FIP VIRTUAL EVENT SEP 2020

Standardised interpretation of CYP2D6 genotypes and phenotypes: from lab reports to clinical recommendations

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INTRODUCTION

Interpretation of CYP2D6 genotypes to assign phenotypes is critical since clinical recommendations are based on phenotypes. Inconsistencies in CYP2D6 classifications across laboratories have been identified over the years.

Discussions include whether (i) an activity score of 1 should be considered as a genetic normal or intermediate metaboliser, and (ii) crude grouping of allele function overlooks substrate-dependent effects of allelic variants, which may be particularly relevant for *CYP2D6*10* (Gaedigk et al, 2018). The *CYP2D6 Genotype to Phenotype Standardisation Project* addressed concerns of discordant phenotype assignments reaching a consensus (Caudle et al, 2020).

AIM

To determine the practical implications of the consensus on standardised CYP2D6 genotype to phenotype translation.

METHOD

- Buccal swabs were collected from 42 consenting patients on amitriptyline therapy attending Mater Dei Hospital. Ethics approval was granted by the University Research Ethics Committee, Malta.
- Lab analysis, using real-time PCR with SNP genotyping assays, reported *CYP2D6* diplotype (e.g. *1/*1), copy number variation (CNV e.g. 2), and phenotype (e.g. normal metaboliser).
- *CYP2D6* activity scores were calculated and the phenotypes inferred by lab reports reconsidered in line with the newly published standardisation consensus - downgrading a *CYP2D6* activity score of 1 from normal to intermediate and downgrading *CYP2D6*10* activity score from 0.5 to 0.25.

RESULTS

The lab reported 3 intermediate, 35 normal and 4 ultra-rapid CYP2D6 metabolisers (Table 1). Aberrant metabolism was identified in 17% of patients. The reconsideration exercise, updating the CYP2D6 metaboliser status in line with the standardisation consensus, assigned an intermediate metaboliser status to 14 patients previously categorised as normal, rendering around 50% of patients to deviate from the normal phenotype (Figure 1).

Standardised interpretation of CYP2D6 genotypes and phenotypes denoted an update to the lab-reported genotype-inferred phenotypes and corresponding clinical recommendations relevant to amitriptyline therapy in the patients under study (an example is presented in Table 2). The impact of consensus changes was evident in the CYP2D6 intermediate metaboliser status for which tricyclic antidepressant clinical guidelines recommend a 25% reduction in dose and therapeutic drug monitoring for dose adjustments[1].

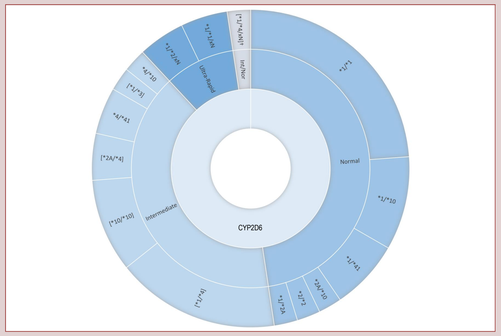

Figure 1: Distribution of patients categorised in line with the consensus on standardised CYP2D6 genotype to phenotype translation (N=42)

† The **1/*4/xN* genotype, with a CNV of 3, reported for 1 patient, triggers further considerations in view of **4* being a no function allele. Activity score is expected to lie between 1.0 and 2.0; **1/*4x2* (intermediate metaboliser) or **1x2/*4* (normal metaboliser). Genotyping panels with high coverage, hybrid detection, and determination of multiplied genes may facilitate additional investigations for accurate provision of phenotype prediction, particularly in such scenarios.

CYP2D6 Characterisation	Presentation	Number (%) in sample
Intermediate metaboliser	**4/*41, *4/*10*	3 (7%)
Normal metaboliser	**1/*1, [*1/*4], *1/*10, [*10/*10], *1/*41, [*2A/*4], *1/*2A, [*1/*3], *2/*2, *2A/*10, [*1/*4/xN]†*	35 (83%)
Ultra-Rapid metaboliser	**1/*1/xN, *1/*2/xN*	4 (10%)

Table 1: CYP2D6 metaboliser status characterised in the sample population (N=42), based on the laboratory report prior to the standardisation consensus - the square brackets [] highlight presentations that, following the consensus on genotype to phenotype, were considered as potential intermediate metabolisers

CYP2D6 diplotype	CNV		Metaboliser Status: lab reported pre-consensus	Metaboliser Status: updated post-consensus
**10/*10*	2		Normal (activity score = 1)	Intermediate (activity score = 0.5)
		Clinical annotation[1]	Normal metabolism to less active compounds. Initiate therapy with recommended starting dose for the tricyclic antidepressant.	Reduced metabolism to less active compounds, compared to normal metabolisers. Higher blood concentrations of active drug may increase the probability of side effects. Consider 25% reduction of recommended starting dose for the tricyclic antidepressant.

Table 2: Implications for a genotyped patient on amitriptyline therapy

[1]PharmGKB. Annotation of CPIC Guideline for amitriptyline and CYP2C19, CYP2D6. Available online: https://www.pharmgkb.org/guidelineAnnotation/PA166105006.

CONCLUSIONS

Lack of standardisation and incoherent groupings may thwart interpretation of results and make the drawing of concordant recommendations difficult. Developments in genomics, such as the latest consensus on CYP2D6 genotype-phenotype interpretation, augur enhanced standardisation across studies and in clinical practice. Pragmatic construal of standardisation concerns may necessitate review of genotype-inferred phenotypes stored in patient health records.

Further research with harmonised phenotype assignments and outcomes that may be unequivocally compared is anticipated to facilitate regulatory integration of genotype/phenotype information in the official drug product literature and throughout the evaluation of safety concerns (Mifsud Buhagiar et al, 2019). In effecting the translational quality of pharmacogenetics, specific factors, such as ethnicity and the potential of phenoconversion, still necessitate careful consideration.

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ACKNOWLEDGEMENTS

This research was funded by the ENDEAVOUR Scholarships Scheme, Malta. The authors thank Dr Anton Grech and Dr Marilyn Casha (Mater Dei Hospital, Msida, Malta) for their support in carrying out the clinical aspects of this work.

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