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PRINTS and its automatic supplement, prePRINTS

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ABSTRACT

The PRINTS database houses a collection of protein fingerprints. These may be used to assign uncharacterised sequences to known families and hence to infer tentative functions. The September 2002 release (version 36.0) includes 1800 fingerprints, encoding ~11 000 motifs, covering a range of globular and membrane proteins, modular polypeptides and so on. In addition to its continued steady growth, we report here the development of an automatic supplement, prePRINTS, designed to increase the coverage of the resource and reduce some of the manual burdens inherent in its maintenance. The databases are accessible for interrogation and searching at http://www.bioinf.man.ac.uk/dbbrowser/PRINTS/.

INTRODUCTION

Fingerprints are groups of conserved sequence motifs that together provide diagnostic signatures for protein families. They derive much of their potency from the context afforded by multiple-motif matching, making them more flexible and powerful than single-motif approaches. Unlike some other pattern-matching methods, fingerprinting is well-suited to the creation of 'hierarchical' discriminators—e.g. this approach has been used to resolve G protein-coupled receptor (GPCR) super-families into their constituent families and receptor subtypes (1), and to sub-classify a variety of channel proteins, transporters and enzymes.

To date, 1800 fingerprints have been developed, manually annotated and deposited in the PRINTS database (2). Overall, the database is still rather small, largely because detailed annotation of entries is extremely time-consuming. However, the extent of manually-crafted annotations sets the database apart from the growing number of automatically-derived 'family' resources, for which there is no biological documentation and no result validation, and in which family groupings may change between database releases.

PRINTS was originally built as a single ASCII (text) file. To facilitate maintenance, we later developed a relational version of the resource, known as PRINTS-S (3). Here, we describe recent progress and a new development aimed at increasing the coverage of the database, notably the creation of an automatic PRINTS supplement, termed prePRINTS.

SOURCE DATABASE AND SEARCH TOOLS

PRINTS is released in major and minor versions: minor releases reflect updates, bringing the contents in line with the current version of the source database [a SWISS-PROT/TrEMBL composite (4)]; major releases denote the addition of new material to the resource. The latter are made quarterly, each release including 50 new annotated families. Four major releases have been made since the last report.

The tools available for searching PRINTS are: (i) a BLAST (5) server, for searches against *sequences* matched in the current version of the database (6); and (ii) the FingerPRINTScan suite (7), for searches against *fingerprints*

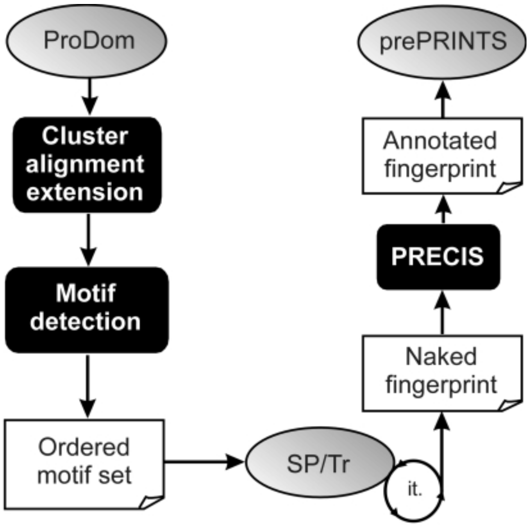

Figure 1. Illustration of the automated prePRINTS pipeline.

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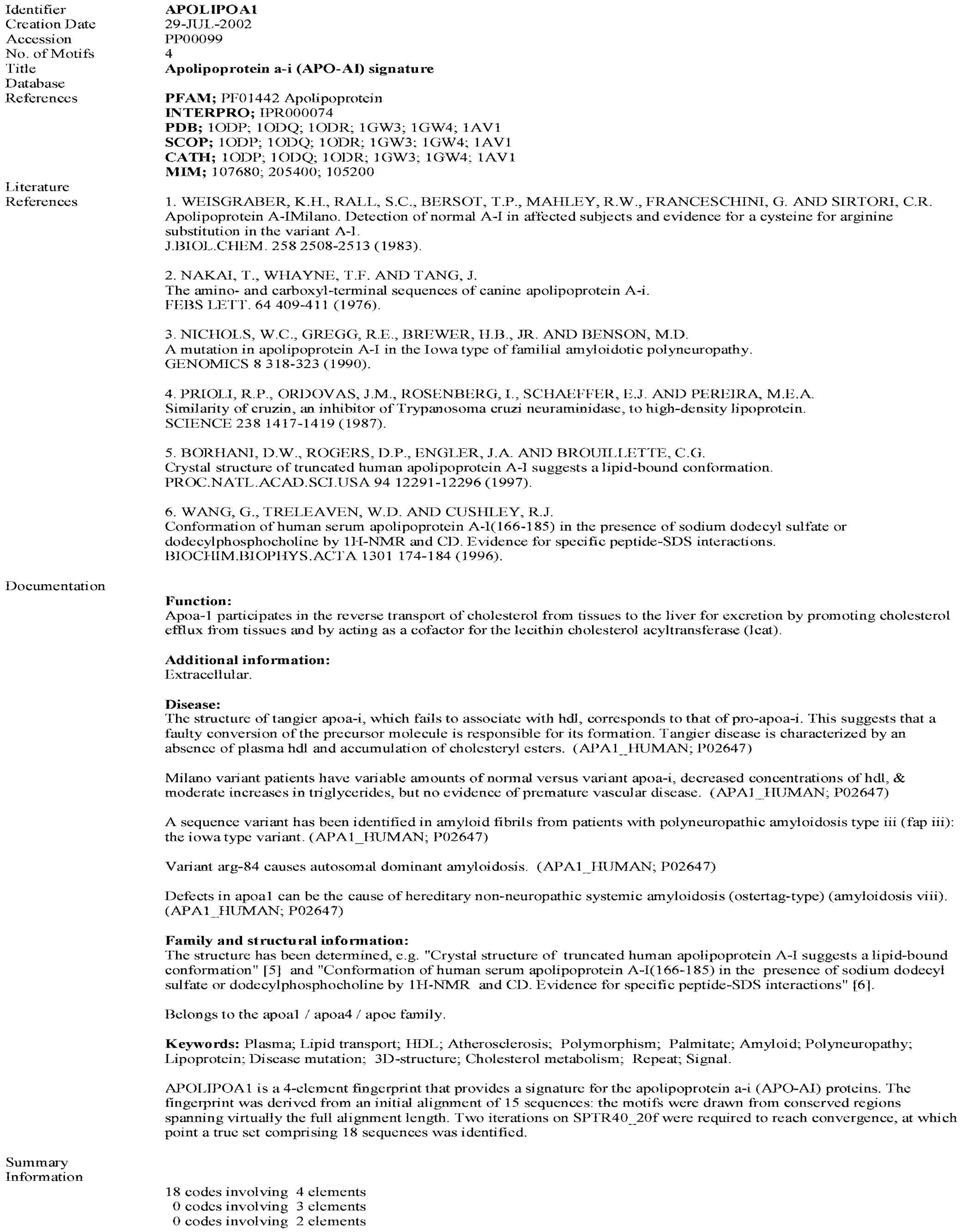

Identifier **APOLIPOA1**
Creation Date 29-JUL-2002
Accession PP00099
No. of Motifs 4
Title **Apolipoprotein a-i (APO-AI) signature**
Database
References

PFAM; PF01442 Apolipoprotein
INTERPRO; IPR000074
PDB; 1ODP; 1ODQ; 1ODR; 1GW3; 1GW4; 1AV1
SCOP; 1ODP; 1ODQ; 1ODR; 1GW3; 1GW4; 1AV1
CATH; 1ODP; 1ODQ; 1ODR; 1GW3; 1GW4; 1AV1
MIM; 107680; 205400; 105200

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Conformation of human serum apolipoprotein A-I(166-185) in the presence of sodium dodecyl sulfate or dodecylphosphocholine by 1H-NMR and CD. Evidence for specific peptide-SDS interactions.
BIOCHIM.BIOPHYS.ACTA 1301 174-184 (1996).

Documentation

Function:
Apoa-1 participates in the reverse transport of cholesterol from tissues to the liver for excretion by promoting cholesterol efflux from tissues and by acting as a cofactor for the lecithin cholesterol acyltransferase (lcat).

Additional information:
Extracellular.

Disease:
The structure of tangier apoa-i, which fails to associate with hdl, corresponds to that of pro-apoa-i. This suggests that a faulty conversion of the precursor molecule is responsible for its formation. Tangier disease is characterized by an absence of plasma hdl and accumulation of cholesteryl esters. (APA1_HUMAN; P02647)

Milano variant patients have variable amounts of normal versus variant apoa-i, decreased concentrations of hdl, & moderate increases in triglycerides, but no evidence of premature vascular disease. (APA1_HUMAN; P02647)

A sequence variant has been identified in amyloid fibrils from patients with polyneuropathic amyloidosis type iii (fap iii): the iowa type variant. (APA1_HUMAN; P02647)

Variant arg-84 causes autosomal dominant amyloidosis. (APA1_HUMAN; P02647)

Defects in apoa1 can be the cause of hereditary non-neuropathic systemic amyloidosis (ostertag-type) (amyloidosis viii). (APA1_HUMAN; P02647)

Family and structural information:
The structure has been determined, e.g. "Crystal structure of truncated human apolipoprotein A-I suggests a lipid-bound conformation" [5] and "Conformation of human serum apolipoprotein A-I(166-185) in the presence of sodium dodecyl sulfate or dodecylphosphocholine by 1H-NMR and CD. Evidence for specific peptide-SDS interactions" [6].

Belongs to the apoa1 / apoa4 / apoe family.

Keywords: Plasma; Lipid transport; HDL; Atherosclerosis; Polymorphism; Palmitate; Amyloid; Polyneuropathy; Lipoprotein; Disease mutation; 3D-structure; Cholesterol metabolism; Repeat; Signal.

APOLIPOA1 is a 4-element fingerprint that provides a signature for the apolipoprotein a-i (APO-AI) proteins. The fingerprint was derived from an initial alignment of 15 sequences: the motifs were drawn from conserved regions spanning virtually the full alignment length. Two iterations on SPTR40_20f were required to reach convergence, at which point a true set comprising 18 sequences was identified.

Summary
Information

18 codes involving 4 elements
0 codes involving 3 elements
0 codes involving 2 elements

Figure 2. Exerpt from a typical prePRINTS entry (for convenience, the initial and final motifs, and the matched sequence identifiers and accession numbers have been omitted). The example illustrates the fingerprint for apolipoprotein A-I, for which 4 motifs were generated by the prePRINTS pipeline. The fingerprint is 'clean', matching 18 sequences completely, with no partial matches, as indicated by the Summary Information. Cross-references have been generated to 6 databases, and 6 literature references have been included, the last two of which relate to crystallographic and NMR structure determinations respectively. The documentation field reports on the function of the protein and its disease associations, together with its structural and familial relationships. Keywords are also provided. In addition, a brief technical description indicates some of the parameters used to create the fingerprint. Except for the Summary Information, which was generated by the fingerprinting process, the rest of the information shown here was created fully automatically by PRECIS.

contained in the current release—this affords greater specificity than the BLAST implementation (6). A recent powerful modification of FingerPRINTScan makes explicit the familial hierarchies encoded in PRINTS-S, allowing associations to be traced from sub-family to super-family relations and, where relevant, to putative distantly related clan members that share no significant sequence similarity (8).

Several other incarnations of PRINTS are also available for searching, including a Blocks-format version at the Fred Hutchinson Cancer Research Center (9), the EMOTIF database at Stanford (10), and InterPro (to which it provides a significant amount of annotation and the bulk of its hierarchical information) (11).

PrePRINTS

The growth of PRINTS is limited by the fact that it is maintained entirely manually, and hence it lags behind databases that are produced automatically. To begin to address this problem, we migrated the resource to a relational database management system (3). Although this facilitates routine maintenance and reduces some of the manual burdens, it does little to address database growth. We, therefore, developed an automatic supplement to PRINTS, termed prePRINTS (http://www.bioinf.man.ac.uk/prePRINTS/). This exploits an automatic pipeline (Fig. 1), which uses as input protein family clusters from ProDom (12). Motifs are detected automatically using a suite of programs, including DIALIGN (13) and CLUSTALW (14), and are used to search a SWISS-PROT/TrEMBL composite database in an iterative fashion. Naked fingerprints generated by this process are then annotated automatically using PRECIS [Protein Reports Engineered from Concise Information in SWISS-PROT (15) http://www.bioinf.man.ac.uk/cgi-bin/dbbrowser/precis/precis.cgi]. Finally, annotated fingerprints are deposited into a relational database (see Fig. 2).

The pipeline generates 30–50 fingerprints per 24 h running on a single-processor desktop PC. The rate of conversion of these fingerprints into entries of sufficient quality for prePRINTS is ~25% across all ProDom clusters, potentially yielding 800–900 entries/quarter — the actual rate is slower, as some human validation is necessary, for example, to discard non-specific 'noisy' motifs, or to eliminate restrictive motifs (i.e. those not found in all family members). The rest of the system is largely automated, so there is likely to be some redundancy with PRINTS. Nevertheless, prePRINTS serves as a valuable PRINTS 'incubator', wherein entries are manually refined before accession to PRINTS itself. PrePRINTS 1.0 contains 250 entries.

AVAILABILITY

For local installation, PRINTS flat-files may be retrieved from the anonymous-ftp servers at Manchester (ftp://ftp.bioinf.man.ac.uk/pub/prints), HGMP-RC (ftp://ftp.hgmp.mrc.ac.uk/pub/database/prints), EBI (ftp://ftp.ebi.ac.uk/pub/databases), EMBL (ftp://ftp.embl-heidelberg.de) and NCBI (ftp:./ncbi.nlm.nih.gov). prePRINTS is available from the Manchester server.

CONCLUSION

A limitation in using protein family databases to infer function of newly-determined sequences is that of coverage; clearly, the diagnostic capability of a database is restricted to the entries it contains. The growth of PRINTS has been restricted by its manual maintenance, causing it to lag behind largely automatically-generated counterparts, such as Pfam (16). However, prePRINTS will help to increase the family coverage of PRINTS, thereby improving its effectiveness as a tool for protein sequence analysis and genome annotation.

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