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Data-driven historical characterization of epilepsy-associated genes

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ABSTRACT

Many epilepsy-associated genes have been identified over the last three decades, revealing a remarkable molecular heterogeneity with the shared outcome of recurrent seizures. Information about the genetic landscape of epilepsies is scattered throughout the literature and answering the simple question of how many genes are associated with epilepsy is not straightforward. Here, we present a computationally driven analytical review of epilepsy-associated genes using the complete scientific literature in PubMed. Based on our search criteria, we identified a total of 738 epilepsy-associated genes. We further classified these genes into two Tiers. A broad gene list of 738 epilepsy-associated genes (Tier 2) and a narrow gene list composed of 143 epilepsy-associated genes (Tier 1). Our search criteria do not reflect the degree of association. The average yearly number of identified epilepsy-associated genes between 1992 and 2021 was 4.8. However, most of these genes were only identified in the last decade (2010–2019). Ion channels represent the largest class of epilepsy-associated genes. For many of these, both gain- and loss-of-function effects have been associated with epilepsy in recent years. We identify 28 genes frequently reported with heterogenous variant effects which should be considered for variant interpretation. Overall, our study provides an updated and manually curated list of epilepsy-related genes together with additional annotations and classifications reflecting the current genetic landscape of epilepsy.

1. Introduction

Epilepsies may result from primary genetic abnormalities or secondary to well-defined structural or metabolic disorders, some of which also have genetic causes [1]. The application of genomic technologies has had a tremendous impact on discovering the genetic basis of epilepsy [2–4]. High throughput genetic testing platforms—including epilepsy gene panels, clinical exome sequencing, and screens using whole exome or genome sequencing—have helped to delineate the phenotypic spectrum of numerous individually rare monogenic epilepsies [3–8]. This improved knowledge, if accessible for caregivers, enables better anticipation of the expected disease prognosis and may directly modify patient management and treatment options [3–7,9].

More than a hundred epilepsy genes with various functions in the human body have been identified [3–5,7]. Multiple types of common [10], rare [3], and/or *de novo* [4] genetic variants in these genes have been associated with epilepsy—from single nucleotide variants (SNV) [3,10] to copy number variants [11,12]. As such, the genetic etiology of epilepsy is as complex and heterogeneous as the disease. Still, two major mechanisms can be identified: common variants with low effect sizes [10] and rare variants with strong effect sizes [3,4].

Several epilepsy genes have also been associated with other complex and severe neurodevelopmental disorders without epilepsy, expanding the heterogeneity observed in these patients [13,14]. Genetic testing and the systematic aggregation of multiple patients has enabled the identification of clinically meaningful genotype-phenotype associations,

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paving the way for precision medicine. For example, in patients with pathogenic *SCN2A* variants, gain of function (GoF) variants—which cause increased activity of the affected voltage-gated sodium channel—are associated with early seizure onset (<3 months). In this patient population a good response to sodium channel blocker drugs reduces seizures. In contrast, people with *SCN2A* loss of function (LoF) variants have seizure onset beyond 3 months of age and have poor responses to sodium channel blocker [15,16]. As another example, a ketogenic diet—which shifts brain metabolism from carbohydrates to ketones—is the first choice treatment for patients with GLUT1-deficiency disorder due to disease-causing variants in *SLC2A1*—which encodes the major glucose transporter (GLUT1) in the blood-brain-barrier [17]. Thus, a genetic diagnosis can improve clinical care through a better understanding of disease course and prognosis.

Keeping pace with the rapid rate of ongoing gene discovery and, subsequently, the genes available for clinical testing has become an important challenge. The degree to which heterogeneous variant effects need to be considered for variant interpretation in epilepsy genes also remains unclear. Here, we performed a computational literature review to describe the current state and history of epilepsy-associated genes and variant effects.

2. Methods

2.1. Gene discovery history and characteristics of epilepsy-associated genes

To review the history of epilepsy gene discovery, we queried all NCBI PubMed abstracts, excluding reviews, that mention 'epilepsy' along with at least one clinical (e.g., "patient" or "case") and one genetic term (e.g., "variant" or "mutation") until the December 5, 2021. The full list of clinical and genetic terms used can be found at https://github.com/LalResearchGroup/Text-mining_epilepsy_genes, where the user can also replicate or update the search. From those abstracts (n = 8032), all gene names were extracted using PubTator [18], a web-based system that provides automatic annotations of biomedical concepts such as genes in PubMed abstracts. Next, we generated a gene-based table including all extracted human genes (n = 2632), their NCBI geneID, the number of abstracts, and the year of the earliest published abstract mentioning the gene, as a proxy for the year of discovery.

From all identified epilepsy-associated genes, we classified them into two Tiers. We first generated a broad Tier 2 gene list which included a wide spectrum of established to probable ultra-rare epilepsy genes. Tier 2 is defined by all genes with more than two studies that met the aforementioned search term criteria (or at least two studies in the case of genes discovered in 2021) and included all established epilepsy-associated genes validated in comprehensive genetic screens by Heyne [4] et al. and Lindy [7] et al. or collected by experts in ClinGen [19] (version: 10/1/22). Next, we generated a narrower Tier 1 gene list that included genes that met our screening criteria and were mentioned an average of at least once a year after the first reported association with epilepsy. To filter out false-positive genes in the Tier 1 list, we performed a manual quality control through an iterative process of all remaining genes (n = 197). We first removed gene names that were falsely detected by PubTator or refuted/disputed to be associated with epilepsy, resulting in 143 genes. Next, we verified, and if required, corrected the year of the first study as proxy for the first discovery.

After the generation of our gene lists, we compared them with the epilepsy gene lists of four commonly used gene panels (GeneDx: https://www.genedx.com/tests/detail/comprehensive-epilepsy-panel-317, Invitae: https://www.invitae.com/en/providers/test-catalog/test-03401, Ambry genetics: https://www.ambrygen.com/providers/genetic-testing/8/neurology/epilepsynext, and Labcorp: https://www.labcorp.com/tests/630268/comprehensive-epilepsy-ngs-panel), accessed on March 30, 2022.

To examine patient variant repositories we used the Human Gene Mutation Database (HGMD®, version 1, 2022) [20] Professional release. To increase stringency, we considered the "High Confidence" and "Disease Mutation" classification. We filtered patient variants using Bedtools [21] and in-house Bash/Perl scripts. To analyze variants with epilepsy annotation we filtered variants annotated for epilepsy based on SNOMED annotation (Systematized Nomenclature of Medicine – Clinical Terms, https://browser.ihtsdotools.org/, SCTID: 84757009).

In order to characterize our Tier 1 genes in functional groups, we manually grouped the genes based on associated gene ontology (GO) terms, gene descriptions, and the literature using the functional enrichment analysis tool g:Profiler [22], gene descriptions from GeneCards [23], and the PubMed literature.

2.2. Literature analysis to identify variant function of epilepsy-associated genes

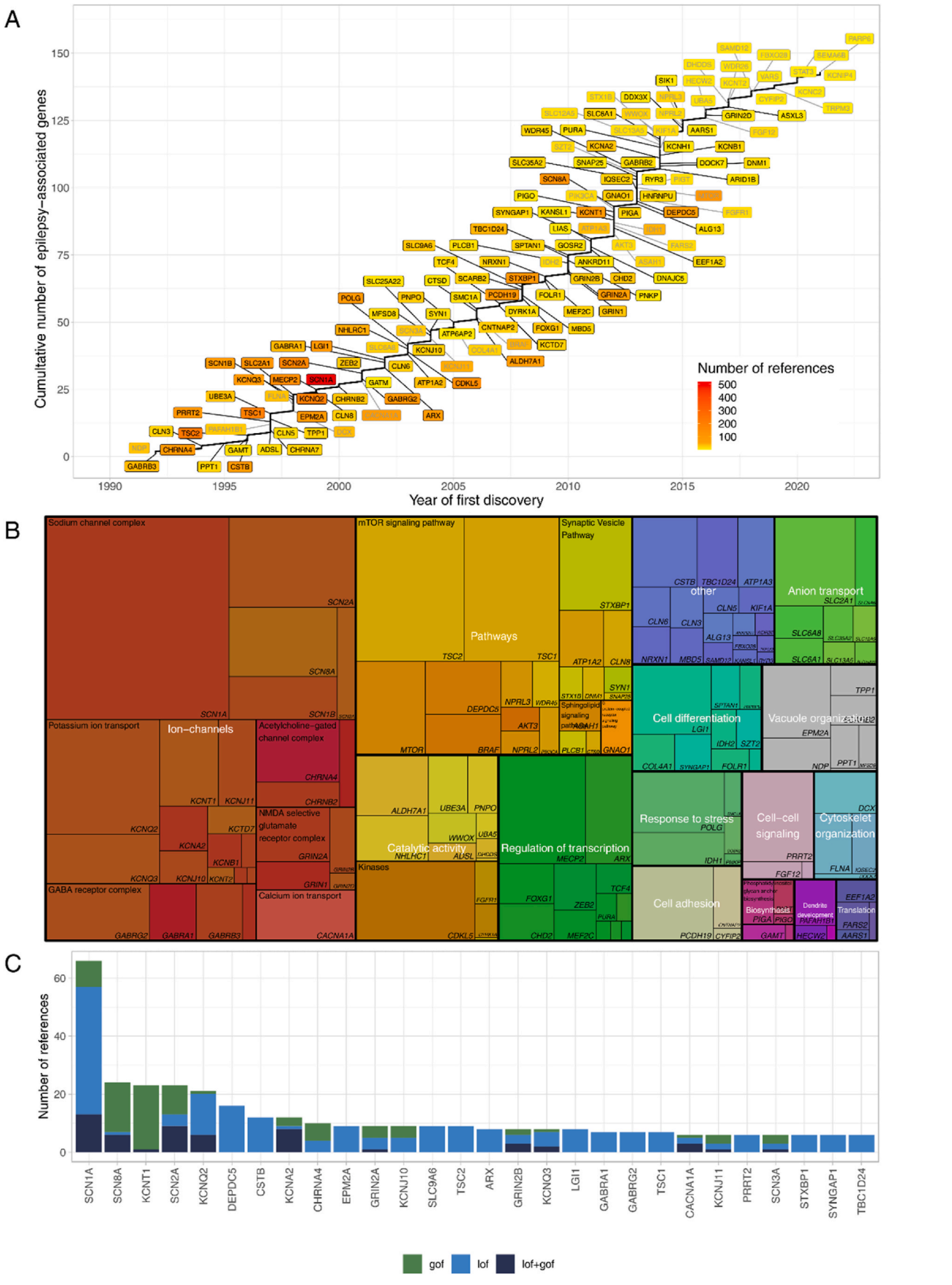
To find out to which degree gain- and loss-of-function (GoF and LoF, respectively) variants have been reported for epilepsy-associated genes, we queried all NCBI PubMed abstracts that mention 'epilepsy' alongside at least one GoF/LoF term (e.g., 'Gain-of-function', 'gof', 'GoF', 'gain-of-function', 'Loss-of-function', 'lof', 'LoF', 'loss-of-function') until the December 5, 2021 (n = 945). From those abstracts, we extracted all genes with human NCBI gene IDs using PubTator [18] and filtered the abstracts for those containing genes with at least five abstracts (number of abstracts = 499, number of genes = 50). To ensure the GoF/LoF terms were mentioned in context with the gene, we performed a manual review of all the abstracts and annotated whether the abstracts mentioned GoF terms, LoF terms, or both. After quality control, we filtered for those genes that still had at least five abstracts, which resulted in 28 genes.

All analyses were performed using the R programming language. The visualizations were generated using the treemap (v. 2.4–3) and ggplot 2 package (v. 3.3.5) in R. All code, data, and specific PubMed queries can be found in GitHub (https://github.com/LalResearchGroup/Text-mining_epilepsy_genes).

3. Results

We performed a computational analysis of the biomedical literature in PubMed to review the history and characteristics of epilepsy-associated genes (for details, see Methods). We defined two Tiers of epilepsy-associated genes: 1) Tier 2 epilepsy candidate genes, composed of 738 genes including both frequently and rarely reported epilepsy genes (Supplementary Table); and 2) Tier 1 epilepsy genes, composed of 143 quality-controlled genes with strong evidence of association with epilepsy that were either mentioned alongside the term 'epilepsy' on average at least once a year after the initial discovery or that were previously defined as epilepsy-associated genes (Fig. 1A). The average yearly number of identified Tier 1 epilepsy genes in the 30 years between 1992 and 2021 was 4.8. The decade with the highest yearly number was between 2010 and 2019, with an average of 7.1 Tier 2 epilepsy genes identified per year. The year with the most identified Tier 1 genes was 2014, with 14 genes. In the last 5 years, we identified 14 new Tier 1 epilepsy genes showing that gene discovery has slowed down but is still ongoing.

Next, we compared our gene lists with four commonly used epilepsy gene panels (GeneDx, Invitae, Ambry genetics, and Labcorp) that collectively contain 895 genes, with 112 overlapping genes across all four panels. Three of these 112 genes (i.e., *SATB2*, *PACS1* and *PHGDH*) were not included in neither our Tier 1 nor Tier 2 gene lists. These genes were not detected by PubTator in the abstracts and thus, did not meet our search criteria. The majority of Tier 1 epilepsy genes (126/143) were also found in at least one of the four assessed gene panels. Those 17 high-confidence genes not included in the assessed panels include genes both gene associated with somatic variants (e.g., *BRAF* [24]) and genes that should be added to gene panels (e.g., *FBXO28* [25] or *KCNC2* [26]). When comparing our comprehensive Tier 2 gene list of 738 genes with



(caption on next page)

Fig. 1. History of epilepsy-associated genes, their characterization, and variant function. A) A literature-wide screen of all NCBI PubMed abstracts that mention 'epilepsy' along with at least one clinical and one genetic term was performed (see Methods). All genes, along with the first year of discovery and the cumulative number of studies, were extracted from abstracts. Shown are all Tier 1 epilepsy genes after quality control (n = 143, see methods) that were, on average, mentioned at least once a year after initial discovery or that are defined as epilepsy-associated genes by Heyne et al., Lindy et al., or ClinGen (shown in bold). B) Treemap of all 143 Tier 1 epilepsy genes characterized in Gene Ontology term (GO) groups. The size of the boxes represents the number of studies for each gene. C) A literature-wide screen of all NCBI PubMed abstracts that mention 'epilepsy' along at least one gain-of-function (GoF) or one loss-of-function (LoF) term was performed (see methods). Shown are all genes with at least five abstracts (n = 28) and their association with LoF and/or GoF variants.

the gene panel genes, we found that almost 50% of those genes (n = 365) are included in at least one of the gene panels. The remaining Tier 2 genes might include both ultra-rare and false-positive genes and should therefore be taken with caution.

Next, we compared the number of epilepsy patient variant reports in the Human Gene Mutation Database [20] with the number of references observed for Tier 1 genes, and observed a strong correlation (Pearson correlation $r = 0.86$, $p < 0.001$, Supplementary Figure). However, our results do not provide gene–disease validity towards epilepsy. Established expert curation efforts such as the Gene Curation Coalition (GenCC) Database (DB) [27] provide evidence for gene-disease validity with different degrees of confidence (e.g. Definitive, Strong and/or Moderate). Direct comparison with our catalog (Supplementary Table) showed that out of the 143 genes in Tier 1, only 46 (32.1%) show non-refuted definitive, strong, moderate, or supportive gene-disease validity towards epilepsy (n = 98.

Next, we grouped the identified Tier 1 genes into 15 groups based on GO (gene ontology) terms (Fig. 1B). 'Ion channel' was the largest GO group, including 20.3% of all identified Tier 1 epilepsy genes and 37.3% of all studies for Tier 1 epilepsy genes that met our inclusion criteria. The well-studied voltage-gated sodium channel genes were the largest epilepsy-associated subgroup. The second-largest GO group included 'molecular pathways' with the mTOR signaling pathway as the most prominent pathway associated with epilepsy. Other groups included genes involved in various cellular processes such as transcription and translation, stress response, vacuole organization, cell differentiation, anion transport, cell adhesion, cell-cell signaling, cytoskeleton organization, biosynthesis, and dendrite development, and showed frequent catalytic activity.

Next, we explored to which degree gain- and loss-of-function variants have been reported for epilepsy-associated genes (for details see Methods). We identified 28 epilepsy-associated genes that had at least five abstracts that reported LoF variants, GoF variants, or both categories (Fig. 1C). The gene with the most abstracts including the terms 'LoF' or 'GoF' in combination with 'variants' was *SCN1A*, the gene most published gene overall (Fig. 1A). In those abstracts, *SCN1A* was most frequently reported with LoF terms (n = 44), followed by GoF terms (n = 9) and both LoF and GoF terms (n = 13). Following *SCN1A*, the next five genes with the most LoF or GoF referenced studies included *SCN8A, KCNT1, SCN2A, KCNQ2,* and *DEPDC5*. *SCN8A* and *KCNT1* studies primarily reported GoF while *KCNQ2* and *DEPDC5* primarily reported LoF variants. Conversely, many studies reported *SCN2A* associated with both GoF and LoF variants. Overall, we could identify a six-fold increase of publications with abstracts mentioning GoF/LoF variants effects in those genes (31.6 publications per year in the last 10 years vs. 5 publications per year before 2010).

4. Discussion

Epilepsies are complex and heterogeneous disorders. In particular, severe and drug resistant pediatric epilepsies often originate from genetic changes that lead to multiple phenotypic manifestations which ultimately result in abnormal neuronal excitation. We performed the first comprehensive computational literature review of established epilepsy-associated genes and identified 143 Tier 1 and 738 Tier 2 epilepsy genes that have been associated with epilepsy in the last decades and show that this number is still increasing. Our analysis informs clinical genetic testing and provides researchers with a comprehensive overview of the history and current landscape of epilepsy gene discovery. Genes with a greater number of references are better studied, might reflect larger patient populations, and could be prioritized for small gene panels and more emphasized in educational material for neurologists. Similarly, the biological grouping (Fig. 1b) might be useful for teaching the diversity of molecular etiologies leading to epilepsy. We share the code for our analysis framework, enabling readers to seamlessly execute similar analyses for other disorders or refine our epilepsy study and perform more granular analyses.

We show that, for three decades, epilepsy researchers have been methodically identifying the molecular mechanisms that result in the development of seizures. Great strides have been made and we are entering an era of "precision medicine" with the goal of treating each epilepsy based on its unique etiology. However, we also observe increasing phenotypic complexity associated with differential to opposing disease mechanisms associated with variants in the same gene. This potential roadblock for application of precision medicine is already apparent for many channelopathies, the largest class of monogenic epilepsies. Further pre-clinical research is needed to overcome this limitation for designing clinical trials. In this regard, the implementation of machine learning algorithms [28,29] and the aggregation of information from multiple related genes have proven successful in facilitating variant pathogenicity interpretation [30–32] and the prediction of functional effects (GoF vs LoF) [31,33]. Further, the aggregation of genetic data in combination with clinical data has allowed the development of prognosis prediction models beyond pathogenicity prediction [34]. These resources and established prediction tools are publicly available and will contribute to the design of pre-clinical research and the future application of precision medicine.

One of the limitations of our study is that our results don't measure the incidence or prevalence of specific gene disorders. Generally, genes that have been identified earlier will have more research studies, which doesn't necessarily correlate with greater patient populations. For example, while the genes *KCNT1* and *PNKP* were discovered around the same time, *KCNT1* was published on more frequently but has less pathogenic/likely pathogenic variants in ClinVar than *PNKP* (42 vs. 68 variants). Studies that estimate the epidemiology of monogenic epilepsies have been published previously [35,36]. In addition, our approach is not suitable for gene curation. Established frameworks that include a standardized and manual approach by experts to determine the clinical validity for a gene-disease pair such as ClinGen [19], or that harmonize various gene-disease evidence resources such as GenCC [27] are more appropriate for this purpose. Here, gene-disease validity can be determined from consensus aggregation of individual variant reports coming from patient variant repositories (Public and private) that are not necessarily in the literature. Thus, our framework will not be able to capture all GenCC genes with gene-disease validity towards epilepsy. Nonetheless, the results of this study are valuable as they provide researchers and clinicians with the first large-scale data-driven historical overview on epilepsy gene discovery and current trends in combination with the gene curation initiatives.

Genetic studies of epilepsy are at an exciting and crucial phase, with the combination of advances in technology and unprecedented large-scale international collaborations rapidly escalating our understanding of the causes of this clinically and genetically heterogeneous group of disorders. As we increase our knowledge of the genes implicated in epilepsy and the range of resulting clinical manifestations, the interpretation of results from genetic testing may become easier. The next

advances are likely to include the development of personalized genetic profiles which can be combined with other related information such molecular data on a tested genetic variant or outcome prediction algorithms. This knowledge will be used to generate individualized treatments designed to control seizures or even change the course of the disease on the basis of the specific genetic variation identified.

Conflict of interest

The authors report no conflicts of interest relevant to this manuscript.

Author contributions

M.M. and D.L. designed the study; M.M. performed the data analysis; PM provided data; M.M., J.L, A.I. and R.S.M. performed the quality control; M.M., E.P., and D.L. wrote the manuscript. D.L. supervised the study. All authors interpreted the data and revised the manuscript.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declaration of competing interest

The authors report no conflicts of interest relevant to this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2022.12.005.

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