

Review

Filaggrin Gene, Chromosome band 9q34.3, SPINK5, ALCAM and Transepidermal Water Loss

Megha Rajput, B.S.¹, Howard Maibach, M.D.²

¹ College of Osteopathic Medicine, William Carey University, ² Dermatology, University of California, San Francisco

Keywords: Transepidermal water loss, gene, chromosome, immune response

<https://doi.org/10.62186/001c.116923>

Academic Medicine & Surgery

Background

Epidermal integrity and transepidermal water loss (TEWL) are highly correlated and crucial to healthy skin.

Aim

Review recent on the genetic control of transepidermal water loss and understand the resulting skin abnormalities due to negative gene control.

Methods

Searched scientific web pages, Pubmed, Science direct, Google Scholar, for recent (year: 2010 to 2020) experimental data. (N=7 scientific studies were analyzed)

Results

Relevance of these studies relates to major topics in the genetics of transepidermal water loss, but few concluded that genetic markers such as filaggrin, 9q34.3, and ALCAM correlates with transepidermal water loss. These genetic markers suggest that they can increase water diffusion and decrease when the markers are detected. It is crucial to understand how TEWL is controlled in order for sufficient barrier function.

Conclusion

The dependence on water regulator proteins such as aquaporins and tight junction proteins decreases as skin matures, and the level of these proteins and TEWL relate to gestation age. Molecular control of TEWL through such proteins is an indication of healthy skin. Further elaboration on these proteins and genes discussed should help understand their regulatory patterns to protect the stratum corneum.

BACKGROUND

Epidermal integrity and transepidermal water loss (TEWL) are well correlated and provide water and other barrier properties to human skin. TEWL passively diffuses water from the dermis to the skin surface (Elias et al., 2008). Stratum corneum (SC) controls TEWL which results in downstream signals into the skin maintaining homeostasis.¹ TEWL levels are used to compare skin water barrier function in compromised skin such as atopic dermatitis (AD), which damages the water barrier resulting in increased transepidermal water loss and increased percutaneous penetration of lipophilic and hydrophilic substances.² Filaggrin gene (FLG) is a loss of function gene, a stratum corneum (SC) tape stripping test concluded that although FLG is an important component in increasing water loss and changing skin integrity, it is not the only gene involved. Variants at 9q34.3 loci on chromosome band may correlate with TEWL.³ Compound K (CK), a ginsenoside

metabolite, is associated with serine protease inhibitor Kazal type-5 (SPINK5) by increasing its activity.⁴

SPINK5 partially helps explain barrier efficiency, as compound K is explored for its relation to skin barrier function.⁴ Activated leukocyte cell adhesion molecule (ALCAM), a member of the immunoglobulin family found on dendritic cells, where it works with CD6 to activate T cells. ALCAM and its relation to atopic dermatitis help understand its role in TEWL regulation.⁵ Finally, skin barrier function is crucial to survival for the fetal stage in life as it is used for water and gas exchange.⁶ The barrier changes immediately after birth and then progressively matures (Taieb, 2019). TEWL change in neonates is an important part of development that arises from molecular and cellular levels which is explored to understand the role of genetics as infants develop. This overview synthesizes recent topics in the genetics of transepidermal water loss and understand common controls of TEWL.

Table 1. Summary of studies

Study	Purpose	Sample size	Outcome measures	Relevant Findings
Flohret al. ⁷	Correlation between FLG mutations and skin barrier functions in humans with or without eczema	88 infants below age 3 months	SCORAD eczema severity scale, TEWL measurement from forearm, venous blood samples to identify FLG mutations	- High median of TEWL measurements in children with FLG mutation carriers even if child did not acquire eczema compared to wild type infants. - Positive correlation between FLG mutation carriers and diagnosis of eczema by the age of 3 months. - Skin barrier impairment precedes eczema instead of being a characteristic of skin condition.
Zhang et al. ³	Explore genetics behind skin barrier functions and TEWL	611 healthy skin samples	Determining P values statistically significant correlation ($p < 0.05$)	- P value of 3.11×10^{-8} significant correlation between TEWL and genetic marker 9q34.3 variant. - Ancestral gene (G) is which carries the 9q34.3 variant reduced TEWL by almost 19% therefore increasing barrier function.
Park et al. ⁴	Investigate association of compound K	Six-week-old female hairless mice skin	SPINK5 mRNA expression levels in CK	CK regulates SPINK5 expression.
	and SPINK5 in regard to barrier function		compared to the TEWL levels and skin health	- CK can enhance skin barrier function that is weakened by UVB. - Upregulating SPINK5 expression regulated TEWL to a healthy level.
Oh et al. ⁵	Understand role of ALCAM on atopic dermatitis	44 healthy controls, and all children treated for atopic dermatitis	ALCAM serum levels, flow cytometry rate to measure lymph nodes drainage, statistical analysis of results ($p < 0.05$)	- ALCAM negatively affects skin barrier health and TEWL. - ALCAM increases T-helper 2 cell production in AD patients to aggravate = symptoms.
Taïeb A. (2018).	Review molecular and cellular changes during neonates that help shape TEWL	Compiled data from 21 studies.	Used measured TEWL data from previous studies on neonatal infants for several weeks postnatal	Neonates had an increased amount of aquaporin and tight junction dependence which decreased as skin matured and TEWL levels started to decrease several weeks after birth.

METHODS

Pubmed, Science Direct, and Google Scholar were searched. The strategy utilized one word or a short phrase to identify articles on specific genetic components that control transepidermal water loss function and were published from 2011 to 2021. Key terms were: gene, Chromosome, immune response, transepidermal water loss, and protein. The search resulted in four main genetic components that might control TEWL: Filaggrin Gene, Chromosome band 9q34.3, SPINK5, ALCAM. Human and animal studies were included. Seven recent articles were found and 5 discussed in-depth research findings [Table 1].

FILAGGRIN GENE

Flohret et al.⁷ studied filaggrin loss of function (FLG) mutations correlated with atopic dermatitis to understand

whether FLG results in skin barrier impairment and eczema for the age group of 3 months old. Eighty-eight 88 infants were examined for eczema; Flohr concluded that TEWL levels in gm-2h-1 were significantly higher in infants with eczema compared to unaffected infants. FLG mutation carriers had significantly more clinically dry skin compared even when not diagnosed with eczema with $P = 0.04$. FLG mutation carriers were more likely to have eczema by 3 months of age and the mutations resulted in higher TEWL even if the child did not acquire any visible skin disease other than skin barrier impairment due to FLG mutation.

CHROMOSOME BAND 9Q34.3

Zhang et al. (2016) assessed the genetics component of water barrier function in healthy epidermis. Two genome-wide association studies (GWAS) were performed using 611 healthy skin samples from Jiangsu Province of China and measuring TEWL levels with DermaMeter Professional 100.

The findings suggested that from the 795,279 genotyped single-nucleotide polymorphisms (SNPs), a variant on chromosome band 9q34.3 was significantly correlated with TEWL with a P value of 3.11×10^{-8} . Further searching nine specific SNPs on chromosome band 9q34.3, suggested that ancestral allele (G) at rs11103631 were correlated with decreased TEWL levels and 19.5 % reduced skin permeability.

COMPOUND K AND SERINE PROTEASE INHIBITOR KAZAL TYPE-5 (SPINK5)

Park et al.⁴ studied serine protease inhibitor Kazal type-5 (SPINK5) which is hypothesized to be associated with skin barrier function and TEWL due to its association with compound K (CK), a well studied metabolite improving barrier efficiency. RT-PCR and western blot were conducted to correlate expression levels of SPINK5 to TEWL and histological skin barrier changes. Results suggested increased SPINK5 levels when induced CK on UVB-irradiated and atopic dermatitis like skin models. CK decreased TEWL to normal levels to reduce epidermal hyperplasia.⁴ Hence, compound K is activated once SPINK5 is activated resulting in restoration of protective skin barrier and increased TEWL.

ALCAM

Oh et al.⁵ researched activated leukocyte cell adhesion molecule (ALCAM) to understand its relation to immune response in atopic dermatitis (AD). As this is an animal and human study, ALCAM levels were measured in AD deficient mice and AD pediatric patients. ALCAM serum levels were measured to understand its association to atopic dermatitis - a condition that also has increased TEWL. ALCAM serum levels were significantly higher in AD pediatric patients. When testing the ALCAM-deficient mice the T helper 2 cell counts released during AD and TEWL levels were significantly lower.

TEWL IN NEONATES

Taieb⁶ examined skin barrier functions and growth in neonates. Using noninvasive methods and measuring TEWL which can also identify the gestational age at birth,

showed increased aquaporin 3 and tight junction protein levels in neonatal skin suggesting that molecular mechanisms regulating water flux during the first few weeks of birth are heavily dependent on proteins to help conserve water. Significant change in TEWL occurred at a decreasing rate from week 25 to 41 postnatal. This helps determine gestational age and TEWL signifies maturity to begin protecting the water barrier.

DISCUSSION AND CONCLUSION

These studies display major topics in transepidermal water loss genetics, yet few conclude that certain genetic markers such as filaggrin, 9q34.3, and ALCAM convincingly correlate with transepidermal water loss. Control of these markers can increase water diffusion and decrease when the markers are defective. TEWL control changes during the early months after birth are crucial to understanding how TEWL develops. Dependence of water regulator proteins such as aquaporins and tight junction proteins decreases as skin matures, and then levels can estimate gestation. The proteins and genes discussed should be further examined to understand their regulatory patterns to protect skin water barrier and decrease TEWL. Discussion of genetic markers lead to the confirmation that there is an association between TEWL and this genetic marker but in order to thoroughly understand the functions of this genetic marker it is crucial to understand its mechanism. A future research area would correlate change in 9q34.3, filaggrin, and ALCAM levels to a skin disease which also changes transepidermal water loss.

After compiling data regarding the most studied genetic components of TEWL it is also noticed that further work is needed to better understand the association between the genes, proteins, and changes in TEWL levels during the first few months of life. Taken together, these recent findings document the complexity of the structures and functional control of the stratum corneum barrier providing stimulus for further research to enhance efficient interventions.

Submitted: April 21, 2024 EDT, Accepted: April 22, 2024 EDT



REFERENCES

1. Alexander H, Brown S, Danby S, Flohr C. Research Techniques Made Simple: Transepidermal Water Loss Measurement as a Research Tool. *The Journal of investigative dermatology*. 2018;138(11):2295-2300.e1. [doi:10.1016/j.jid.2018.09.001](https://doi.org/10.1016/j.jid.2018.09.001)
2. Jakaša I, Koster E, Calkoen F, et al. Skin barrier function in healthy subjects and patients with atopic dermatitis in relation to filaggrin loss-of-function mutations. *Journal of investigative dermatology*. 2011;131(2):540-542. [doi:10.1038/jid.2010.307](https://doi.org/10.1038/jid.2010.307)
3. Zhang M, Li B, Wu S, et al. A Genome-Wide Association Study of Basal Transepidermal Water Loss Finds that Variants at 9q34.3 Are Associated with Skin Barrier Function. *The Journal of investigative dermatology*. 2017;137(4):979-982. [doi:10.1016/j.jid.2016.11.030](https://doi.org/10.1016/j.jid.2016.11.030)
4. Park NJ, Bong SK, Lee S, et al. Compound K improves skin barrier function by increasing SPINK5 expression. *Journal of ginseng research*. 2020;44(6):799-807. [doi:10.1016/j.jgr.2019.11.006](https://doi.org/10.1016/j.jgr.2019.11.006)
5. Oh MS, Hong JY, Kim MN, et al. Activated Leukocyte Cell Adhesion Molecule Modulates Th2 Immune Response in Atopic Dermatitis. *Allergy, asthma & immunology research*. 2019;11(5):677-690. [doi:10.4168/aair.2019.11.5.677](https://doi.org/10.4168/aair.2019.11.5.677)
6. Taïeb A. Skin barrier in the neonate. *Pediatric dermatology*. 2018;35 Suppl 1:s5-s9. [doi:10.1111/pde.13482](https://doi.org/10.1111/pde.13482)
7. Flohr C, England K, Radulovic S, et al. Filaggrin loss-of-function mutations are associated with early-onset eczema, eczema severity and transepidermal water loss at 3 months of age. *The British journal of dermatology*. 2010;163(6):1333-1336. [doi:10.1111/j.1365-2133.2010.10068.x](https://doi.org/10.1111/j.1365-2133.2010.10068.x)