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Human Genomics

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Re: "A novel splice-altering frameshift variant in the *COL1A1* gene underlies osteogenesis imperfecta type I: molecular characterization of a four-generation Chinese pedigree and literature review"

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Abstract
A paper entitled "A novel splice-altering frameshift variant in the *COL1A1* gene underlies osteogenesis imperfecta type I: molecular characterization of a four-generation Chinese pedigree and literature review" was recently published in this journal. Unfortunately, it contains a number of errors that the authors should correct. The most serious errors are incorrect sequence variant descriptions and inappropriate use of AI-assisted protein structure prediction.

Keywords Variant nomenclature, Protein structure modelling

Main text

A paper entitled "A novel splice-altering frameshift variant in the *COL1A1* gene underlies osteogenesis imperfecta type I: molecular characterization of a four-generation Chinese pedigree and literature review" was recently published in this journal [1]. Unfortunately, it contains a number of errors that the authors should correct.

First, the frameshift variant is described in the Abstract and the Methods as c.370_379delGGACCCGCAG but this description is not compliant with the HGVS recommendations for the description of sequence variants [2]. In fact, the cause of the frameshift is later described in the Results as "NM_000088.3, c.370-2 A > C", although it ought to have been described as NC_000017.11(NM_000088.4):c.370−2A>C. It is standard practice to describe the consequences of a frameshift at the level of the protein sequence, which is what the authors have done in the Abstract by reporting it as p.Gly124Alafs*138. However, there is no account in the paper of direct sequencing having been carried out of RT-PCR amplified mRNA expressed from the patient's mutated allele, hence the description ought perhaps to be NP_000079.2:p.(Gly124AlafsTer138) to indicate that it is a prediction. Analysis of mRNA from a transiently transfected minigene construct may not accurately reflect the true in vivo consequence of the variant [3]. The authors should note that the actual deleted nucleotide sequence is never reported for a deletion variant as it can be deduced from the reference sequence with respect to the deletion

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endpoints. In addition, nucleotide coordinates of the deletion should have been corrected to comply with the HGVS "3′rule": for all descriptions, the most 3′ position possible of the reference sequence is designated to have been changed. Furthermore, the correct sequence variant prefix in this instance is "r.", not "c." resulting in the variant description being NM_000088.4:r.371_380del. The HGNC ID for *COL1A1* (HGNC:2197) should also have been reported. The authors ought to have validated the variant descriptions using a software tool such as VariantValidator [4] and have presented HGVS-compliant gene and variant descriptions as required by the journal [5]. Variant reports generated using VariantValidator are included as Supplementary Material.

The second issue is the authors' use of AlphaFold3-based protein structural modelling to reveal "…the loss of the triple-helical domain in this truncated protein." This is pointless use of an AI-aided system in an attempt to give credence to the assertion that a truncated protein is produced. If sequence analysis predicts the possibility of a truncated protein, there is no value in modelling the truncated protein to visualise the possible missing amino acids as it does not add any level of confirmation. AlphaFold3 can generate protein structures but does so based solely on the sequence information that is used as input. The authors do not report the wild-type and mutant amino acid sequences which were used as input to AlphaFold 3. In reality, the wild-type COL1A1 protein is not a globular structure as depicted in the left panel in Fig. 4A of the published paper. The real value of programs such as AlphaFold3 lies in predicting subtle structural changes resulting from, say, single amino acid substitutions. The pointless use of structure prediction tools when considering "truncated" collagen molecules has been pointed out previously [6].

It is not clear from the presented evidence whether stable truncated mRNAs are expressed from the mutated allele which might then be translated into truncated non-functional proteins. The authors have only analysed transcripts and proteins expressed from mini-gene constructs in HEK293 cells as a proxy for what might be happening in patient cells that natively express type I collagen. The authors do acknowledge that analyses performed in cultured primary skin fibroblasts derived from the patients would have confirmed whether variant transcripts escape Nonsense Mediated Decay (NMD). Such analyses would have been more useful and are standard practice, using the presence or absence of cycloheximide, which inhibits MMD, in the culture medium to reveal whether NMD occurs [7].

The authors cite a paper by Byrd et al. 2024 [8] in support of the view that "…previous studies have demonstrated that the mutant mRNA produced by truncating variants is not completely degraded by the NMD mechanism, regardless of the location of the variant within the exon, or the gene." In spite of that view being acknowledged as generally true, the cited paper makes no mention of mRNA degradation.

In Table 2 of the published paper, individuals are categorised according to several criteria. The first criterion should be "sex" rather than "gender" as the two terms have different meanings.

The five formally recognised types of osteogenesis imperfecta (OI) are numbered using Arabic numerals (i.e. OI1) rather than the Roman numerals used by the authors [9].

The spreadsheet provided as supplementary material contains rows of data which cannot be viewed until a filter that is hiding these rows is removed.

In summary, the authors should correct their errors in the use of the HGVS variant nomenclature and remove any mention of using AlphaFold3 to generate predicted protein structures. The additional noted errors should also be corrected.

Abbreviations

HGVS	Human Genome Variation Society
OI	osteogenesis imperfecta

Supplementary Information

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Supplementary Material 1

Author contributions

R.D. wrote the manuscript text and prepared the supplementary material.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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