ABSTRACT
Motivation: Beta-lactamases confer resistance to a broad range of antibiotics and inhibitors by accumulating mutations. The number of beta-lactamases and their variants is steadily increasing. The horizontal gene transfer likely plays a major role in dissemination of these markers to new environments and hosts. Moreover, information about the beta-lactamase classes and their variants was scattered. Categorizing all these classes and their associated variants along with their epidemiology and resistance pattern information on one platform could be helpful to the researcher working on multidrug-resistant bacteria. Thus, the beta-lactamase database (BLAD) has been developed to provide comprehensive information (epidemiology and resistance pattern) on beta-lactamases. Beta-lactamase gene sequences in BLAD are linked with structural data, phenotypic data (i.e. antibiotic resistance) and literature references to experimental studies. In summary, BLAD integrates information that may provide insight into the epidemiology of multidrug resistance and enable the designing of novel drug candidates.

Availability: The database can be accessed from the website www.blad.co.in.

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Supplementary information: Supplementary data are available at Bioinformatics online.

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1 INTRODUCTION
Beta-lactamases are one of the major causes of resistance against beta-lactam antibiotics (Ghuysen, 1991). Carbapenem-resistant Enterobacteriaceae has been increased in bacterial strains isolated from nosocomial infections in past 10 years (Jacob et al., 2013). Based on the sequence, the beta-lactamases are divided into four classes A–D (Barry and Barlow, 2005). Class A, C and D are serine beta-lactamases, whereas class B enzymes are metallo-beta-lactamases. Class A provides the most commonly encountered mechanism of bacterial resistance to beta-lactam antibiotics. It appears to be the most widely distributed class of beta-lactamases and capable of hydrolyzing penicillins and classical cephalosporins (Jan and Niels, 2007). The genes of class B beta-lactamases are implicated in the hydrolysis of cephalosporins and carbapenems and are located on both chromosomes and plasmids. Some of the most prevalent class B enzymes include IMP, VIM, NDM and SPN. The NDM-1 was a recent addition to this class, which was isolated from a patient hospitalized in India (Khan and Nordmann, 2012).

Another class of enzyme is a serine-hydrolyzing class C belonging to the cephalosporinases family, which confers resistance to broad-spectrum cephalosporin including cefoxime and cefazidine. Some of the most prevalent enzymes of this class are AmpC, CMY, ACC, produced by gram-negative bacteria (Gregg et al., 2001). The enzyme OXA beta-lactamases belongs to class D, and 240 OXA type beta-lactamases have been characterized so far. Several recent efforts (Thai and Pleiss 2010; Thai et al. 2009) have been made to partially unify the information about the beta-lactamases with limited functionalities. The main limitation of such resources is lack of information for all types of beta-lactamases class. Thus, to address these limitations and to facilitate the characterization of these beta-lactamases, we have integrated sequence, structural and experimental information on a common platform. Although, the information available in the previously published resources are useful (Thai and Pleiss 2010; Thai et al., 2009), such resources do not provide the information for all types of beta-lactamases. Moreover, other resources (Liu and Pop, 2009; Singh et al., 2008) lack the information about the 3D structures and inhibitors resistance profile of the beta-lactamases. Beta-lactamase database (BLAD) represents the most extensive catalog for maximum type of beta-lactamases (Class A–D) along with other unique features such as search by source, country, type, variant along with local alignment, restriction enzyme digestion analysis tools, which are lacking in previously published databases of this kind. Hence, our annotated and updated database will provide broad information to the researchers.

2 DATABASE CONTENT
BLAD (version 1.0) consists of four search fields. (i) Database: It contains information about the sequences (nucleotide and protein). Each entry has been cross-linked to NCBI and Pubmed database. With the export option, users can easily download all information for their search type. (ii) Resistance: It contains information about beta-lactamases that confer resistance to drugs or inhibitors. (iii) PDBS: It contains information about the 3D structure of enzymes and their variants along with the description of physicochemical properties of bound ligands. (iv) Genome: Contains the information of the plasmids harbor the beta-lactamase gene. This information is included as type, variant, organism, resistance, mutant, protein and nucleotide sequences with NCBI links, literature reference with the PubMed links and export option. Cross-reference to the UniProt protein...
sequence database is also provided. The current version of BLAD holds ~2000 gene sequences along with ~200 crystal structures for different types of beta-lactamases. All the data were collected from literature, NCBI, protein data bank (Sussman et al., 1998) and other authentic resources (Supplementary Fig. S1).

3 DATABASE INTERFACE AND TOOLS
BLAD was built on Apache server 2.2.11 (http://www.apache.org/) with Hypertext preprocessor program PHP (http://www.php.net/). The database tables were stored in MySQL 5.0 relational database. This database has six options for users. (i) Home: Provides the basic introduction about the beta-lactamases. (ii) Database: Users can use this option for searching the gene query of their interests. (iii) Resistance Pattern: Provides the information about the resistance pattern of each query. (iv) PDBS: This is used to search and analyze the 3D structure of beta-lactamase. (v) Contacts: Provides the contact address of the developer. (vi) Feedback: Allows the users to send the suggestions and comments for the further development of this database. BLAD can be searched using class, type, variant, organism, country, resistance type as keywords. The search output includes a summary table (Supplementary Fig. S2a-d) for all the matched entries. We have also integrated the bioinformatics tools as BLADrestrict and BLAST for analyzing the sequences.

4 DISCUSSION AND FUTURE PROSPECTS
BLAD is the first comprehensive database especially developed to catalog, and categorize, the resistance pattern about all classes of beta-lactamases identified by experimental studies. It also provides the information about the 3D structure along with the physiochemical properties of bound ligands. This database is equipped with flexible search features including user-friendly browse and hypertext link-outs to nucleotide and protein sequence databases. We trust that BLAD will be a useful platform for experimental and computational analyses of beta-lactamases. Future update of BLAD will contain the information about primers for each class and their variants. This database will be updated manually by incorporating new data and resources as soon as they become available.

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