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Role of microRNAs in Genodermatoses

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Abstract—*Dermatoses are becoming a major economic trouble for the world's population and it can affect a person at any age. Advancement in understanding of associations of disorders and human genome, particularly microRNA, has revealed its substantial contribution to skin disorders. In the present study, we have tried to create a comprehensive information resource of microRNAs that have been previously shown to be associated with genodermatoses. Manual curation of association studies revealed 632 relationships between 290 human microRNAs and 35 dermatological disorders. Some of the microRNA–disease relationships represent the adverse roles of ill-regulated microRNA in genodermatological disorders, while in some cases microRNAs are biomarkers of the disease. Each data entry provides detailed information on a microRNA–disease relationship, including a microRNA ID, the disease name, and a brief description of the microRNA–disease relationship and PubMed IDs of the referred texts. We believe that extensive research on the link between miRNAs and dermatological disorders may facilitate scientists to understand the biology behind dermatoses causation.*

1. INTRODUCTION

These Many observations, analysis and hence discoveries have been made after the publishing of first draft of human genome in February 2001. This showed the complexity of the human genome. For the past few years, many types of diseases are being diagnosed at an initial stage with the application of bioinformatics technologies for early detection of diseases. After the human genome studies revealed that less than 2% of the human genome is coding and rest 98% is non-coding DNA, the researchers have shifted their focus from mRNAs to noncoding RNAs as a major regulator of human genome. The presence of noncoding RNAs and its role in many human diseases make these molecules important mediators which have to be understood in medical research.

1.1. microRNA

Micro ribonucleic acids (also known as miRNAs or microRNAs) are small stretches of RNA molecules which lie in non coding region. In some cases they bind to target gene (mRNA), resulting repression in gene regulation and gene silencing [1]. miRNA are found in all eukaryotic cells. They target specific mRNAs by binding to complementary sites in the 3′-untranslated regions of target genes to degrade and/ or repress translation to control gene expression [2]. There exist approximately 2200 miRNA genes in the mammalian genome, from which over 1000 belong to the human genome [3,4]. miRNAs regulate many crucial cellular functions such as development, differentiation, growth, and metabolism [5-8].

In the nucleus, transcription of miRNAs takes place and the primary pri-miRNA is formed. The pri-miRNA forms the precursor pre-miRNA stem loop structure after processing. Then it is transported into the cytoplasm and is cleaved by the Dicer RNAase III endonuclease to produce a mature miRNA (21-23 nucleotides) [9].

1.2. miRNA Databases

In past few years, many microRNA-related database systems have been developed. Complete repositories for microRNA annotation and nomenclature are provided by miRBase [10], miRGator [11] and miRGen [12]. Experimentally validated and/or computationally predicted microRNA–target relationships are stored in TarBase [13], microRNAMap 2.0 [14] and microRNA.org [15]; a collection of microRNA expression profiles in different tissues is also provided by microRNA.org. Such database systems offer great resources in investigating the function of microRNA in gene regulation. In addition, several computational algorithms and web-based programs have been developed to computationally predict target genes/sites of microRNAs, such as TargetScan [16], PicTar [17], RNAhybrid [18] and PITA [19].

1.3. Role of miRNA in Skin

Role of miRNAs [26] is involved in hair follicle morphogenesis, autoimmune and chronic inflammatory diseases affecting skin [20 - 24]. Dermal fibroblasts are important cells involved in the wound healing process

Table 1 List of various genodermatoses included in microDerma

Dermatose	Type	No. of related miRNA
Androgenic Alopecia	Alopecia, Hair	5
Burns	Injury	2
Carcinoma, Basal Cell	Cancer	33
Carcinoma, Oral	Cancer, Oral	1
Carcinoma, Squamous Cell	Cancer	51
Cholesteatoma	Squamous Epithelial	5
Cicatrix	Wound	2
Dermatitis, Atopic	Inflammation	3
Dermatomyositis	Inflammation	32

Eczema (Dermatitis)	Inflammation	1
Focal Epithelial Hyperplasia	Viral infection, Oral	1
Hamartoma Syndrome, Multiple	Hamartoma	2
Hand, Foot and Mouth Disease	Cutaneous Disease	7
Hemangioma	Tumor	1
HPV Infection	Viral infection	6
Keloid	Wound	2
Leprosy	Bacterial Infection	1
Lichen Planus, Oral	oral	8
Lupus Erythematosus, Systemic	Autoimmunity	38
Lupus Vulgaris	Bacterial Infection	62
Melanoma	Cancer	74
Mycosis Fungoides	Fungal Infection	11
Neoplasms, Squamous Cell	Tumor	32
Pemphigus, Benign Familial, (Hailey-Hailey Disease)	Epidermal	2
Psoriasis	Epidermal	23
Scleroderma, Systemic	Autoimmunity	15
Skin Neoplasms	Tumor	4
Vitiligo	Hypopigmentation	1
Wounds and Injuries	Injury	1
Sarcoidosis	Inflammation	1
Bloom Syndrome	Photosensitivity	12
Xeroderma Pigmentosum	Photosensitivity	1
Chronic Granulomatous Disease	Immune deficiency Disease	1
Melasma	Hyperpigmentation	1

[24]. Analysis of the potential involvement of miRNAs in regulating the transition to proliferation has been performed and a cluster of 33 miRNAs were reported to be involved in regulation of expression of target genes required for the entry of fibroblasts into the cell cycle and proliferation [21]. A recent review has outlined the potential importance of miRNAs' involvement in wound angiogenesis and abnormal healing sequence in chronic wounds [22, 25].

1.4. microDerma

microDerma is a manually curated database aimed at providing a freely accessible interactive database of the relationships of human micro ribonucleic acids (miRNAs) and skin-related disorders along with the supporting evidence. By doing so, microDerma hopes to facilitate access to and analysis of the relationships asserted between human gene and observed disease conditions. microDerma collects disease-miRNA associations as well as their significance.

1.5. Construction and content of microDerma

The primary data in the microDerma represents association of miRNA with various genodermatoses. All the complex genetic disorders that are believed to be related to skin have been considered as genodermatoses for the purpose of this work. The information on genodermatoses was obtained from the articles published in high-quality journals and various online medical forums discussing aging and associated diseases. All the compiled genodermatoses were then explained by the type of disease for constructing the diseasome. Table 1 lists all the genodermatoses included in microDerma along with their types and number of miRNAs related. The disease-miRNA associations for these genodermatoses were manually curated from the relevant articles published in PubMed extracted using the keywords such as ‘‘Disorder name AND miRNA” or ‘‘Disorder name AND microRNA” and existing databases. The data from the existing databases was carefully assessed and corrected with reference to the original articles. All miRNA-disease associations were mined and included in microDerma. A data model was then created using the Microsoft Excel tool. Each entry in microDerma contains the information on miRNA, the associated disease and the literature reference.

2. METHODOLOGY

Initial entries describing the relationships between microRNA deregulation and occurrences of skin disease were collected from HMDD (Human MicroRNA Disease Database). After that TargetScan, mirBase were also searched for skin related diseases. After that some entries were searched manually from the PubMed database with a list of keywords, such as “microRNA” AND “Skin Disease”, “miRNA” AND “Skin Disease”, “microRNA melanoma”, etc. The term “Skin Disease” was replaced by names of various genetic skin disorders each time for searching. In the current release of *MicroDerma*, more than 200 literatures were reviewed, and 632 curated relationships between 290 human microRNAs and 35 human diseases have been documented. Each entry in the database contains detailed information on a microRNA–disease relationship, including a microRNA ID, the disease name, a brief description of the microRNA–disease relationship or an expression pattern of microRNA (upregulated or downregulated) in the disease and a literature reference (PubMed ID).

3. RESULTS AND CONCLUSIONS

In the present work, an offline repository of the miRNAs associated with genodermatoses, microDerma has been developed. To the best of my knowledge, this is the first resource that hosts genetic association information on human genodermatoses. This knowledge may eventually be helpful in understanding the biology of skin.

The database is in first normal form (1NF), that is, the domain of each column (attribute) contains only atomic (indivisible) values, and the value of each attribute contains only a single value from that domain.

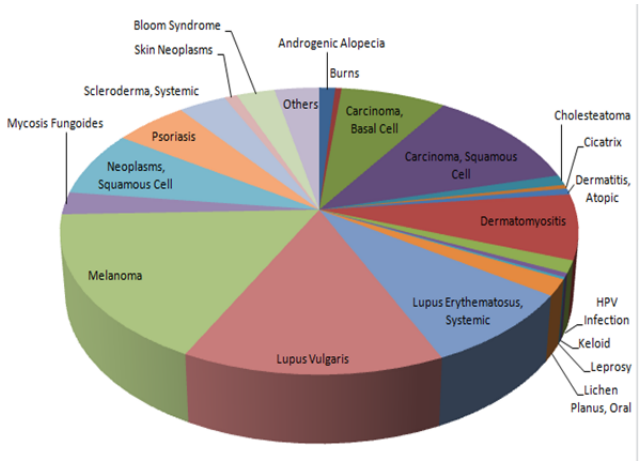

Fig. 1: Distribution of Genodermatoses in microDerma

There are 6 attributes for each of the 632 tuples, namely – serial number, miRNA name, associated disease, PubMed ID for reference, and description about the relation of miRNA and the disease in a comment.

It is believed that the present database may be used to uncover hidden links of various skin-related disorders providing valuable perspective to dermatologists and biomedical researchers.

The data of microDerma was analysed so as to see the distribution of various miRNA related genodermatoses with respect to the proportion (percentage) of microRNAs related to the disorders. This distribution is depicted with the help of a pie-graph, as shown in Fig. 1.

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