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EPIDEMIOLOGY (R DELLAVALLE, SECTION EDITOR)

Genetic Risk Factors for Development of Atopic Dermatitis: a Systematic Review

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Abstract
Purpose of Review The purpose of this study is to systematically review studies conducted between April 2015 and April 2017 for the genetic risks for the development of atopic dermatitis (AD). We sought to identify (1) specific loci and genes associated with AD, (2) the proportion of studies for each gene, and (3) genetic risks that need further investigation.
Recent Findings Studies have found that genetic predisposition and environmental triggers are involved in the pathogenesis of AD. Thirty-four loci and 46 genes have been identified as genetic risk factors, of which filaggrin gene null mutations and genes in the type 2 T-helper lymphocyte (Th2) signaling pathway have been the most extensively studied.
Summary Our systematic review found that in the last 2 years, 46 loci and 53 genes have been studied in the development of AD. Genes involved in epidermal barrier, immune regulation, and intracellular functions were identified. We suggest that future research should investigate the intricate interaction of these genes as well as the complex interplay of genetic and environmental factors in the development of AD.

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Introduction

Atopic dermatitis (AD) is a common inflammatory skin condition that results in chronic, pruritic, relapsing symptoms [1]. Approximately 15.2 million children and adults suffer from AD, with prior studies suggesting a prevalence of 8 to 18% in children and 10% in adults within the USA [2, 3]. The cost of AD including prescriptions, outpatient visits, hospital stays, and emergency department visits in the US nears $5 billion annually [4].

More importantly, AD impacts emotional, physical, social and occupational aspects of a patient's life [2, 4, 5]. Quality of life is impaired due to sleep disturbances, fatigue, and overall poor health [6]. Adults suffering from AD have a higher number of missed work days and doctor visits compared to healthy adults [6, 7]. Furthermore, among chronic skin disorders, children and caretakers report AD to be the greatest detriment to a positive quality of life and 75% of caregivers report that controlling AD symptoms would cause the most significant improvement in their child's quality of life [8, 9].

The development of AD involves skin barrier dysfunction with dysregulation of innate and adaptive immunity [10]. The epidermal barrier dysfunction seen in AD has been associated with mutations in genes encoding proteins involved in forming the epidermal barrier, most notably, the gene encoding filaggrin [11]. A recent review of AD genetics identified filaggrin gene null mutations and genes in the type 2 T helper lymphocyte (Th2) signaling pathway as the most extensively studied genetic risk factors for AD

[10]. Thirty-four loci and at least 46 genes have since been linked to the development of AD [10, 11].

AD is undeniably a heritable disease; however, studies suggest that there are environmental triggers that influence atopic disease [12]. Discordance in the expression of atopy among monozygotic twins suggests that environmental factors influence atopy in genetically susceptible individuals [12]. Proposed environmental risk factors for AD include breastfeeding, antibiotic exposure, water hardness, contact with farm animals, and early life exposure to air pollutants [13–17].

The purpose of this study was to systematically review the recent literature evaluating genetic risk factors for the development of AD. We sought to identify (1) specific loci and genes associated with AD, (2) the proportion of studies for each gene, and (3) genetic risks that need further investigation.

Methods

Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017065497.

Literature Search

Comprehensive literature searches were conducted with EMBASE, Ovid MEDLINE, Ovid MEDLINE Daily, and Ovid MEDLINE In-Process and Other Non-Indexed Citations, bibliographic databases for studies from April 01, 2015 to May 01, 2017. Key search terms included "atopic dermatitis," "genetic mutation," "genetic predisposition," and "genetic polymorphism" (Tables 1 and 2). Two reviewers (NK, RP) assessed results for inclusion criteria; a third reviewer was consulted (CD) for disagreements. Studies included met criteria for a primary article discussing human AD, genetic risks, and the development of AD. Both databases were filtered by year; thus, studies published between January 01, 2015 and March 31, 2015 were manually excluded.

Study Selection

Five hundred and fifty-eight records were identified (425 from EMBASE and 133 from Ovid MEDLINE databases) of which 485 were non-duplicates (Fig. 1). Of these 485 articles, 95 were published prior to April 01, 2015, 157 were not related to AD, 93 were not related to genetic risks, 31 were not primary literature, 44 were not related to development/pathogenesis of AD, 15 were abstract only publications, and 8 were not in English.

Review articles and systematic reviews were excluded since they were not primary sources. Studies that assessed the severity or treatment response of AD were excluded on the basis that they were not related to the development of AD. The remaining 36 articles were included in the systematic review (Fig. 1; Table 3).

Results

Thirty-six full-text articles were reviewed [30, 38•, 50–57, 58•, 59–72, 73•, 74–83]. Genes included in data extraction were identified by authors to be significant for genetic susceptibility of AD (Table 3). One study by Ghosh et al. identified 89 genes from five different microarray studies of which the top 10 upregulated genes are included in Table 3. Paternoster et al. identified 10 new loci in addition to 21 prior loci; the 10 new loci were included in our data.

Our systematic review determined 53 genes contributing to the development of AD in the past 2 years. The classes of these genes included epidermal development and barrier function related genes, immune regulatory genes, protease genes, antimicrobial genes, cellular function genes, and genes whose functions are not yet elicited. Genes with immune regulatory functions were the most frequently represented class with 23 genes (43%). This was followed by 12 genes (23%) contributing to epidermal development and barrier function, 10 genes (19%) regulating cellular function, 5 genes (9%) with unknown function, two protease genes (4%), and one antimicrobial gene (2%). We identified that in the past 2 years, 46 loci have been studied as risk loci for the development of AD.

Discussion

Our systematic review found several genes and loci identified as genetic risk factors for the development of AD. Many genes were determined to be associated with the development of AD among various ethnic groups, thus suggesting similar genetic risks regardless of ethnicity.

Immune Regulatory Genes

The immune system plays a crucial role in the pathogenesis of AD. At least nine immunological components are involved in either the Th2 pathway or the production of IgE, which is a hallmark of the atopic triad. Our systematic review found that mutations in IL-4, IL-10, IL-13, IL-18, IL-22, IL-36, and receptors of IL-4, IL-7, and IL-2 can contribute to the development of AD. These mutations were present across multiple ethnicities. Not surprisingly, several of these mutations are directly and indirectly involved in the production of IgE.

Prior studies have indicated the role of Th2 immune-mediated dysfunction in the pathogenesis of AD. In concordance with prior research on abnormal Th2 immune

Table 1 Search query for Ovid MEDLINE, Ovid MEDLINE Daily, and Ovid MEDLINE In-Process and Other Non-Indexed Citations

No.	Query	No. of records
1	(Atopic dermatit* or atopic neurodermatit* or disseminated neurodermatit* or atopic eczem* or infantile eczem*).mp.	19,017
2	exp dermatitis, atopic/	17,170
3	1 or 2	23,711
4	exp Genes/	715,800
5	Mutation/ or exp Genetic Variation/or exp Genetic Predisposition to Disease/or exp Polymorphism, Genetic/	997,648
6	4 or 5	1,446,464
7	3 and 6	1116
8	Limit 7 to last 2 years	133

function in AD, our study found the transcription activator STAT6, Th2 cytokine RAD50, and TSLP genes involved in the pathogenesis of AD. Interestingly, our systematic review identified additional genes involved in Th17 differentiation, such as signal transducer and activator of transcription (STAT3) and ETS transcription factor 1 (ETS1).

Epidermal Development and Barrier Function Genes

We identified six genes involved in epidermal development and barrier function located on loci 1q21.3, representing the epidermal differentiation complex (EDC). Although the most well studied of these is filaggrin, each gene encodes a crucial step for differentiation and cornification of keratinocytes into the impermeable stratum corneum. Our systematic review identified 11 studies that found an association with filaggrin mutation and the development of AD. These studies included populations of Asian, Caucasian, and African-American descents. Importantly, we identified several other genes in the EDC including small proline-rich proteins 1 and 2 (SPRR1, SPRR2), C1orf10 encoding the gene cornulin, and late cornified envelope 3 (LCE3). These genes also play a role in proper epidermal differentiation [20–22].

Beyond the EDC, one study identified Claudin-1 gene (CLDN1) on loci 3q28, a transmembrane protein important for regulation of transepidermal water loss [27], to play a role in the development of AD. Our findings indicate that the proper development and differentiation of the stratum corneum are crucial for maintenance of the barrier function to the external milieu in addition to retaining water in the body, with dysfunction of either aspect contributing to the pathogenesis of AD.

Cellular Function

Genes involved in cell cycle progression, nucleosome and intracellular proteolysis, and transcriptional proteins were identified in our systematic review. Three studies in Chinese, Korean, and Caucasian populations identified mutations on loci 5q31.1 encoding for KIF3A, a kinesin involved in cilia formation. Similarly, a prior meta-analysis showed a significant association of polymorphisms of the KIF3A gene and AD development [84]. KIF3A has been found to be important in hedgehog and beta-catenin-dependent wnt signaling, thus affecting cell proliferation and apoptosis [84]. Additionally, this gene has been studied in psoriasis, asthma, and Crohn's disease [84].

Protease- and Antimicrobial-Related Genes

Patients with AD often suffer from increased rates of skin infection, likely related to antimicrobial dysfunction [85]. In

Table 2 Search query for EMBASE

No.	Query	No. of records
1	atopic AND dermatit* OR atopic AND neurodermatit* OR disseminated AND neurodermatit* OR atopic AND eczem* OR infantileAND eczem*	11,667
2	atopic AND 'dermatitis'/exp	37,069
3	#1 OR #2	38,000
4	'genes'/exp	866,276
5	'mutation'/exp OR genetic AND 'variation'/exp OR genetic AND predisposition AND to AND 'disease'/exp OR polymorphism, AND genetic	319,081
6	#4 OR #5	1,115,107
7	#3 AND #6	2018
8	#4 AND #7 AND [2-2-2015]/sd NOT [2-2-2017]/sd	425

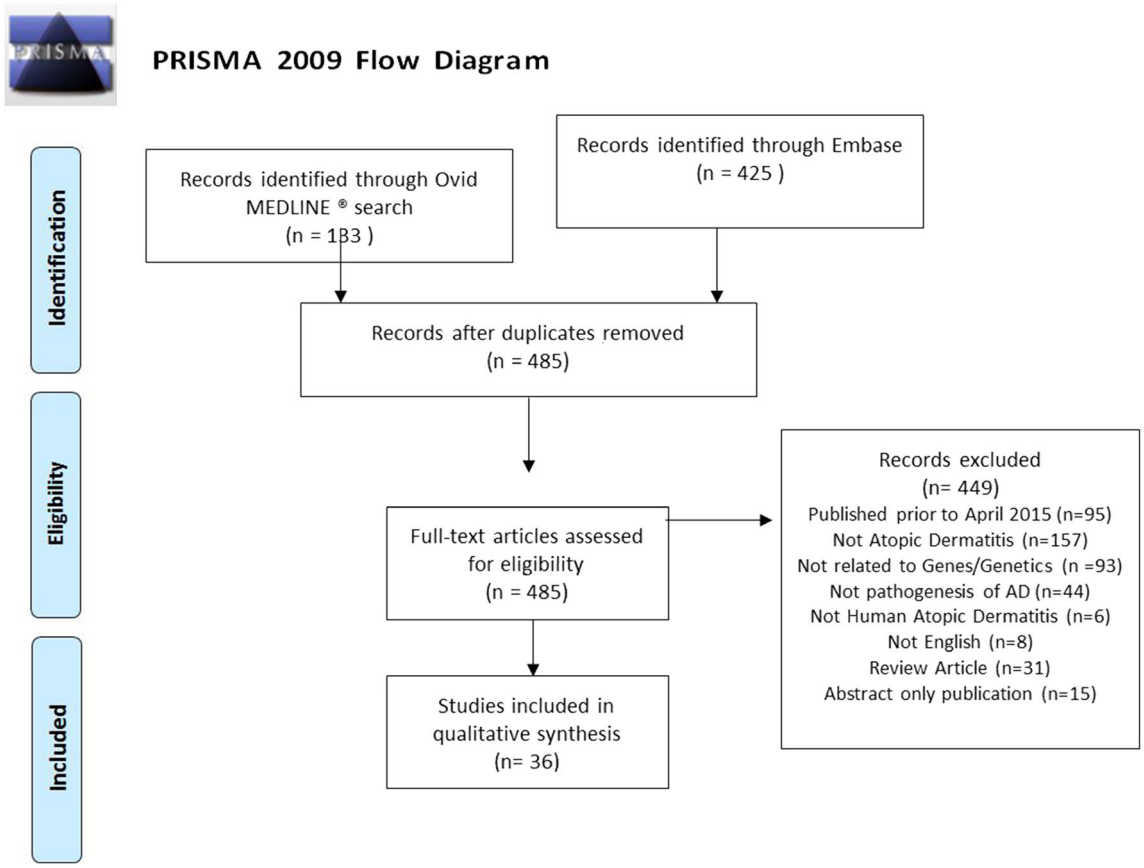

Fig. 1 Flow diagram depicting search process and reasons for exclusion. Modified from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [18]. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:https://doi.org/10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org

concordance with this hypothesis, our systematic review identified the gene DEFB4A, an antimicrobial defensin gene located at loci 8p23.1, to be associated with AD pathogenesis. This finding suggests innate immune dysfunction in the development of AD.

Mutations in proteases and protease inhibitors, including SERPINB3, SERPINB4, and PI3, were also identified. Interestingly, prior studies have identified mutations in epidermal proteolytic networks leading to abnormal stratum corneum and thus skin barrier dysfunction [86]. Likewise, our systematic review indicates that mutations in these proteases can further exacerbate the skin barrier dysfunction seen in the development of AD.

The Paradigm of AD Pathogenesis

The pathogenesis of AD continues to evolve as research provides further explanation on the development of this complex disease. Although originally thought to be a Th2 immune-mediated disease, further studies have elucidated the role of Th17 and Th22, epidermal barrier dysfunction, cellular alterations, and environmental triggers in the pathogenesis of AD. As described by Eyerich and Novak, development of AD may involve the combination of four key factors. Genetic predispositions including "genetic immunology type" such as TSLP and IL-4 and "genetic barrier type" such as filaggrin along with environmental factors including "non-genetic immunology type" such as allergic sensitization and "non-genetic barrier type" such as dryness and scratching play a role in the development of AD [87].

Our systematic review contributes to this evolving theory by providing greater evidence for the multitude of genetic factors involved in the development of AD. Although our results support the role of Th2 mediated immune dysfunction in the pathogenesis of AD, our systematic review also identified epidermal barrier, intrinsic cellular function, protease, and antimicrobial genes. This further justifies the need for ongoing research in this area as well as investigations into environmental triggers in genetically susceptible individuals.

Limitations

Limitations to our study include a narrow time frame and search results limited to two databases. Due to the growing

Table 3 Genes identified by systematic review

	Loci	Gene	Function	Population	Author, year
Epidermal development and barrier function-related genes	1q21.3	FLG Filaggrin	Key protein in the Epidermal Differential Complex (EDC) involved in epidermal differentiation and skin barrier [19]	Korean	On, H.R., March 2017
				Danish	Thomsen, S., 2016
				African-American	Quiggle, May 2015
				Polish	Filipowska-Grońska, February 2016
				Polish	Woźniak M., April 2016
				Caucasian (German)	Schaarschmidt, April 2015
				Polish	Trzeciak, M., February 2016
				Japanese	Sekiya, August 2016
				Caucasian (Denmark)	Martel, B.C., January 2016
				Chinese Han	Zhong, June 2016
				Caucasian (USA)	Ghosh, D., December 2015
		LELP1 Late cornified envelope-like proline-rich 1	Unknown function	Polish	Trzeciak, May 2016
		SPRR1 and SPRR2 Small proline-rich proteins 1 and 2	Cornified envelope precursor proteins important in epidermal differentiation [20]	Caucasian (Denmark)	Martel, B.C., January 2016
		C1orf10	Encodes cornulin (CRNN), a marker of late epidermal differentiation [21]	Caucasian (Polish)	Trzeciak, March 2017
		LCE3 Late cornified envelope 3	Encodes stratum corneum proteins involved in epidermal differentiation [22]	Caucasian (Denmark)	Martel, B.C., January 2016
		S100	Calcium-binding protein that interacts with intracellular proteins to transduce calcium signals [23] and an inflammatory protein found in neutrophils and CD4+ T cells [24]	Caucasian (Denmark)	Martel, B.C., January 2016
				Caucasian (USA)	Ghosh, D., December 2015
	1q21.2	Mitochondrial ribosomal protein MRPS21	Ribosomal proteins important in the translation of proteins in mitochondria [25]	European, African, Japanese, and Latino	Paternoster, L., December 2015
	3q22.1	COL6A6 Collagen type VI	Maintains extracellular matrix structure and skin integrity, expressed in human skin [26]	Caucasian (USA)	Ghosh, D., December 2015
				Korean	Heo, January 2017
	3q28	CLDN1 Claudin-1	Transmembrane protein important for regulation of transepidermal water loss [27]	Ethiopian	Asad, April 2016
	7q33	AKR1B10 Aldo-keto reductase	Regulates keratinocyte differentiation [28]	Caucasian (USA)	Ghosh, D., December 2015
	11q13.5	C11orf30 EMSY	May have a role in epithelial differentiation, growth, or immunity [29]. Plays a role in DNA damage repair.	Chinese Han	Cheng, October 2015
				Caucasian (German)	Schaarschmidt, April 2015
	1q32.1	IL-10		Italian	Esposito, September 2015

Table 3 (continued)

	Loci	Gene	Function	Population	Author, year
Inflammation-related genes, cytokines, and chemokines			Limits inflammatory responses by inhibiting the production of pro-inflammatory cytokines and chemokines [30]		
	2q14.1	IL-36	Regulates IFNγ, IL-17, and IL-4 production [31]	Caucasian	Suarez-Farinas, May 2015
	5q22.1	TSLP Thymic stromal lymphopoietin	Cytokine expressed in skin, involved in Th2 differentiation [32]	Japanese	Miyake, Y., August 2015
				Chinese Han and Caucasian	Wang, I., 2016
	5q31.1	IL-13	Induces IgE synthesis [33]	Caucasian (Polish)	Trzeciak, M., February 2016
				Caucasian (Denmark)	Martel, B.C., January 2016
		IL-4	Promotes IgE synthesis, inhibits interferon gamma (IFNγ) production	Caucasian (German)	Schaarschmidt, April 2015
				Iranian	Gharagozlou, May 2015
				Chinese	Shang, G., February 2016
		RAD50	Th2 cytokine	Caucasian (German)	Schaarschmidt, April 2015
				Korean	Kim, K., September 2015
	5p13.2	IL-7 Receptor	IL-7 receptor	European, African, Japanese, and Latino ancestries	Paternoster, L., December 2015
	6p21.1	TREM1/CD354 Triggering receptor expressed on myeloid cells	Expressed on neutrophils and monocytes, which acts as an activating receptor [34]	Caucasian	Suarez-Farinas, May 2015
	6q23.3	IFNGR1 Interferon gamma receptor 1	IFNγ receptor	Caucasian and African-American	Gao L., December 2015
	10p15.1	IL-2 receptor (alpha subunit)	IL-2 receptor	European, African, Japanese, and Latino ancestries	Paternoster, L., December 2015
	10q21.1	MBL2 Mannose-binding lectin	Involved in innate immune response and complement activation [35]	Italian	Esposito, September 2015
	11q13.5	LRRC32 Leucine-rich repeat containing protein	Encodes GARP, a receptor on activated T regulatory cells that binds latent transforming growth factor-β (TGFβ) [36]	Caucasian (German)	Manz, September 2016
				Caucasian (German)	Schaarschmidt, April 2015
	11q23.1	IL-18	Induces IgE synthesis by enhancing production of IL-4 and IL-13 [33]	Caucasian (Polish)	Trzeciak, M., February 2016
	11q22.2	MMP12, MMP1 Matrix metalloproteinases	Matrix degrading enzymes involved in inflammation and repair of tissue [37]	Caucasian (USA)	Ghosh, D., December 2015
	11q24.3	ETS1	ETS1 is the nearest gene to loci 11q24.3, which has roles in Th17 function and B cell differentiation [38•]	European, African, Japanese, and Latino ancestries	Paternoster, L., December 2015
	12q13.3	STAT6 Signal transducer and activator of transcription	Involved in Th2-induced responses including IgE production [39]	Saudi Arabian	Quiggle A., May 2015
				Taiwan	Lee, Y., May 2015
	12q15	IL-22		Caucasian (Denmark)	Martel, B.C., January 2016

Table 3 (continued)

	Loci	Gene	Function	Population	Author, year
			Produced by Th17 cells and mediates acanthosis and dermal inflammation induced by IL23 [40]		
	16p12.1	IL-4 receptor	IL-4 receptor	Saudi Arabian	Hussein, March 2016
				Caucasian (Polish)	Narozna, August 2015
	17q12	CCL18	Chemokine	Caucasian (USA)	Ghosh, D., December 2015
	17q21.2	STAT3 Signal transducer and activator of transcription	Important in Th17 cell differentiation and IgE production [38•]	European, African, Japanese, and Latino ancestries	Paternoster, L., December 2015
	17q25.3	STRA13 Stimulated by retinoic acid 13	Regulator of lymphocyte activation [41]	Chinese	Ding, July 2016
	19q13	SIRL-1 Signal inhibitory receptor on leukocytes	Inhibitory receptor on leukocytes	Chinese and Caucasian	Kumar, February 2017
		LILR Leukocyte immunoglobulin-like receptor	Expressed on monocytes and several other leukocytes; can act as activating or inhibiting factors of leukocytes [42]	Caucasian (UK)	López-Álvarez, M.R., June 2016
Protease-related genes	18q21	Serpin B4 and B3	Serine proteinase inhibitors with several functions including complement activation and cellular differentiation [43]	Caucasian (USA)	Ghosh, D., December 2015
	20q13.12	PI3 Proteinase inhibitor	Serine proteinase inhibitor that functions at epidermal surfaces as an antiinflammatory mediator [44]	Caucasian (USA)	Ghosh, D., December 2015
Antimicrobial-related genes	8p23.1	DEFB4A Defensin beta	Involved in epithelial antimicrobial defense	Caucasian (USA)	Ghosh, D., December 2015
Cell function-related genes	Xq13.2	NAP1L2 Nucleosome assembly protein 1-like 2	Nucleosome	Chinese	Ding, July 2016
	2p16	PUS10 Pseudouridylate synthase	Involved in posttranscriptional modification [45, 46]	European, African, Japanese, and Latino ancestries	Paternoster, L., December 2015
	3p21.1	SFMBT1 SCM-like protein with 4 MBT domains	Transcriptional repressor [47]	European, African, Japanese, and Latino ancestries	Paternoster, L., December 2015
	5q22.1	SLC25A46 Solute carrier family	Important in mitochondrial function and development, regulates chromatin states in epithelial cells [48]	Chinese Han	Gao, J., December 2015
	5q31.1	KIF3A Kinesin family member	Kinesin involved in cilia formation	Chinese	Kang, October 2015
				Korean	Kim, K., September 2015
				Caucasian (German)	Schaarschmidt, April 2015
	8q21	ZBTB10 Zinc finger and BTB domain containing protein	Encodes zinc-finger protein	European, African, Japanese, and Latino ancestries	Paternoster, L., December 2015

Table 3 (continued)

	Loci	Gene	Function	Population	Author, year
	12q13.11	VDR Vitamin D receptor	Intracellular receptor that binds 1-alpha, 25-dihydroxyvitamin D3	Turkish	Kilic, S., 2016
	14q13.2	PPP2R3C Protein phosphatase 2	Protein phosphatase regulatory subunit	European, African, Japanese, and Latino ancestries	Paternoster, L., December 2015
	15q24.3	SCAPER S-phase cyclin A-associated protein in the endoplasmic reticulum	Regulates cell cycle progression	Korean	Kim, K., September 2015
	19q13.12	PSENEN Presenilin enhancer gamma secretase subunit	Involved in intramembrane proteolysis [49]	Chinese	Ding, July 2016
Unknown functions	2p13.3	VAX2 Ventral Anterior Homeobox 29	–	European, African, Japanese, and Latino ancestries	Paternoster, L., December 2015
	2q24.3	XIRP2 Xin actin-binding repeat-containing protein 2	–	Caucasian (German)	Schaarschmidt, April 2015
	2p25	LINC00299	–	European, African, Japanese, and Latino ancestries	Paternoster, L., December 2015
	9p21.3	DMRTA1 Doublesex and Mab-3-related transcription factor-like family A1	–	Caucasian (German)	Schaarschmidt, April 2015
	11q13.1	OVOL1 Ovo-like 1	–	Chinese	Kang, October 2015
				Caucasian (German)	Schaarschmidt, April 2015

amount of literature on atopic dermatitis in the past decade, our time frame was narrowed to reflect the most up to date literature published in the past 2 years. In addition, some studies used computer mapping to identify numerous possible causal genes related to AD. In Ghosh et al., 89 genes were identified to be differentially expressed, although the top 10 statistically significant genes were included. In Paternoster et al., only the statistically significant, newly discovered genes were used to avoid redundancy. The excluded genes in these two studies would have increased the number of genes identified in our systematic review. However, to our knowledge, our study is the most recent systematic review assessing the genetic risk factors associated with development of AD.

Conclusion

Our systematic review identified 46 loci and 53 genes that increase risk of development of AD. These results indicate that dysfunction in several genes involved in the epidermal barrier, immune regulation, and intracellular function contributes to the genetic susceptibility of AD. With the vast number of genes involved in the development of this disease, it is imperative that further studies investigate the intricate interaction of these genes in the development of AD. Furthermore, it is important to note that AD is a multifactorial disorder due to genetic susceptibility and environmental influences. We suggest that future investigations address the complex interplay of genetic and environmental risks in the pathogenesis of AD. With further knowledge on gene susceptibility and environmental influences, development of targeted therapies can provide better treatment options for patients suffering from AD.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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