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Aldo-keto reductase (AKR) superfamily website and database: An update

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ABSTRACT

The aldo-keto reductase (AKR) superfamily is a large family of proteins found across the kingdoms of life. Shared features of the family include 1) structural similarities such as an $(\alpha/\beta)_8$-barrel structure, disordered loop structure, cofactor binding site, and a catalytic tetrad, and 2) the ability to catalyze the nicotinamide adenine dinucleotide (phosphate) reduced (NAD(P)H)-dependent reduction of a carbonyl group. A criteria of family membership is that the protein must have a measured function, and thus, genomic sequences suggesting the transcription of potential AKR proteins are considered pseudo-members until evidence of a functionally expressed protein is available. Currently, over 200 confirmed AKR superfamily members are reported to exist. A systematic nomenclature for the AKR superfamily exists to facilitate family and subfamily designations of the member to be communicated easily. Specifically, protein names include the root "AKR", followed by the family represented by an Arabic number, the subfamily-if one exists-represented by a letter, and finally, the individual member represented by an Arabic number. The AKR superfamily database has been dedicated to tracking and reporting the current knowledge of the AKRs since 1997, and the website was last updated in 2003. Here, we present an updated version of the website and database that were released in 2023. The database contains genetic, functional, and structural data drawn from various sources, while the website provides alignment information and family tree structure derived from bioinformatics analyses.

1. Introduction

The aldo-keto reductase (AKR) superfamily consists of proteins found across all forms of life, archebacteria, prokaryotes and eukaryotes. These proteins form a group based on their enzyme function to catalyze the reduction of carbonyl groups and their similar three-dimensional structure [1]. The superfamily is distinct from related functional proteins that belong to the short-chain dehydrogenase/reductase family and the medium chain alcohol dehydrogenase family [2]. The AKR superfamily contains over 200 confirmed members and over 30 potential members as of writing.

AKRs are phase I enzymes that catalyze the reduction of carbonyl groups of various substrates. This function enables the resulting alcohol to undergo conjugation reactions for elimination. AKRs conduct oxidoreduction by using the cofactor nicotinamide adenine dinucleotide (phosphate) reduced (NAD(P)(H)) [3]. The protein structure of AKRs is characterized by an $(\alpha/\beta)_8$-barrel structure, three additional large loops, a cofactor binding site, and a catalytic tetrad [1,4,5].

Despite their similarities, some members of the AKR superfamily have additional functions such as the reduction of nitro-groups in nitro containing xenobiotics (AKR1C1-AKR1C4) [6–10], the reduction of steroid double bonds (AKR1D) [11–13], the oxidation of proximate carcinogen *trans*-dihydrodiol polycyclic aromatic hydrocarbons [14,15], and the activation of β-subunits of potassium gated ion channels (AKR6 family) [16,17].

Given the diverse roles AKRs have in many important and distinct biological processes, they have been the subject of much research for decades. In the five-year period from 2019 to 2023, over 900 AKR-related research articles accessible via PubMed from its underlying database Medline were published. Among these contributions were publications in high impact journals [18,19], as well as discoveries regarding the role of AKRs in oncology [20–24], chemotherapeutic drug

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resistance [25–27], endocrinology [28–31], toxicology [32–37], prognostic and diagnostic biomarker identification [38–49], the inactivation of glyphosate [50], and the presence of substrate cooperativity and allosteric sites that may extend across multiple family members [51].

Due to the size of, and interest in the superfamily, the need for a centralized database regarding the AKRs was evident and began in 1997, and an AKR superfamily webpage was created in 2003 to provide access to the database [1]. Since then, the database has been updated continuously via investigator-initiated submission. As many new family members have become available and tools for their analysis have improved, a newly configured website was released in 2023 (https://akrsuperfamily.org//). The database acts as a central location to access information regarding the AKR superfamily. Information gathered elsewhere such as protein database (PDB) structures and genetic sequences (NCBI) are directly linked from the website. New information that is generated by compiling all the members to provide multiple sequence alignments and family dendrograms is also provided. The AKR Superfamily webpage is publicly available and maintained by the Center of Excellence in Environmental Toxicology at the University of Pennsylvania.

2. Material and methods

2.1. Multiple sequence alignment

MAFFT [52] was used to perform multiple sequence alignment. Protein sequences of the AKR superfamily were aligned via the L–INS–i algorithm, an iterative refinement method that employs a local pairwise alignment with the affine gap cost [53]. The aligned sequences were visualized using the *msaR* R package [54] that provides an interface to MSAViewer [55] for web visualization.

2.2. Percent identity

Percent identity, which measures the number of matches in relation to the length of the alignment, was calculated using the *seqinr* R package [56]. Gapped positions were excluded from the identity calculations. Identity measures were used to delineate AKR subfamilies.

2.3. Phylogenetic tree

IQ-TREE [57] was used to infer maximum-likelihood phylogenies, incorporating ModelFinder [58] to improve the accuracy of phylogenetic estimates by identifying the best-fitting model of sequence evolution. The resulting phylogenies were visualized using the *ggtree* R package [59].

2.4. Shiny web application

The revamped AKR website uses the Shiny web framework [60] to enable real-time user interaction with data, including filtering, selection, and manipulation of tables and visuals. The website's tables are rendered using the DT R package [61] that leverages the JavaScript DataTables library to deliver a responsive user experience. A new sequence submission form was created with the help of the shinyjs R package [62] that provides common JavaScript operations within Shiny

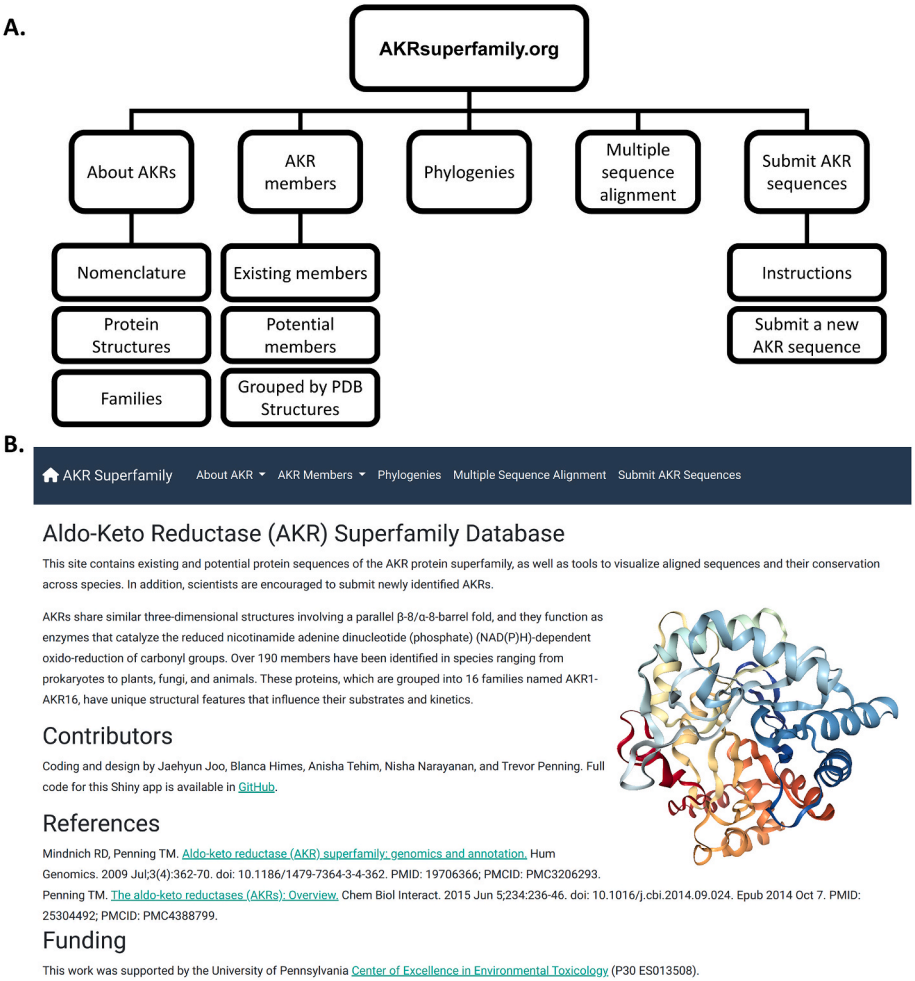

Fig. 1. A. Architecture of the AKR Superfamily website. **B.** Screenshot of the AKR Superfamily website landing page (https://akrsuperfamily.org//).

web applications.

3. Results

The website is organized through five major tabs: 'About AKR', 'AKR Members', 'Phylogenies', 'Multiple Sequence Alignment', and 'Submit AKR Sequences'. Fig. 1 provides an overview of the website organization and a screenshot of its homepage.

3.1. About AKR

The about AKR tab has a section on nomenclature, protein structure and function, families.

Nomenclature

The AKR superfamily naming conventions follow a specific nomenclature adopted by the 8th international Workshop on Enzymology and Molecular Biology of Carbonyl Metabolism in 1997 [63]. All members of the superfamily start with the root "AKR," followed by an Arabic number denoting the family. In families where a subfamily is present, the subfamily is represented by a letter. Lastly, the final Arabic number denotes the enzyme identity, which is numbered chronologically in order of discovery. An example of this nomenclature can be seen in Fig. 2. For genes encoding the AKR proteins, the gene name is identical to the protein name, but denoted in italics. Each AKR protein has its own unique name to avoid misclassifying proteins from other species as orthologs when this is not known with certainty. The use of lower case AKR names italicized or unitalicized to denote genes and proteins, respectively, is discouraged since this assumes that the homology that exists predicts conservation of function.

Families are defined by its members having 40 % amino acid sequence identity, meaning two members of the family should be at least 40 % identical. Currently, there are 17 AKR families according to phylogenetic tree analysis. Within families exist subfamilies that are defined by their members having 60 %–97 % amino acid sequence identity [63]. Members of the same subfamily with over 97 % amino acid sequence identity are considered alleles of the same gene unless they have distinct activities, are encoded by different mRNA transcripts, and come from structurally different genes. An example of this exception is seen with AKR1C1 and AKR1C2, two AKR 1C members with 96 % sequence identity which differ by only seven amino acids but are still considered two different members since they are coded by different genes and have distinct functions [64–67].

Most AKRs exist as monomeric proteins, however, some members of the superfamily have been observed to form multimers. In this case, the naming should contain the composition of proteins, and stoichiometry. A tetramer containing one AKR7A1 monomer and three AKR7A4 monomers should be denoted as AKR7A1: AKR7A4 (1:3) [1].

We note that with the updated AKR database, the nomenclature of some members appears out of sequence, and that is largely due to the fact that as new members are discovered, some of the relationships among existing members have changed. Previously named AKR proteins' names have been kept to preserve consistency with the published record.

Fig. 2. Naming nomenclature for the AKR superfamily for AKR1C3. The root AKR, followed by family 1, then the subfamily C, finally the individual member 3.

3.1.1. Protein structure and function

AKRs function as phase I enzymes, catalyzing the carbonyl reduction on a variety of endogenous and xenobiotic substrates. Thus, aldehydes are reduced to primary alcohols and ketones are reduced to secondary alcohols. The alcohol functional group is then available for conjugation reactions so that the reactive carbonyl containing compound can be eliminated. All AKRs catalyze a sequential ordered bi reaction in which the cofactor binds first and leaves last [68,69]. AKRs catalyze the nicotinamide adenine dinucleotide (phosphate) reduced (NAD(P)H)-dependent reduction of carbonyl groups and the reverse oxidation reaction, thus classifying AKRs as oxidoreductases [3]. However, *in vivo,* these enzymes act as reductases due to their high affinity for NADPH and favorable $K_{eq.}$ [70,71].

Due to the similar reaction catalyzed, members of the AKR superfamily possess structural similarities [72]. These features include an $(\alpha/\beta)_8$-barrel fold (Fig. 3A), also known as a triose-phosphate isomerase TIM barrel with two additional helices and loop structures at the back of the barrel. A novel NADP(H)-binding motif is located in the elliptical pocket at the *C*-terminal end of the β-sheet [68,72–74]. Interestingly, AKRs have stereoselectivity for 4-pro-R hydride transfer from NADPH to the acceptor carbonyl group [68]. The animo acids that bind NADPH are highly conserved [5,68,75] (T24, D50, S166, N167, Q190, Y216, L219, S221, R270, S271, F272, R276, E279, and N280 in AKR1C9 numbering) (Fig. 4). Interaction with S166, N167 and D50 ensure that the carboxamide side-chain is tethered so that the nicotinamide head group is in the *anti*-configuration and the nicotinamide ring pi-stacks with Y216.

To define substrate specificity, three large loops exist behind the barrel motif [4] depicted in Fig. 3B. The binding of the NADPH coenzyme causes a conformational change that reorients the loops [76]. Tight binding of the cofactor is due to anchoring the 2′ phosphate of AMP by R276 or equivalent residue [77]. In some AKRs, the tight binding is enhanced by a clamping loop which acts as a "safety-belt" across the pyrophosphate bridge of the cofactor. The carbonyl-containing substrate binds perpendicularly to the cofactor. The preference for NADP(H) over NAD(H), can be reversed if R276 is replaced with an acidic group to repel the 2′-phopsphate of AMP [78].

Another structural motif that exists in the AKRs is the conserved catalytic tetrad that includes the residues Y55, L84, H117, and D50 [5] (AKR1C9 numbering convention) which catalyze a "push-pull" mechanism for hydride transfer [79]. In some AKRs H117 is replaced by a glutamic acid to increase the acidity of the active site to promote carbonyl group enolization for double bond reduction as seen in AKR1D1 [80]. In general, AKRs have a molecular mass between 34 and 37 kDa and are monomeric and soluble [1,5,68].

3.1.2. Families

The AKR superfamily has 17 separate families, denoted by their first

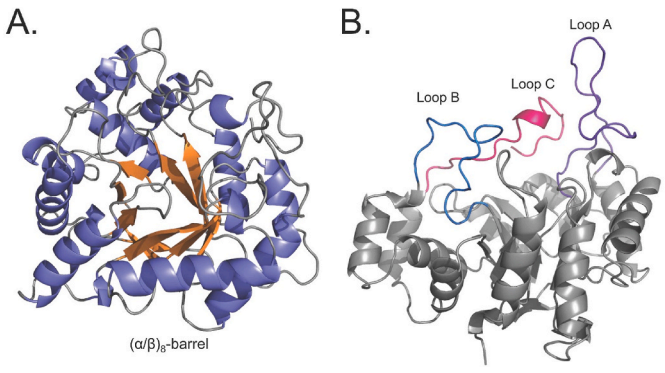

Fig. 3. A. Crystal structure of AKR1C9 (PDB: 1AFS) highlighting the $(\alpha/\beta)_8$-barrel structure, α-helix in purple, β-sheets in orange. **B.** AKR1C9 crystal structure with distinct loops A, B, and C colored in purple, blue, and magenta respectively.

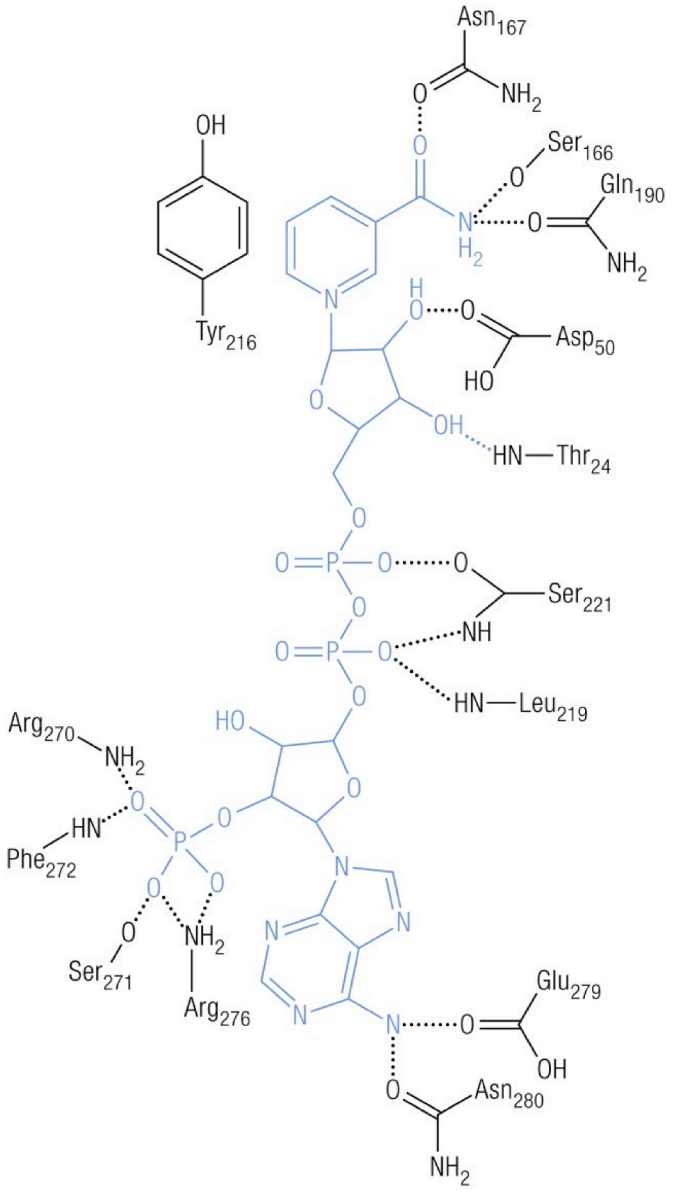

Fig. 4. Schematic of $NADP^+$ binding residues, with residues following AKR1C9 numbering. Reproduced from Jez et al. Comparative anatomy of the aldo-keto reductase superfamily. Biochem. J., (1997) (Pt 3) 625–26 [5] with permission form Portland Press.

Arabic number (Table 1).

3.2. AKR members

The AKR members tab lists existing and potential members that are grouped by PDB structures.

3.2.1. Existing members

There are 207 AKR member entries in our current database. Each entry contains the nomenclature name, National Center of Biotechnology Information (NCBI) accession number, species expressed, enzyme name, link to protein database (PDB) entry, and alternative splicing transcripts. The NCBI accession number is an identifier for the protein in the GenBank database and links to the protein's NCBI entry, containing alternative names, FASTA file, source organisms, amino acid sequence, and references [81]. The *species expressed* column reports the species where the protein was found to be present. The *enzyme name* column reports the type of protein (e.g., oxidoreductase, dehydrogenase) and common or alternative names for the protein. The *PBD* column contains a link to the structure of the AKR member in the PDB database when available. Information contained in the PBD includes the 3D structure, the depositing authors, the expression system, and experimental data and validation of the structure [82]. When multiple structures are available in the PDB, the chronologically first published structure is used. The other structures are available through the Grouped by PDB Structure section. The *alt splicing column* links to the Ensembl database for the AKR member. Ensembl contains genetic information, including the summary of the gene name, location, and its transcripts [83]. Physiological functions of human AKR members are described in Table 2.

Table 1
Brief description of the 17 AKR families including the presence of subfamilies.

Family	Subfamilies	Description	Citation[a]
AKR1	Yes; AKR1A-AKR1I	The largest family contains enzymes involved in aldehyde reduction (AKR1A), aldose and retinal reduction (AKR1B). They are also involved in regulating ligand access to nuclear receptors (AKR1C), steroid hormone metabolism (AKR1C) and bile acid synthesis (AKR1D) among other processes.	[4,87]
AKR2	Yes; AKR2A-AKR2E	Enzymes that consist of xylose and mannose reductases.	[88–90]
AKR3	Yes; AKR3A-AKR3G	Enzymes found in yeast	[91,92]
AKR4	Yes; AKR4A-AKR4C	AKR enzymes found in plants. Involved in various functions such as stress defense, production of metabolites, and plant microbe interactions.	[93]
AKR5	Yes; AKR5A-AKR5G	Enzymes that act as gluconic acid reductases	[94]
AKR6	Yes; AKR6A-AKR6D	Human AKRs containing β-subunits of the potassium gated voltage channels. Structurally distinct than most AKRs due to its ability to form tetramers.	[16,95]
AKR7	No	Function as aflatoxin dialdehyde reductases. Members typically reduce an aldehyde to an alcohol.	[96]
AKR8	No	Microbial enzymes found in yeast. Catalyze the NADPH-mediated reduction of pyridoxal to pyridoxine	[97–99]
AKR9	Yes; AKR9A-AKR9C	Microbial enzymes found in archaebacteria, yeast, and fungi with varied functions.	[100,101]
AKR10	No; only AKR10A	Bacterial AKRs found in *Streptomyces*.	[102,103]
AKR11	Yes; AKR11A-AKR11E	Bacterial AKRs involved in the reduction of DL-glyceraldehyde, d-erythrose and methylglyoxal	[104,105]
AKR12	Yes; AKR12A-AKR12D	*Streptomyces* sugar aldehyde reductases	[106–108]
AKR13	Yes, AKR13A-AKR13E	Bacterial AKRs found in hyperthermophiles. Involved in protein thermostabilizing.	[109]
AKR14	No: only AKR14A	Bacterial AKRs found in *Escherichia coli* and *Salmonella enterica*	[110]
AKR15	No; only one member	AKR found in *Microbacterium luteolum,* functions as a pyridoxal 4-adehydrogenase	[111]
AKR16	Yes; AKR16A-AKR16B	AKRs found in *Vibro cholera* and *Agrobacterium fabrum*, involved in the reduction of 6-oxo-gluclose	[112,113]
AKR17	No, Only one member	Aldehyde and Ketone reductase found in *Cyanobacteria anabaena*	[114]

[a] Citation for discovery of family or otherwise relevant review of entire family is provided.

Table 2
The 15 human aldo-keto reuctases.

[a]Gene	[a]Enzyme	[a]Tissue expression	[a]Physiological function	[a]Associated pathology	[b]Citation
AKR1A1	Aldehyde reductase	CNS; Kidney; Liver; Duodenum; Small intestine	Reduction of biogenic and xenobiotic aldehydes, including glyceraldehyde to glycerol; and melvadate reductase	Alcohol associated liver disease; Diabetic kidney disease; Schizophrenia	[115–118]
AKR1B1	Aldose reductase	Adrenal kidney; Placenta	Reduction of aldehydes, including glucose to sorbitol	Diabetic complications: Cataract genesis; retinopathy; neuropathy nephropathy	[119–123]
AKR1B10	Aldose reductase	Duodenum; Gall bladder; Small intestine; Stomach; Esophagus; Colon	Reduction of aliphatic and aromatic aldehydes, including all *trans*-retinaldehyde	Non-small cell lung cancer; Hepatocarcinogenesis Cell proliferation	[124–132]
AKR1B15	Aldose reductase	Prostate; Testis; Uterus; Ovaries; Stomach	Predicted to be involved in estrogen biosynthetic process; 9-cis-retinaldehyde reductase; keto-acyl-CoA reductase		[133,134]
AKR1C1	3α(20α)-hydroxysteroid dehydrogenase	CNS; Prostate; Testis; Lung; Liver; Breast; Endometrium; Uterus; Ovaries; Adipose	Elimination of progesterone by catalyzing progesterone to the inactive form 20α-hydroxy-progesterone.	Parturition Endometrial cancer Endometriosis	[135–138]
AKR1C2	Type 3 3α-hydroxysteroid dehydrogenase	CNS; Prostate; Testis; Lung; Liver; Breast; Endometrium; Uterus; Adipose	Elimination of dihydrotestosterone by reduction to the inactive form 3α-androstanediol; conversion of 5α-dihydroprogesterone to allopregnanolone GABAa receptor modulator	Androgen insufficiency; Premenstural syndrome	[67, 139–143]
AKR1C3	Type 5 17β-hydroxysteroid dehydrogenase; Type 2 3α-hydroxysteroid dehydrogenase	CNS; Prostate; Testis; Lung; Adrenal kidney; Liver; Breast; Endometrium; Uterus; Adipose	Formation of testosterone and 17β -estrodial by reduction of 17 ketosteroids; Prostaglandin F synthesis; Androgen receptor coregulator	Advanced prostate cancer; Breast cancer; Polycystic overy syndrome Acute myeloid Leukemia	[23,29,136, 144–150]
AKR1C4	Type 1 3α-hydroxysteroid dehydrogenase	Liver; Gall bladder	Hepatic elimination of steroids and xenobiotics; Bile acid synthesis	Androgen insufficiency Bile acid homeostasis disruption	[140,151]
AKR1D1	Steroid 5β-reductase	Liver	Reduction of Δ^4-3-ketosteroids to 5β-dihydrosteroids; Bile acid synthesis	Bile acid deficiency	[152–154]
AKR1E2	1,5-Anhydro-d-fructose reductase	Testis; Thyroid; Adipose	Reduction of 1,5 anhydro-d-fructose, part of the anhydrofrutose pathway of glycan catabolism		[155–158]
AKR6A3	Potassium voltage gated channel, β-subunit-1	Thyroid; Prostate; Adipose; CNS; Cardiovascular; Endometrium	Neurotransmitter release; Heart rate; Insulin secretion; Neuronal excitability; Epithelial electrolyte transport; Smooth muscle contraction; Cell volume	Aberrant redox regulation of Kev channels; Cardiovascular disease	[17,159,160]
AKR6A5	Potassium voltage gated channel, β-subunit-2	CNS; Bone marrow; Appendix; Lymph node; Spleen; Kidney	Neurotransmitter release; Heart rate; Insulin secretion; Neuronal excitability; Epithelial electrolyte transport; Smooth muscle contraction; Cell volume	Aberrant redox regulation of Kev channels; Cardiovascular disease	[17,159,160]
AKR6A9	Potassium voltage gated channel, β-subunit-3	Endometrium; CNS;	Neurotransmitter release; Heart rate;		[17, 159–161]

(*continued on next page*)

Table 2 (*continued*)

[a]Gene	[a]Enzyme	[a]Tissue expression	[a]Physiological function	[a]Associated pathology	[b]Citation
		Lymph node; Bone marrow; Appendix	Insulin secretion; Neuronal excitability; Epithelial electrolyte transport; Smooth muscle contraction; Cell volume		
AKR7A2	Aflatoxin aldehyde reductase; Succinic semialdehyde reductase	Kidney; Duodenum; Small intestine; Ovaries; Colon; Adrenal kidney	Reduction of succinic semialdehyde to the endogenous neuromodulator, γ-hydroxybutyrate; Reduction of aflatoxin	Alzheimer's; Hepatocellular carcinoma	[162–165]
AKR7A3	Aflatoxin aldehyde reductase	Duodenum; Kidney; Liver; Small intestine; Gall bladder; Pancreas; Stomach; Colon	Reduction of aflatoxin	Hepatocarcinogenesis; Breast cancer; Gastric cancer	[96, 164–167]

[a] Gene and enzyme names given, tissue expression data from NCBI reported, physiological function and associated pathologies described.
[b] Citations for physiological function and associated pathologies provided.

3.2.2. Potential members

To have full status as an AKR superfamily member, the member must be a functional protein associated with the gene. If the member is derived from a partial cDNA sequence or genomics project then it is not included in the database, but some are listed as potential members to be included pending functional analyses. There are currently 34 potential members listed in the database. Each entry contains *species expressed*, *name*, and NCBI accession number. Unlike the existing members, potential members are grouped together by the species in which they were detected. The actual number of potential AKR members is much larger than the ones submitted to the AKR database as evidenced by the large number of AKR genetic sequences observed across all species, many of which do not have a known function.

3.2.3. Groupings according to PDB structure

Multiple PDB entries can exist for a single AKR member, often because structures reflect diverse conformational states that occur under differing conditions or upon binding to different ligands. The purpose of the *Grouped by PDB Structure* section is to provide all available PBD structures and provide relevant comments regarding the structure. Our table contains the AKR family member name, the taxonomy, resolution, complex, and PDB link. In the *AKR* column, the AKR nomenclature name is reported alongside any common names. If multiple protein names exist, all are listed. The *taxonomy* column lists the species in which the AKR protein or complex was purified from to obtain the structure. The column *Res. (Å)* lists the resolution of the structure reported by the PDB entry. In simple terms, the resolution of a protein structure is the distance of the smallest observable feature, thus a smaller value indicates higher resolution. Resolutions are reported in angstroms (Å), equal to 10^{-10} m [84]. The *complex* column provides a description of the contents of the structure in more detail. Finally, the *PBD* column is a direct link to the PBD entry. Most structures contain a bound cofactor, and apoenzyme structures are scarcely available, likely due to the intrinsic disorder of the loops when NAD(P)H is not bound [73,74,85].

3.3. Phylogenies

The phylogeny tab provides information on the evolutionary relationships among AKRs. The AKR superfamily is thought to be a product of divergent evolution due to its members having common 3D structures and a highly conserved NADPH binding pocket to accommodate diverse substrates. There is also evidence of convergent evolution because AKRs are distinct from other oxidoreductase superfamilies such as long chain alcohol dehydrogenase and short chain dehydrogenase/reductase [5]. That is, genetic alignment studies have not found significant similarities between these oxidoreductase superfamilies [3,86]. Furthermore, the presence of AKRs across diverse life domains suggests that AKRs are an ancient protein superfamily [1].

To examine evolutionary relationships within the AKR superfamily, phylogenic trees were created using the multialign program, to provide an update to the previous versions constructed with the GCG program [1]. AKR phylogeny dendrograms provide an overview of the entire AKR superfamily (Fig. 5A), for each AKR family with at least three members (Fig. 5B contains an example), and for each of the following taxonomic groups: *Animalia, Bacteria, Fungi, Plantae, Insecta, Mammalia, Langomorpha, Rodentia,* and *Homo sapiens*.

3.4. Multiple sequence alignment

Multiple sequence alignment (MSA) is a bioinformatics technique used to align biological sequences, such as DNA, RNA, or amino acid sequences, in order to compare similarities and differences. Visualization of such data is paramount to MSA. We provide users the ability to visualize aligned AKR protein sequences from various families and taxonomic groups in our database. The alignments are generated using MSAViewer, offering an interactive JavaScript-based representation of multiple sequence alignment [55]. To use the tool, first the group of AKRs a user would like to compare are selected. The groups include all, by family, and by taxonomic group, consistent with the phylogenies available. All families are present regardless of the number of members. For families with multiple subfamilies, each entry is listed alphabetically and numerically (e.g., AKR1C2 is listed before AKR1C3, and both are listed before AKR1D1). The default visualization can be adjusted according to options for *Importing, Sorting, Filter, Selection, Visual elements, Color scheme, Extras, Exporting, and More* as listed in Table 3. As an example, the alignment of the catalytic tetrad residues for AKR1C1 members 1–35 using the MSAviewer available on the website is depicted in Fig. 6.

3.5. Submission of AKR sequences

Sharing the discovery of new members to the AKR superfamily is highly encouraged. To facilitate this process, a section of the website is dedicated to this activity. Submitted AKRs should have a functionally expressed protein and an amino acid sequence determined by cDNA or other direct methods. The protein must be purified or overexpressed

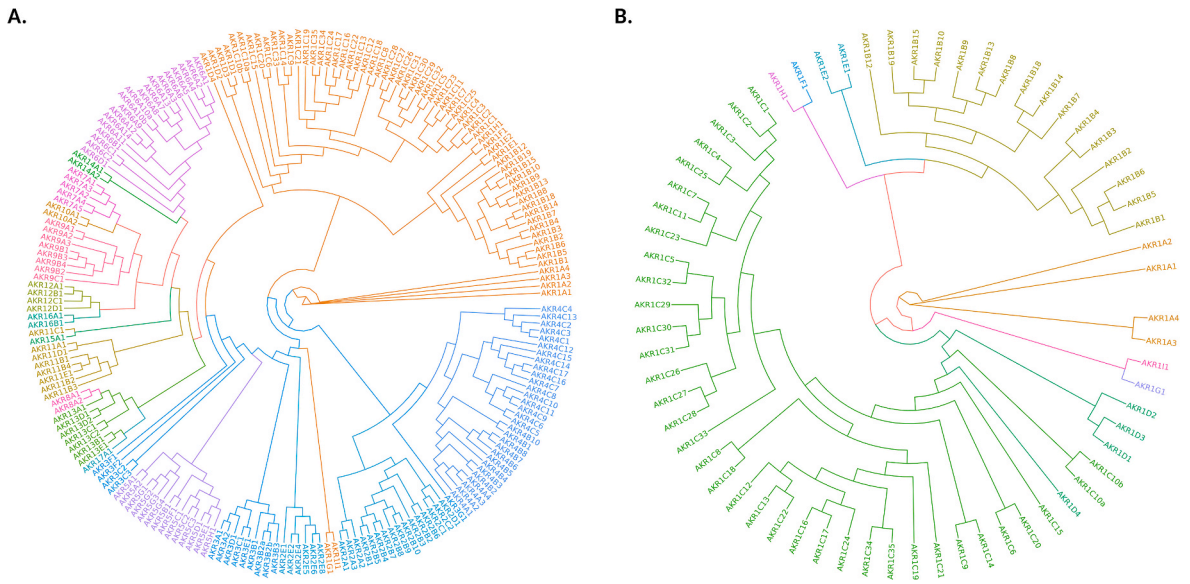

Fig. 5. AKR dendrograms available; **A.** entire superfamily and **B.** AKR1 family.

Table 3
Description for viewing multiple alignment sequences on akrsuperfamily.org.

[a]Feature	Description	Options
Import	Allows input file upload	URL; From file; Drag & Drop
Sorting	Alignment sorting by unique sequence identifiers, ascending or descending	ID; Label; Sequence; Identity; Gaps; Consensus to top
Filter	Hide or show sequences and/or columns	Columns by threshold; columns by selection; columns by gaps; seqs by identity; seqs by selection; seqs by gaps; Reset
Selection	Search an alignment for a motif or invert the selection of column and/or rows	Find Motif; Invert columns; Invert rows; Reset
Vis. Elements	Chose to hide or show. You can use your ctrl Key or meta Key to select multiple residues, column, or sequences	Residues indices; ID/Label; meta info; overview panel; sequence logo; gap weights; conservation weights; scale slider; label; ID; gap %; identity score; Reset
Color scheme	Chose one of the 15 pre-defined color schemes or select to use none	Taylor; buried; cinema; clustal; clustal 2; helix; hydrophobicity; lesk; MAE; nucleotide; purine; PID; strand; turn; zappo; no color
Extras	Allows extra additions and/or navigations	Add consensus seq; Jump to a column
Export	Export the URL of the visualization for other uses	Share view (URL); View in Jalview; export alignment (FASTA); export alignment (URL); selected sequences (FASTA); export features (GFF); export MSA image (PNG)
Help	Gives more information about the MSAviewer project	About the project; Report issues; User manual

[a] Adapted from the original MSAviewer github manual [55].

from either its natural source or recombinantly. Mutant AKRs are not represented in this database.

The submission should include the following information.

- Protein sequence from cDNA or direct methods
- Trivial name
- Species of origin
- Expression system
- Enzyme activity substrate
- Accession number (GenBank, Swiss-Prot, PIR)
- Status of publication
- Citations
- Contact information of submitter

Once submitted, the proposed member will be matched against the current AKRs and placed within the evolutionary tree. The location within the superfamily cluster will determine the nomenclature designation. If needed, new families and subfamilies will be created.

Upon completion of the cluster analysis, the assigned designation and location in the AKR superfamily are communicated to the submitter. The new AKR will be made available on the website once the submission has been published.

4. Discussion

The AKR superfamily is an extensive family with much interest regarding its over 200 members. The superfamily benefits from having a centralized portal of information, a function that the website has performed for over 20 years. Since this time, the scientific research landscape has undergone many changes, and the new website has been updated accordingly. The updated cluster analysis to designate the AKR families and subfamilies, resulted in some families needing to be restructured by the analysis designation. However, our analysis is also regularly updated and upon the discovery of other members, the families might undergo other changes, representing the most updated knowledge. A new feature of the current AKR superfamily website includes the retention of past iterations, allowing for outdated information to be clearly documented. The AKR superfamily database also links to other databases such as GenBank, Ensembl, and the PDB, facilitating access to carefully curated and up-to-date information regarding the members.

CRediT authorship contribution statement

Andrea Andress Huacachino: Writing – original draft, Visualization, Conceptualization. **Jaehyun Joo:** Visualization, Software, Formal analysis. **Nisha Narayanan:** Validation, Software, Formal analysis, Data

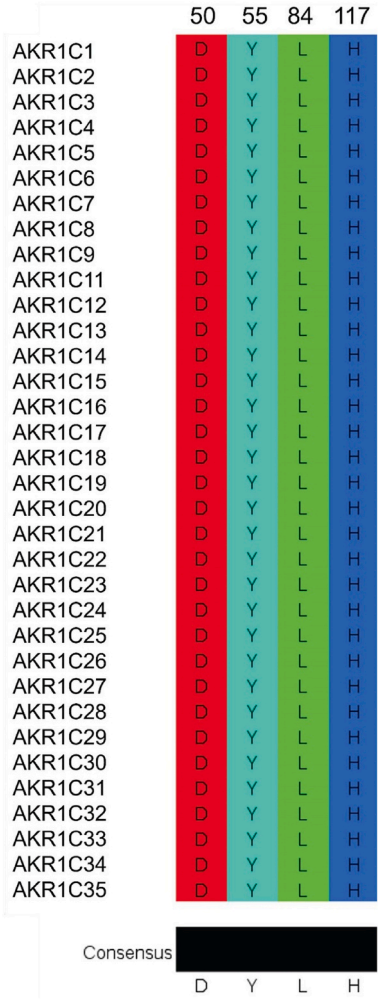

Fig. 6. The conserved catalytic tetrad amino acid residues represented by their one letter code of in the AKR1C subfamily. Residue numbering follows AKR1C9 numbering. Visualized using the MSA tool on AKRsuperfamily.org. Note that AKR1C10a and AKR1C10b sequences are not included because they are structural proteins (ρ-crystallin), not enzymes [168,169].

curation. **Anisha Tehim:** Validation, Data curation. **Blanca E. Himes:** Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Conceptualization. **Trevor M. Penning:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Trevor M. Penning reports financial support was provided by National Institutes of Health.

Data availability

Data will be made available on request.

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