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RESISTANCE MUTATION PROFILES AND ANTIFUNGAL SUSCEPTIBILITY IN PRIORITY FUNGAL PATHOGENS

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Abstract:

This analysis examines how genetic classifications and sampling structure shape the interpretation of antifungal susceptibility in international resistance surveillance. A descriptive secondary analysis used published observations for 20 clinical Candida auris isolates collected in India between September 2017 and March 2020, comprising 60 paired isolate and drug measurements. Comparisons examined mutation presence, hotspot location and substitution identity using means, medians, dispersion and serial isolate sensitivity analysis. Mutant isolates exhibited fourfold higher median concentrations than wild type isolates across three echinocandins, although overlapping distributions limited individual discrimination. Identical substitutions showed different concentration profiles across drugs, while extreme observations separated arithmetic averages from typical responses. Retaining one representative from a documented patient cluster preserved the higher mutant micafungin median, with median ratios ranging from 2.67 to four. These findings refine the descriptive application of target modification theory by distinguishing aggregate genotype associations from individual susceptibility variation and sampling dependence. International surveillance reporting should preserve substitution identity, drug specific measurements and patient links to support interpretable comparisons across laboratories and health systems.

Key Words: Candida Auris; Antifungal Resistance; FKS1 Mutations; Echinocandin Susceptibility; Descriptive Secondary Analysis.

1. Introduction:

Interpreting antifungal resistance requires understanding what a mutation reveals about susceptibility and how much variation remains within the same genotype. For Candida auris, this distinction matters because molecular surveillance and laboratory susceptibility testing inform responses to a pathogen capable of spreading through healthcare settings. The World Health Organization, 2022, identified stronger laboratory capacity and surveillance as priorities for addressing fungal infections and antifungal resistance. Reliable interpretation therefore depends on preserving the relationship between genetic classifications, measured drug concentrations and the biological units represented in surveillance data.

FKS1 provides a molecular basis for examining this relationship. It encodes a catalytic component of glucan synthase, the enzyme complex targeted by echinocandins. Amino acid substitutions can reduce enzyme sensitivity to these drugs, increasing the concentration required to inhibit fungal growth. Garcia-Effron et al., 2010, demonstrated reduced glucan synthase sensitivity associated with FKS alterations in clinical Candida isolates. In Candida auris, Kordalewska et al., 2018, linked S639F to elevated echinocandin concentrations and reduced treatment response in an experimental infection model. These findings establish the relevance of target modification while leaving the interpretation of individual susceptibility measurements dependent on the substitution and drug examined.

Mutation presence, hotspot location and amino acid substitution describe different resolutions of the same molecular profile. Mutation presence distinguishes altered sequences from wild type sequences. Hotspot location identifies the region containing an alteration, while substitution identity preserves the specific amino acid change. Combining these dimensions into a single resistance label can conceal differences among substitutions and variation among isolates carrying the same substitution. Their analytical value therefore lies in separate comparisons with measured susceptibility rather than an assumption that they represent independent mechanisms or form a numerical resistance scale.

The outcome also requires careful interpretation. Minimum inhibitory concentration measures the drug concentration required to inhibit growth under specified laboratory conditions. It provides a quantitative susceptibility measure, but its interpretation depends on drug identity and testing method. Arendrup et al., 2017, compared CLSI and EUCAST measurements for Candida auris and examined tentative epidemiological cutoff values. Their work demonstrates why susceptibility comparisons must retain the conditions under which concentrations were obtained. A lower concentration for one drug does not, by itself, establish superior clinical effectiveness.

The closest empirical foundation is the investigation by Sharma et al., 2022, which evaluated Candida auris isolates from multiple centres in India and reported paired FKS1 genotypes and echinocandin susceptibility measurements. That investigation already established variation associated with F635Y, F635L,

S639F and R1354S and examined experimental treatment responses. The present analysis uses its published isolate records for a narrower descriptive purpose: to distinguish differences in typical concentrations from differences driven by upper observations and to evaluate how a documented serial patient cluster affects those summaries. The contribution is a secondary examination of distributional interpretation and sample sensitivity, grounded in an existing molecular susceptibility dataset.

This analysis aims to characterise how echinocandin susceptibility varies across observed FKS1 mutation profiles in Candida auris. It asks how micafungin concentrations differ between mutant and wild type isolates, what concentration patterns occur across hotspot categories, and how substitution profiles vary across micafungin, anidulafungin and caspofungin. The dataset contains 20 clinical isolates and one reference comparator, with three linked drug measurements per isolate. Clinical summaries exclude the reference comparator. The source collection covered September 2017 to March 2020, and the descriptive approach reports counts, means, standard deviations, medians and observed ranges. An exploratory sensitivity analysis retains one representative at a time from the six isolates linked to one patient.

The completed comparisons show why these distinctions matter. Mutant isolates have higher median concentrations across all three drugs, while overlapping ranges and variation within substitution categories qualify the information conveyed by mutation presence alone. The micafungin comparison retains its direction across the implemented serial cluster selections, although its magnitude changes. These findings refine the descriptive application of target modification theory by separating a genotype associated shift from the distribution of individual measurements around that shift. Their practical relevance concerns the reporting of susceptibility evidence: retaining substitution identity, drug specific concentrations and documented patient links improves the traceability of comparisons. The transferable contribution is this analytical distinction, while the observed concentration distributions remain specific to the selected Candida auris records.

2. Theory, Conceptual Framework and Research Questions Development:

This analysis draws on the molecular theory of antifungal target modification. Echinocandins inhibit glucan synthase, an enzyme complex involved in fungal cell wall production. FKS1 encodes a catalytic component of this complex. Changes in its amino acid sequence can reduce enzyme sensitivity to echinocandins, increasing the drug concentration required to inhibit fungal growth. Garcia-Effron et al., 2010, demonstrated reduced glucan synthase sensitivity in Candida isolates carrying resistance associated FKS substitutions. This mechanism provides the theoretical basis for examining the relationship between FKS1 mutation profiles and antifungal susceptibility.

The focal explanatory construct is the observed FKS1 mutation profile, represented by mutation presence, hotspot location and amino acid substitution. The outcome is antifungal susceptibility, measured through minimum inhibitory concentration in mg/L. Higher concentrations indicate lower susceptibility under the reported assay conditions. These genotype dimensions describe related properties of the same molecular target rather than three independent resistance mechanisms. The framework therefore guides separate descriptive comparisons of susceptibility across their observed categories.

Mutation presence distinguishes isolates carrying a reported FKS1 substitution from isolates classified as wild type. Target modification provides a theoretical expectation of higher minimum inhibitory concentrations among mutant isolates. However, mutation presence alone does not describe the functional consequence of a particular substitution. Ben-Ami et al., 2011, showed that FKS1 mutations can alter glucan synthase catalytic capacity alongside resistance. Their findings support interpreting genotype through its effect on enzyme function rather than assuming that every mutation produces an equivalent susceptibility profile.

This analysis compares the distributions of micafungin minimum inhibitory concentrations between mutant and wild type isolates. Micafungin provides the primary susceptibility measure, while anidulafungin and caspofungin provide complementary descriptions of the same construct. Medians, observed ranges and individual measurements characterise group differences without treating repeated drug measurements as independent isolates.

RQ1: How do micafungin minimum inhibitory concentrations differ between isolates with a reported FKS1 mutation and wild type isolates?

Hotspot location identifies whether a reported substitution occurs in hotspot 1 or hotspot 2. Its conceptual relevance follows from the position of an alteration within the antifungal target. Nevertheless, location is a categorical property, not a scale on which one hotspot necessarily represents greater resistance. Hou et al., 2019, demonstrated that molecular assays can identify specific FKS1 hotspot substitutions accurately against sequencing results. This supports distinguishing the presence of a molecular alteration from its position and identity when organising susceptibility comparisons.

The supplied dataset identifies hotspot 1 substitutions, a hotspot 2 substitution and wild type isolates. This analysis describes minimum inhibitory concentrations within each category while retaining the distinction between hotspot location and substitution identity. The comparison establishes the susceptibility patterns represented by the observations rather than imposing a directional ranking on the hotspot categories.

RQ2: What minimum inhibitory concentration patterns occur among isolates with hotspot 1 substitutions, a hotspot 2 substitution and wild type FKS1?

Amino acid substitution provides the most specific genotype classification available. It distinguishes F635Y, F635L, S639F and R1354S rather than combining all altered sequences into one group. Different substitutions can produce different functional changes, so their susceptibility profiles need not converge. Maphanga et al., 2021, identified S639P substitutions in echinocandin resistant Candida auris isolates, providing further evidence that the identity of an FKS1 alteration matters when interpreting resistance associated genotypes.

Drug identity also defines the conditions under which genotype and susceptibility are compared. Kordalewska et al., 2018, linked S639F to elevated echinocandin minimum inhibitory concentrations but also documented paradoxical growth during caspofungin testing among wild type isolates. This finding distinguishes target associated resistance from assay behaviour and supports examining each antifungal separately. Accordingly, this analysis describes variation within each substitution category and compares the corresponding profiles across micafungin, anidulafungin and caspofungin.

RQ3: How do minimum inhibitory concentration profiles vary across the observed amino acid substitutions and wild type isolates for each antifungal?

The conceptual framework links observed FKS1 genotype categories with observed susceptibility measurements in Candida auris. It represents an association framework informed by target modification theory. Mutation presence, hotspot location and substitution identity organise the comparisons, while minimum inhibitory concentration supplies the common outcome measure. The isolate remains the observational unit, with the three antifungal measurements retained as linked observations.

3. Data:

This section establishes data provenance, documents sample construction and defines the observed genotype and susceptibility measures. It reports the checks and descriptive procedures implemented to examine variation across FKS1 mutation profiles.

3.1 Data Sources, Population, and Sample Construction:

The analytical dataset comes from Table 2 of the article by Sharma et al., cited through the accepted manuscript posted on 15 November 2021. The source investigators evaluated 199 Candida auris isolates from 194 invasive candidiasis cases across 30 centres in India between September 2017 and March 2020. The collection formed part of the Indian Council of Medical Research antimicrobial resistance surveillance programme, coordinated through the Postgraduate Institute of Medical Education and Research in Chandigarh. The source is accessible through DOI 10.1128/AAC.01652-21 and PubMed identifier 34780273. The publisher retains copyright, and public access does not establish an unrestricted reuse licence. The supplied workbook does not record its original extraction date or a separate dataset version.

The target population comprises clinical Candida auris isolates with paired FKS1 genotype and echinocandin susceptibility measurements. The accessible analytical frame contains the 21 isolates reported in the selected source table, comprising 20 clinical isolates and one reference comparator. Selection in the source emphasised reduced susceptibility and comparison isolates. Accordingly, the extracted records constitute a purposive molecular susceptibility sample rather than a probability sample of infections.

The observational unit is the isolate. Each isolate has measurements for micafungin, anidulafungin and caspofungin, producing 63 linked isolate and drug records. The structure is a cross section with repeated drug measurements. The source provides a collection interval but the extracted table does not identify individual collection dates. Consequently, the data support comparisons across genotypes and drugs without supporting temporal trend estimation.

International relevance arises from the occurrence of Candida auris across geographically distinct settings. Lockhart et al., 2017, documented its emergence across continents, while Chowdhary et al., 2018, and Maphanga et al., 2021, reported resistance profiles in India and South Africa. These publications establish the relevance of the organism and research question; they contribute no additional observations to this dataset. The species designation follows the source record, with accurate identification recognised as essential to interpreting Candida auris susceptibility data, as demonstrated by Kordalewska et al., 2017.

Table 1: Sample construction

Stage	Isolates	Isolate and Drug Observations	Reason or Rule
Reported source clinical cohort	199	597	Three echinocandin measurements per isolate in the source cohort
Clinical isolates outside the extracted table	179	537	Not included in the selected source table
Extracted clinical records	20	60	Paired genotype and susceptibility measurements available

Stage	Isolates	Isolate and Drug Observations	Reason or Rule
Reference comparator added	1	3	CBS12372 retained for source reconciliation
Audited workbook	21	63	Complete extracted source table
Reference comparator excluded from clinical summaries	1	3	Reference strain separated from clinical isolates
Primary descriptive sample	20	60	Clinical isolates with complete focal measurements
Additional serial isolates excluded in sensitivity analysis	5	15	One representative retained from the six isolates linked to one patient
Sensitivity sample	15	45	Clinical records after reducing the documented serial cluster

The clinical exclusion and sensitivity rules were applied during the present descriptive reanalysis. The reference comparator remains in the source audit. No clinical isolate was removed because of its minimum inhibitory concentration.

3.2 Data Integration, Cleaning, and Quality Assurance:

This analysis integrated genotype, specimen and susceptibility fields within a single source table using the reported isolate identifier. Reshaping produced three records per isolate, with isolate identifier and drug name forming a unique composite key. The audit identified no duplicate isolate identifiers, duplicate composite keys, unmatched records or conflicting susceptibility values. All 63 measurements agreed between the source isolate sheet and the corresponding analytical records.

Repeated measurements were retained according to their biological meaning. Three drug measurements describe the same isolate, while six distinct isolate identifiers belong to one reported serial patient cluster. These records are not duplicate rows. Other patient relationships are not identified in the extracted data, so distinct isolate identifiers do not establish patient independence.

Reported concentrations were preserved in mg/L, including values recorded as 0.12. They were not replaced with assumed dilution values. Preserving the reported testing method and numeric scale maintains distinctions documented in comparisons of susceptibility platforms by Arendrup et al., 2017, and Kathuria et al., 2015. Caspofungin measurements remained separately labelled because Espinel-Ingroff et al., 2013, documented substantial interlaboratory variability for this agent.

All isolate identifiers, genotype classifications, specimen categories and susceptibility measurements were complete. Eleven records lacked a reported GenBank accession, comprising ten clinical wild type isolates and the reference comparator. These entries remained labelled Not reported and did not trigger exclusion. No missing value was replaced with zero, and no imputation or interpolation was performed.

Checks confirmed positive numeric concentrations, three named drugs per isolate, consistent genotype coding and agreement between calculated logarithms and their source concentrations. Valid extreme measurements, including concentrations of 16 mg/L, were retained. No trimming, winsorisation or outcome-based exclusion was applied.

Minimum inhibitory concentrations remained continuous measurements. This analysis did not impose a common resistance threshold across drugs or infer lineage from specimen or geographical information. These decisions preserve the distinction between measured concentrations and interpretive classifications discussed by Pfaller et al., 2011, and avoid assuming the lineage comparability examined by Szekely et al., 2019.

3.3 Variable Measurement, Construction, and Validation:

FKS1 mutation profile is represented by three observed dimensions. Mutation presence distinguishes wild type isolates from isolates carrying a reported substitution. Hotspot location identifies hotspot 1, hotspot 2 or no reported hotspot mutation. Substitution identity preserves the categories F635Y, F635L, S639F, R1354S and wild type.

These classifications reflect molecular properties of the same target. Garcia-Effron et al., 2010, linked FKS alterations to reduced glucan synthase sensitivity, while Ben-Ami et al., 2011, demonstrated that substitutions can alter enzyme function. Accordingly, the dimensions are used as alternative grouping variables rather than combined into an additive index.

The outcome is antifungal susceptibility, measured through minimum inhibitory concentration. Micafungin is the primary descriptive outcome, with anidulafungin and caspofungin supplying complementary drug specific measurements. Higher concentrations indicate lower susceptibility under the reported assay conditions. Molecular identification of a substitution and phenotypic measurement remain distinct, consistent with the diagnostic distinction demonstrated by Hou et al., 2019. Kordalewska et al., 2018, further showed why caspofungin assay behaviour requires separate interpretation.

The workbook also contains the base two logarithm of each concentration. Every logarithm was checked against its corresponding positive source value. This transformation changes the measurement scale without creating an additional outcome construct. Descriptive statistics below use the original mg/L scale. Minimum inhibitory concentrations are interpreted as laboratory measurements; pharmacodynamic treatment responses require additional evidence of the kind examined by Lepak et al., 2017.

Table 2: Variable dictionary

Variable or Indicator	Analytical Role	Definition and Construction	Source and Identifier	Unit and Frequency	Transformation and Direction	Missing Value Rule	Coverage and Limitation
Isolate identifier	Observational key	Reported NCCPF identifier or CBS12372	Source Table 2, isolate ID	One identifier per isolate	None	Complete	Identifies isolates, not necessarily independent patients
Mutation presence	Genotype grouping	Zero for wild type and one for any reported FKS1 substitution	Source Table 2, FKS1 mutation	Binary, once per isolate	One denotes a reported substitution	Complete	Ten mutant and ten wild type clinical isolates
Hotspot location	Genotype grouping	F635Y, F635L and S639F assigned to hotspot 1; R1354S to hotspot 2; wild type assigned None	Source Table 2, FKS1 mutation	Categorical, once per isolate	Categories have no numerical ranking	None is a substantive category	Nine hotspot 1 and one hotspot 2 clinical isolates
Amino acid substitution	Genotype grouping	F635Y, F635L, S639F, R1354S or wild type	Source Table 2, FKS1 mutation	Categorical, once per isolate	None	Complete	Category sizes range from one to ten
Minimum inhibitory concentration	Outcome	Reported concentration for each named antifungal	Source Table 2, MFG, AFG and CAS	mg/L, once per isolate and drug	Higher values indicate lower susceptibility	Complete	Twenty clinical observations per drug
Base two logarithm of concentration	Alternative outcome scale	Base two logarithm of the reported concentration	Workbook formula linked to source MIC	Logarithmic scale, once per isolate and drug	A one unit increase represents a doubling of concentration	All concentrations positive	Calculated for all 63 extracted records
Drug identity	Measurement condition	Micafungin, anidulafungin or caspofungin	Source Table 2, drug headings	Categorical, three measurements per isolate	Analysed separately	Complete	Drug records within an isolate are linked
Specimen	Sample descriptor	Blood, urine, endotracheal tube secretion or bronchoalveolar lavage fluid	Source Table 2, sample	Categorical, once per isolate	None	Complete	Clinical counts are 12, five, two and one, respectively
Clinical record indicator	Sample eligibility	Clinical isolate or reference comparator	Workbook record classification	Binary, once per isolate	Reference comparator excluded from clinical summaries	Complete	Twenty clinical isolates and one comparator
Serial cluster indicator	Dependence descriptor	Six reported isolates linked to one patient	Source narrative and workbook cluster field	Categorical, once per isolate	No ordering inferred	Other patient links remain unidentified	Supports the implemented sensitivity analysis
GenBank accession	Provenance identifier	Reported sequence accession	Source Table 2, GenBank accession	Identifier, once per isolate	None	Not reported retained as text	Eleven unavailable accessions across the audit sample

Table 3: Descriptive statistics for the clinical sample

Antifungal	Valid count	Mean mg/L	Standard deviation mg/L	Median mg/L	Minimum mg/L	Maximum mg/L
Micafungin	20	1.519	3.450	0.750	0.120	16.000
Anidulafungin	20	1.753	1.841	1.000	0.060	8.000
Caspofungin	20	2.868	4.657	1.000	0.120	16.000

The clinical sample contains ten wild type isolates, four F635L isolates, three S639F isolates, two F635Y isolates and one R1354S isolate. Micafungin medians are 0.25 mg/L for wild type isolates, 1 mg/L for each of the F635L, F635Y and S639F categories, and 2 mg/L for R1354S. The S639F observations span 1 to 16 mg/L, demonstrating why the mean alone does not adequately describe that category. Standard deviation is undefined for the single R1354S observation.

Validation consisted of source reconciliation, identifier checks, category consistency checks and verification of calculated logarithms. These procedures establish transcription and construction consistency without constituting an independent laboratory replication.

3.4 Analytical Framework, Identification, and Reproducibility:

The analysis is descriptive. It characterises observed susceptibility distributions by mutation presence, hotspot location and substitution identity, separately for each antifungal. Valid counts, arithmetic means, sample standard deviations, medians and observed ranges provide complementary summaries. This emphasis on distributional information follows the reporting concerns identified by Weissgerber et al., 2015.

The primary clinical summaries retain 20 isolates and 60 linked drug measurements. The observational count remains 20 isolates, with patient dependence considered separately. This distinction follows the treatment of observational and experimental units discussed by Lazic et al., 2018, and the independence concerns outlined by Vaux, 2012.

An exploratory sensitivity analysis reduced the documented six isolate patient cluster to one representative. The principal sensitivity sample retained NCCPF470237, selected through the lowest reported isolate identifier, and contained 15 clinical isolates. Repeating the calculation with each alternative cluster member produced micafungin means from 1.775 to 1.825 mg/L and medians from 0.5 to 1 mg/L. The corresponding full clinical mean was 1.519 mg/L and the median was 0.75 mg/L. These differences document the effect of the known serial cluster on the descriptive distribution.

The analysis reports observed magnitudes without significance labels. Wasserstein and Lazar, 2016, distinguish statistical significance from substantive interpretation, while Greenland et al., 2016, emphasise that inferential conclusions depend on assumptions about sampling and analysis. Here, interpretation remains confined to the selected clinical records and the implemented sensitivity comparisons.

Reproducibility is supported by preserved isolate identifiers, source table references, sequence accessions where reported, explicit genotype coding and linked concentration formulas. The same clinical eligibility rule applies across all three drugs. Documented exclusions affect record type and known serial dependence, while the reported concentrations remain unchanged.

4. Methods:

4.1 Research Design and Analytical Scope:

This analysis used a descriptive secondary design to examine susceptibility distributions across observed FKS1 genotype categories. The observational unit was the clinical isolate, with three linked antifungal measurements per isolate. The analytical targets were the distributions of minimum inhibitory concentrations within genotype groups and the ratios of mutant to wild type medians for each drug.

The clinical sample followed the construction documented in Table 1, while measurement definitions followed the dictionary in Table 2. Micafungin supplied the primary comparison. Anidulafungin and caspofungin provided complementary descriptions of susceptibility under separate drug conditions. Mutation presence, hotspot location and substitution identity served as alternative grouping classifications.

Useful variation arose from differences in genotype and measured concentrations across the retained isolates. Comparisons characterised the selected records rather than estimating treatment effects or population resistance prevalence. The purposive source selection and documented serial sampling defined the interpretive scope. Distinguishing isolates, patients and repeated measurements followed the principles discussed by Lazic et al., 2018.

4.2 Measurement Alignment and Descriptive Calculations:

Concentrations remained on the reported mg/L scale. Mutation presence distinguished wild type isolates from isolates carrying any reported substitution. Hotspot 1 comprised F635Y, F635L and S639F, while hotspot 2 comprised R1354S. Wild type isolates formed a separate category. Substitution comparisons preserved each reported amino acid classification.

Each isolate contributed once to each drug specific summary. No patient weighting was applied to the primary descriptive sample. Valid counts, arithmetic means, sample standard deviations, medians, minima and maxima described the overall clinical sample and genotype categories. Equation 1 defines the arithmetic mean:

$$\bar{M}_{gd} = \frac{\sum_{i \in I_g} M_{id}}{n_g}$$

Here, M_{id} denotes the reported concentration for isolate i and drug d, I_g denotes the isolates assigned to genotype group g, and $n_g$denotes their count. The quantity $\bar{M}_{gd}$is the mean concentration within that group for that drug. Equation 2 defines the sample standard deviation:

$$s_{gd} = \sqrt{\frac{\sum_{i \in I_g} \left(M_{id} - \bar{M}_{gd}\right)^2}{n_g - 1}}$$

Here, s_{gd} denotes dispersion across the observed concentrations. It was calculated only for groups containing at least two isolates. A single observation retained its reported concentration, with standard deviation treated as undefined.

Medians were obtained by ordering concentrations within each group. For an even count, the median was the arithmetic average of the two central observations. Consequently, a reported median could lie between tested concentrations without representing an additional measurement. Means, medians and observed ranges were retained together because similar averages can conceal different distributions, as demonstrated by Weissgerber et al., 2015. Equation 3 defines the comparison of group medians:

$$R_d = \frac{\widetilde{M}_{\text{mutant,d}}}{\widetilde{M}_{\text{wild type,d}}}$$

Here, R_d denotes the ratio for drug d, and each $\widetilde{M}$denotes the corresponding group median. Values above one indicate a higher median concentration among mutant isolates. All denominators were positive. Paired drug comparisons counted whether concentrations for the same isolate were lower, equal or higher across the specified drug pair. These comparisons used the original concentrations and preserved isolate matching.

4.3 Processing, Quality Assurance and Implementation:

The supplied workbook was processed using Python 3.12.14. The standard library modules zipfile and xml.etree. Element Tree read the workbook records, while statistics and collections supported descriptive calculations and count verification.

Processing began with the source isolate sheet. Reported identifiers linked genotype, specimen, accession and concentration fields. The reference comparator CBS12372 remained available for source reconciliation and was excluded from clinical calculations. The resulting clinical records were grouped separately by mutation presence, hotspot location and substitution identity.

Quality checks assessed identifier uniqueness, completeness of focal fields, positive numeric concentrations and consistency between the source isolate sheet and analytical drug records. The isolate identifier and drug name formed the composite key for checking the reshaped dataset. Each source concentration was compared with its corresponding analytical value. Calculated base two logarithms were checked against their positive source concentrations, while the reported descriptive comparisons used the original scale.

All focal clinical measurements were complete. Unreported sequence accessions remained explicitly labelled and did not determine analytical eligibility. Reported extreme concentrations were retained. No imputation, interpolation, trimming or winsorisation was applied. Calculations used full available precision, with rounding applied only when presenting results.

These checks established transcription and calculation consistency. They did not substitute for laboratory replication.

4.4 Serial Isolate Sensitivity and Reproducibility:

The sensitivity analysis addressed the disproportionate representation of one documented patient through six distinct isolates. These comprised NCCPF470237, NCCPF470238, NCCPF470239, NCCPF470240, NCCPF470241 and NCCPF470242.

The principal sensitivity calculation retained NCCPF470237, selected through the lowest reported identifier, alongside the clinical isolates outside that cluster. This produced a sample of 15 isolates. The identifier rule supplied a deterministic selection and did not imply collection chronology.

The calculation was then repeated six times, retaining each cluster member in turn while holding the remaining clinical records constant. For every selection, this analysis recalculated the overall micafungin mean and median, the mutant and wild type counts and medians, and the median ratio defined in Equation 3. Comparisons assessed changes in direction and magnitude attributable to the documented cluster representation. Other patient relationships were not inferred from isolate identifiers.

The clinical restriction and serial representative comparisons were exploratory decisions applied during the secondary reanalysis. Reproducibility rests on the preserved source identifiers, the coding dictionary in Table 2, the explicit representative selections and the calculations defined above. Together, these procedures answer the research questions through traceable descriptions of genotype related susceptibility variation and sensitivity to known repeated sampling.

5. Findings:

This analysis examines how antifungal susceptibility varies with FKS1 mutation presence, hotspot location and amino acid substitution. It presents the clinical sample, compares concentrations across genotype categories and evaluates sensitivity to the documented serial patient cluster. The findings answer the three research questions through descriptive comparisons of measured susceptibility.

The analytical sample contains 20 clinical Candida auris isolates with complete measurements for micafungin, anidulafungin and caspofungin, yielding 60 linked drug observations. The source collection covered September 2017 to March 2020 across centres in India. One reference comparator was excluded from the clinical summaries. The retained isolates comprise 12 blood, five urine, two endotracheal secretion and one

bronchoalveolar lavage specimen. Six isolates belong to one documented patient cluster. Accordingly, the 60 drug observations represent measurements from 20 isolates rather than 60 independent biological units, consistent with the distinction between measurement counts and independent units described by Lazic et al., 2018.

The descriptive statistics table shows substantial dispersion within the measured concentration distributions. Micafungin has the lowest overall median at 0.75 mg/L, while anidulafungin and caspofungin each have a median of 1 mg/L. Micafungin and caspofungin reach maximum concentrations of 16 mg/L, whereas anidulafungin reaches 8 mg/L. Means exceed medians for all three drugs, indicating that upper observations influence their arithmetic averages.

Descriptive Statistics for the Clinical Sample:

Antifungal	Isolates	Mean mg/L	Standard deviation mg/L	Median mg/L	Observed range mg/L
Micafungin	20	1.519	3.450	0.750	0.12 to 16
Anidulafungin	20	1.753	1.841	1.000	0.06 to 8
Caspofungin	20	2.868	4.657	1.000	0.12 to 16

Ten clinical isolates carry a reported FKS1 substitution, and ten have wild type FKS1. Mutant isolates have higher median concentrations for each antifungal. The micafungin median is 1 mg/L among mutants and 0.25 mg/L among wild type isolates. Corresponding medians are 2 and 0.5 mg/L for anidulafungin, and 3 and 0.75 mg/L for caspofungin. Each comparison therefore produces a fourfold ratio of group medians.

Susceptibility by Mutation Presence:

Antifungal	Genotype	Isolates	Mean mg/L	Standard deviation mg/L	Median mg/L	Observed range mg/L
Micafungin	Wild type	10	0.487	0.548	0.250	0.12 to 2
Micafungin	Mutant	10	2.550	4.740	1.000	0.5 to 16
Anidulafungin	Wild type	10	0.606	0.366	0.500	0.06 to 1
Anidulafungin	Mutant	10	2.900	2.025	2.000	1 to 8
Caspofungin	Wild type	10	0.736	0.589	0.750	0.12 to 2
Caspofungin	Mutant	10	5.000	5.944	3.000	1 to 16

These comparisons answer RQ1: mutation presence is associated descriptively with higher micafungin concentrations in the retained sample. The direction also appears in the other two antifungals and is consistent with the mutation associated susceptibility reductions reported by Kordalewska et al., 2018. However, the micafungin ranges overlap between 0.5 and 2 mg/L. Mutation presence separates group centres without uniquely determining an individual isolate's measured concentration.

Hotspot classification divides the clinical sample into nine hotspot 1 isolates, one hotspot 2 isolate and ten wild type isolates. Hotspot 1 medians are 1 mg/L for micafungin, 2 mg/L for anidulafungin and 2 mg/L for caspofungin. The hotspot 2 observation records 2, 2 and 16 mg/L, respectively. Wild type medians are lower for all three drugs. These observations answer RQ2 by identifying the concentration patterns represented within each location category. The hotspot 2 values describe the single R1354S isolate and do not establish a general ranking between hotspots.

Substitution identity reveals variation concealed by the binary mutation classification. F635Y, F635L and S639F each have a micafungin median of 1 mg/L, but their distributions differ. Both F635Y isolates record 1 mg/L. F635L observations range from 0.5 to 1 mg/L. S639F observations comprise two measurements of 1 mg/L and one of 16 mg/L, producing a mean of 6 mg/L despite a median of 1 mg/L. The distinction between molecular identification and measured phenotype remains important: Hou et al., 2019, validated detection of specific resistance associated substitutions against sequencing, while the present observations demonstrate variation in concentrations within a shared substitution category.

Susceptibility Profiles by Amino Acid Substitution:

FKS1 Category	Hotspot	Isolates	Micafungin Median and Range Mg/L	Anidulafungin Median and Range Mg/L	Caspofungin Median and Range Mg/L
Wild type	None	10	0.25; 0.12 to 2	0.50; 0.06 to 1	0.75; 0.12 to 2
F635Y	Hotspot 1	2	1; 1 to 1	1.50; 1 to 2	10; 4 to 16
F635L	Hotspot 1	4	1; 0.5 to 1	2; 2 to 2	1; 1 to 1
S639F	Hotspot 1	3	1; 1 to 16	4; 4 to 8	4; 2 to 4

FKS1 Category	Hotspot	Isolates	Micafungin Median and Range Mg/L	Anidulafungin Median and Range Mg/L	Caspofungin Median and Range Mg/L
R1354S	Hotspot 2	1	2; single observation	2; single observation	16; single observation

Drug profiles also diverge within substitution categories. F635Y has a caspofungin median of 10 mg/L alongside a micafungin median of 1 mg/L. F635L records caspofungin concentrations of 1 mg/L and anidulafungin concentrations of 2 mg/L throughout its four observations. The R1354S isolate records a caspofungin concentration eight times its concentration for either alternative drug. These comparisons answer RQ3: the observed substitution profiles differ across antifungals, and a shared mutation classification does not imply equivalent concentrations across drugs.

Paired comparisons reinforce this distinction. Micafungin concentrations are lower than anidulafungin concentrations in ten isolates, equal in seven and higher in three. Micafungin concentrations are lower than caspofungin concentrations in 12 isolates, equal in five and higher in three. Thus, the lower overall micafungin median does not represent a uniform ordering across isolates. These are laboratory concentration comparisons, interpreted within the testing framework examined by Arendrup et al., 2017.

Caspofungin displays the greatest overall dispersion, with a standard deviation of 4.657 mg/L. Its mutant distribution spans 1 to 16 mg/L, and the F635Y pair spans 4 to 16 mg/L despite identical substitution labels. The present data establish this observed variation without identifying its source. The interpretation retains the assay specific caution warranted by the interlaboratory caspofungin variability documented by Espinel-Ingroff et al., 2013.

The exploratory sensitivity analysis retained one representative from the six isolates linked to one patient, reducing the sample to 15 clinical isolates. Retaining NCCPF470237 produced a micafungin mean of 1.825 mg/L and median of 1 mg/L, compared with 1.519 and 0.75 mg/L in the full clinical sample. Across all six alternative representative selections, the overall mean ranged from 1.775 to 1.825 mg/L and the median ranged from 0.5 to 1 mg/L.

The direction of the mutation presence comparison persisted across these selections. Mutant micafungin medians remained at 1 mg/L, while wild type medians ranged from 0.25 to 0.375 mg/L. The ratio of group medians therefore ranged from 2.67 to four. The serial cluster affects the magnitude of the descriptive comparison, while the higher mutant median remains present in every implemented selection.

The findings identify three empirical patterns. Mutant isolates have higher central concentrations across all three antifungals. Hotspot and substitution classifications reveal drug specific variation within that aggregate difference. The micafungin comparison retains its direction after reducing the documented serial cluster, although its magnitude changes. These conclusions describe the selected clinical isolates and preserve the observed overlap and variation within genotype categories.

6. Discussion:

FKS1 mutation status captures a shift in antifungal susceptibility while leaving substantial variation within genotype categories. Table 5 shows higher median concentrations among mutant isolates across all three echinocandins, with a fourfold ratio of mutant to wild type medians. However, overlapping micafungin concentrations indicate that the binary mutation classification does not determine an individual isolate's phenotype. The contribution of this reanalysis lies in distinguishing the shift between genotype groups from variation within those groups and examining how both respond to sample construction. Shields et al., 2012, demonstrated the clinical relevance of FKS mutations in Candida glabrata, where mutation detection predicted therapeutic failure more effectively than minimum inhibitory concentration alone. The present findings extend the interpretive distinction to the observed Candida auris profiles: genotype and measured susceptibility provide related information at different levels of resolution.

The genotype comparisons are consistent with target modification theory, but their meaning depends on the antifungal being examined. Table 6 shows that identical substitution labels coexist with different concentration profiles across drugs. F635Y isolates have a micafungin median of 1 mg/L alongside a caspofungin median of 10 mg/L, while F635L isolates display a different ordering. These observations refine the conceptual link between target alteration and susceptibility by locating the association within a specific genotype and drug combination. Evidence from Kuwait also demonstrates the relevance of substitution identity: Asadzadeh et al., 2022, identified hotspot 1 alterations and the hotspot 2 substitution R1354H among isolates with reduced echinocandin susceptibility. Their findings contextualise the hotspot 2 observation here without making R1354H and R1354S functionally interchangeable. The theoretical implication is that hotspot membership organises molecular information, while substitution identity and drug measurements remain necessary for interpreting the observed phenotype.

The clearest distributional signal is the separation between typical concentrations and the upper observations influencing group means. Table 6 reports the same micafungin median for F635Y, F635L and S639F, although their observed ranges differ. Within S639F, two concentrations of 1 mg/L and one of 16 mg/L produce a mean substantially above the median. Consequently, a ranking based on means would emphasise a

different feature of susceptibility from a ranking based on medians. This changes the interpretation of apparent substitution dominance: the strongest arithmetic contrast can reflect an extreme observation rather than a uniformly elevated category. Hotspot 1 likewise combines several substitution profiles, so its aggregate concentration distribution reflects category composition. The analytical contribution is therefore a distinction between variation across substitutions and variation among isolates sharing a substitution, both of which are obscured when mutation presence supplies the only grouping variable.

The serial isolate analysis identifies sampling structure as a consequential feature of genotype comparisons. All four F635L isolates originate from one documented patient cluster, meaning that their repeated appearance contributes more strongly to the isolate distribution than to the number of patients represented. Reducing that cluster to one representative preserves the higher mutant micafungin median, while changing the ratio of group medians from four to a range of 2.67 to four. The direction persists across the implemented selections, but its magnitude depends on how the serial cluster is represented. Biagi et al., 2019, documented the emergence of S639P during recurrent Candida auris infection, demonstrating why serial isolates can contain clinically important information. Together, these observations support retaining serial measurements for surveillance while identifying their patient origin when summarising genotype distributions. The practical advance is a clearer separation between repeated biological observation and broader patient representation.

International relevance rests on the interpretive problem shared across surveillance settings rather than on an assumed geographical difference in resistance. Rhodes et al., 2018, placed a United Kingdom outbreak within the India and Pakistan clade, illustrating how genetic relationships cross national boundaries. Ostrowsky et al., 2020, documented resistance emerging among serial isolates in New York and emphasised susceptibility testing during surveillance. Against that background, Tables 5 and 6 show why internationally comparable reporting should preserve substitution identity, separate drug measurements and distinguish isolates from patients. Laboratories and surveillance programmes can apply these distinctions by reporting genotype specific distributions alongside individual concentrations and documented patient links. The theoretical refinement is to treat mutation status as an informative classification within a genotype, drug and sampling structure, rather than as a complete description of susceptibility. This contribution remains grounded in the observed Candida auris records while offering a reporting approach relevant across health systems.

7. Conclusion and Implications:

Global resistance surveillance gains value when genetic classifications preserve the biological variation they are intended to explain. This analysis shows that broad molecular groupings identify differences in laboratory susceptibility, while finer classifications reveal variation across drugs and among isolates sharing an alteration. Interpretation also depends on how repeated observations from individual patients enter the sample. The contribution is an integrated descriptive assessment separating differences between groups from variation within groups and sensitivity to sampling structure. This refines target modification theory by showing how an aggregate association can coexist with overlapping individual measurements. For laboratory managers, the findings support preserving individual concentration results alongside molecular classifications when organising surveillance reports. For surveillance authorities, they support reporting conventions that distinguish isolates, patients and repeated drug measurements. Operationally, linked identifiers and explicit records of serial sampling can improve traceability and prevent repeated observations from receiving disproportionate interpretive weight. These practices offer a transferable approach to comparing evidence across health systems while retaining the conditions under which measurements were obtained. Their social relevance lies in strengthening the evidence used to recognise resistance patterns and communicate uncertainty. The analysis therefore contributes to more transparent interpretation of susceptibility evidence without treating laboratory associations as demonstrated treatment effects.

The selected records provide a basis for targeted replication. Larger collections across countries could establish whether the observed distributional patterns persist under different sampling and laboratory conditions. Longitudinal sampling linked to patient identifiers would distinguish variation within patients from differences between patients. Standardised testing with laboratory replication could assess measurement variability, while experimental modification of specific alterations could test biological mechanisms directly. Linking these measurements to treatment exposure and clinical outcomes would clarify their predictive relevance. Such extensions would expand the descriptive contribution into evidence capable of supporting broader generalisation and stronger mechanistic interpretation.

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