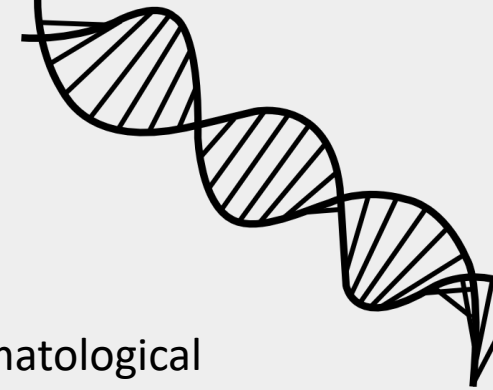


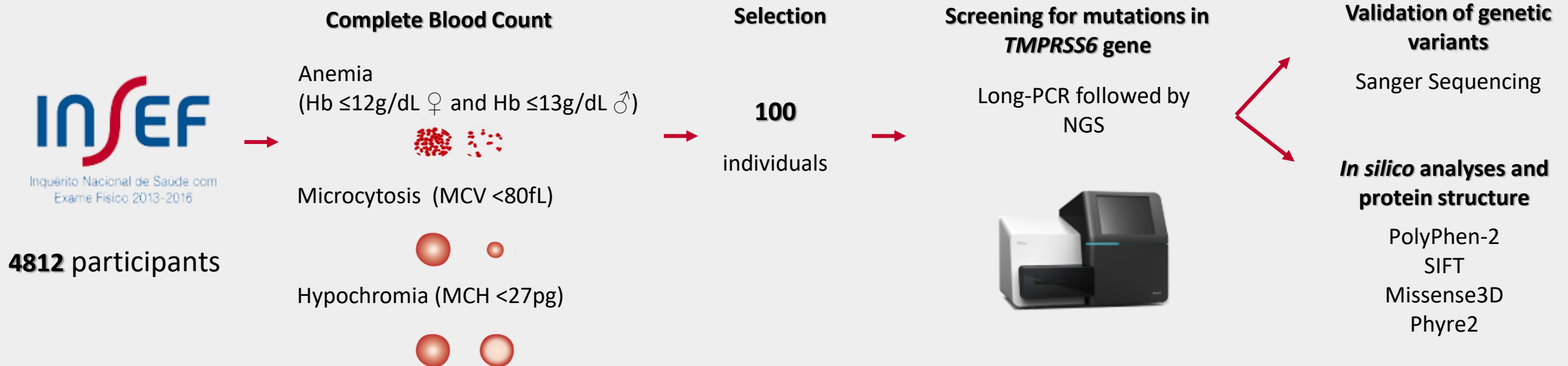
Figure 1. Regulation of hepcidin expression by Matriptase-2. Adapted from [1].

AIMS



- ❖ To identify genetic variants in *TMPRSS6* in a sample of the Portuguese population with a hematological phenotype suggestive of iron deficiency (anemia and/or microcytosis and/or hypochromia).
- ❖ To evaluate the performance of Next Generation Sequencing (NGS) for genetic screening of *TMPRSS6*.

METHODS



RESULTS



- ❖ 24 coding variants found by NGS: 13 missense, 11 synonymous (Figure 2).

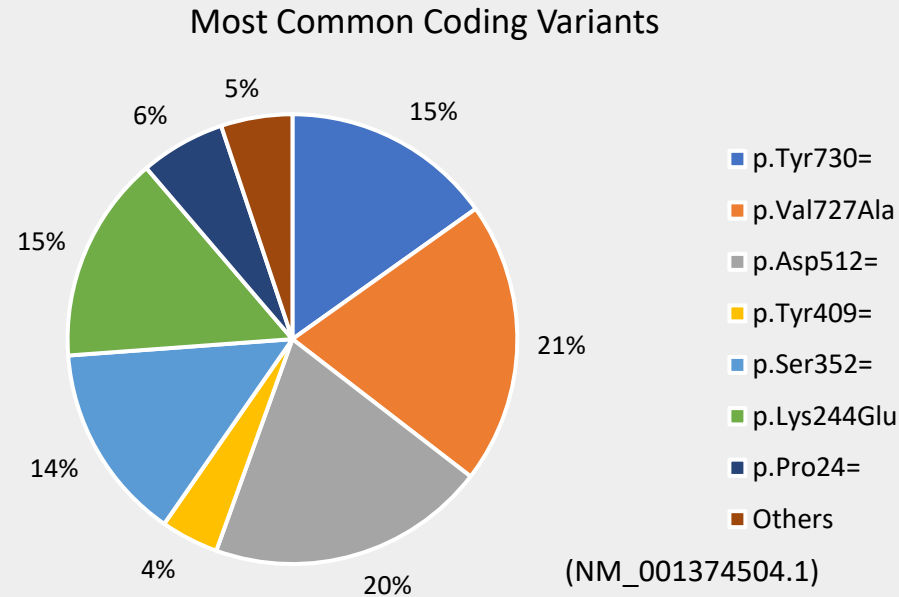
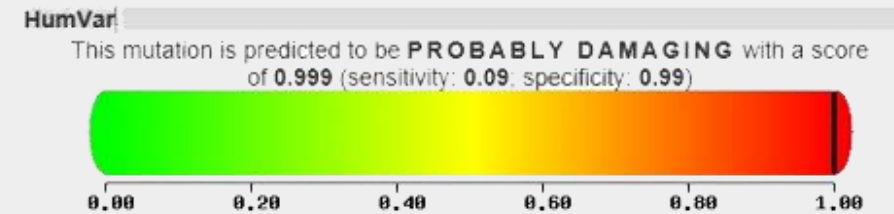
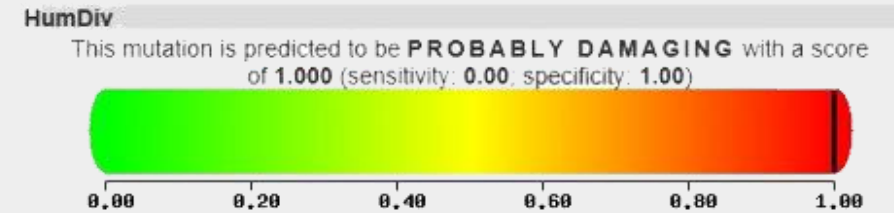


Figure 2. Most common variants found by NGS in the coding regions of *TMPRSS6* gene.

- ❖ We found two novel coding variants in *TMPRSS6* gene: **c.1585T>C (p.Cys529Arg)** and **c.1580T>G (p.Phe527Cys)**. These novel mutations were classified as pathogenic by *in silico* analyses through Polyphen2, SIFT, Missense3D and others (Figure 3).
- ❖ Through Phyre2 [3] we obtained the structure prediction for Matriptase-2 (Figure 4).

c.1585T>C (p.Cys529Arg)



c.1580T>G (p.Phe527Cys)

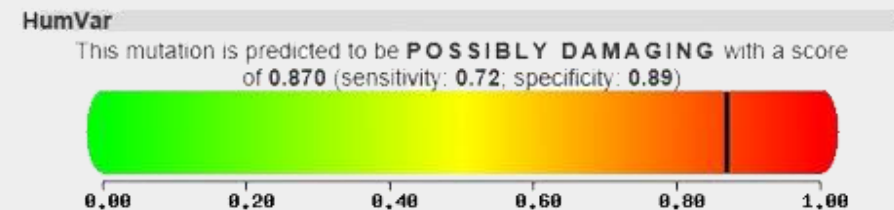
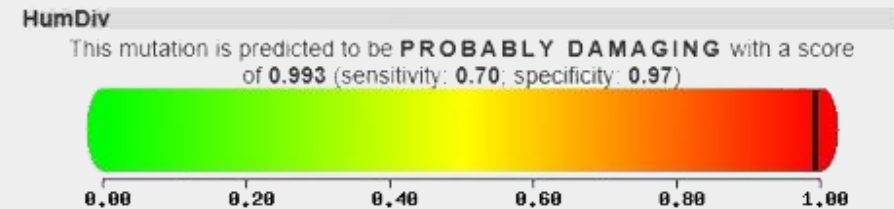


Figure 3. Prediction of the pathogenic effect of p.Cys529Arg and p.Phe527Cys alterations on Matriptase-2 protein by PolyPhen-2 software.

DISCUSSION AND CONCLUSIONS

- ❖ Our results widened the spectrum of *TMPRSS6* pathogenic variants underlying hereditary iron deficiency-related pathologies.
- ❖ With this study we found two novel pathogenic mutations in *TMPRSS6* gene: c.1585T>C (p.Cys529Arg) and c.1580T>G (p.Phe527Cys).
- ❖ NGS revealed to be an appropriate tool for *TMPRSS6* genetic screening.
- ❖ Functional studies should be performed to validate these findings.

References:

- [1] Cui Y *et al.*. *Kidney International* 76, 1137-41 (2009).
- [2] Poggiali E *et al.*. *American Journal of Hematology* 90, 306-309 (2014).
- [3] Kelley LA *et al.*. *Nature Protocols* 10, 845-858 (2015).

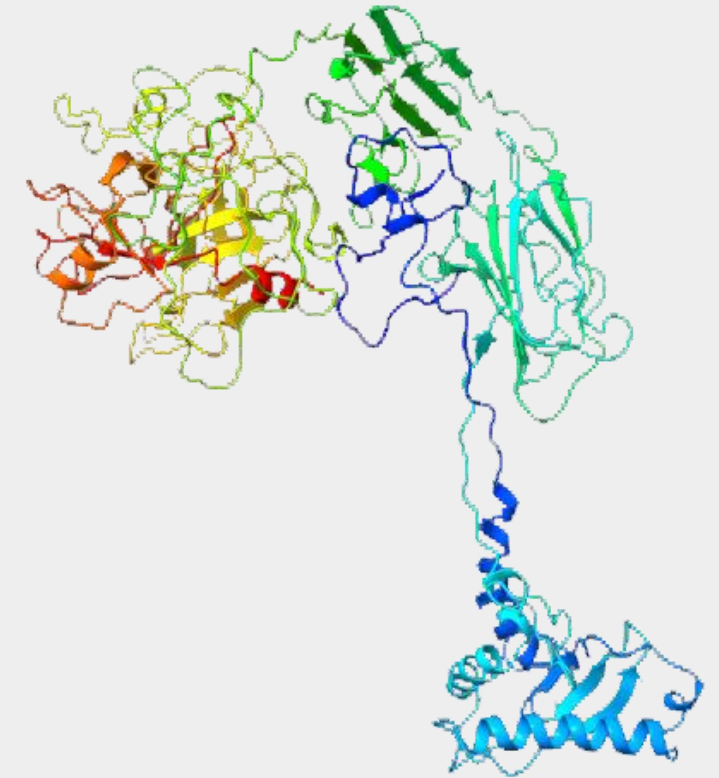


Figure 4. Matriptase-2 structure prediction by Phyre2 software.

Funding:

