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Evaluation of Fat Mass and Obesity Associated (FTO) Gene Polymorphism in Male Androgenetic Aloplecia Patients

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Abstract
Background: Androgenetic alopecia (AGA), commonly referred to as male pattern baldness, is a prevalent condition affecting up to 50% of men by age 50. The pathogenesis of AGA involves a complex interplay of genetic and environmental factors, with a key role played by androgens such as dihydrotestosterone (DHT). Recent studies have suggested that the Fat Mass and Obesity Associated (FTO) gene, known for its role in adiposity and metabolic syndrome, may also be implicated in AGA. Understanding the potential link between FTO gene polymorphisms and AGA could provide new insights into the genetic and metabolic factors contributing to male pattern baldness. **Objective:** This narrative review aims to evaluate the current evidence on the association between FTO gene polymorphisms and androgenetic alopecia in male patients, exploring how FTO variants might influence hair follicle health through pathways involving androgen levels, insulin resistance, and adipose tissue distribution. **Methods:** A comprehensive literature review was conducted, analyzing studies that investigate the relationship between FTO gene polymorphisms, particularly the rs9939609 variant, and AGA. The review also examined the role of metabolic syndrome components, such as obesity and insulin resistance, in the pathogenesis of AGA, and how these factors might interact with FTO gene variants. **Conclusion:** The FTO gene polymorphisms, particularly the rs9939609 variant, may contribute to the development and severity of AGA by influencing metabolic processes and androgen levels. The findings highlight the need for further research to elucidate the exact mechanisms through which FTO variants affect hair follicle biology and to explore potential therapeutic targets for AGA.

Keywords: Androgenetic alopecia, FTO gene polymorphism, metabolic syndrome, rs9939609, hair follicle biology.

Introduction

Androgenetic alopecia (AGA), commonly known as male pattern baldness, is the most prevalent form of hair loss in men, affecting up to 50% of men by the age of 50. AGA is characterized by a progressive thinning of the hair on the scalp, primarily affecting the frontal hairline, vertex, and mid-scalp regions [1]. The condition is largely hereditary, with a strong genetic predisposition, and is influenced by androgens, specifically dihydrotestosterone (DHT). DHT binds to androgen receptors in hair follicles, leading to the miniaturization of hair follicles and the shortening of the anagen (growth) phase of the hair cycle, which results in finer and shorter hair [2].

The pathogenesis of AGA is complex and involves both genetic and environmental factors. While the androgen receptor gene (AR) on the X chromosome has been identified as a major genetic contributor, other genes also play a role in AGA. Environmental factors such as diet, stress, and lifestyle may exacerbate or modulate the expression of the genetic predisposition to AGA. Despite extensive research, the precise genetic mechanisms underlying AGA remain only partially understood, and ongoing studies continue to explore the potential involvement of various genetic loci in the development of this condition [3].

The Fat Mass and Obesity Associated (FTO) gene, located on chromosome 16q12.2, was first identified in genome-wide association studies (GWAS) as a significant contributor to obesity and body mass index (BMI) in various populations. The FTO gene encodes an enzyme that is involved in the regulation of energy homeostasis, appetite control, and adipogenesis. Variants in the FTO gene, particularly single nucleotide polymorphisms (SNPs), have been strongly associated with an increased risk of obesity, leading to its characterization as an "obesity gene" [4].

FTO exerts its effects on body weight through its influence on the hypothalamus, the region of the brain that regulates hunger and satiety. Individuals carrying risk alleles in the FTO gene are more likely to have higher levels of fat mass and a predisposition to obesity,

potentially through increased food intake and reduced energy expenditure. Furthermore, FTO gene polymorphisms have been linked to metabolic disorders such as type 2 diabetes and cardiovascular disease, suggesting a broader impact on metabolic health [5].

Recent studies have begun to explore the potential link between FTO gene polymorphisms and androgenetic alopecia. While the FTO gene is primarily known for its role in adiposity and metabolic processes, there is growing interest in understanding how its variants might influence hair growth and the development of AGA. The rationale behind this exploration lies in the interconnectedness of metabolic pathways and hormonal regulation, both of which are implicated in AGA [6].

One hypothesis is that FTO gene polymorphisms could affect AGA by modulating androgen levels, insulin resistance, or adipose tissue distribution, all of which can influence hair follicle health. Additionally, as obesity and metabolic syndrome have been associated with an increased risk of AGA, it is plausible that FTO variants could contribute to this association. Although the exact mechanisms remain to be elucidated, the potential role of the FTO gene in AGA represents a novel area of research that could provide new insights into the genetic and metabolic underpinnings of male pattern baldness.

The aim of this narrative review is to evaluate the current evidence on the association between FTO gene polymorphisms and androgenetic alopecia in male patients. By synthesizing existing research, this review seeks to clarify the potential role of the FTO gene in the pathogenesis of AGA, identify gaps in the literature, and suggest directions for future research.

❖ **Androgenic Alopecia**

Androgenetic alopecia (AGA), also known as male pattern hair loss (MPHL) in men and female pattern hair loss (FPHL) in women, is the most common form of alopecia globally. It is characterized by the progressive loss of terminal hair follicles after puberty, resulting in visible hair thinning and baldness. AGA involves the gradual miniaturization of hair follicles, which is primarily due to alterations in the hair cycle dynamics. This miniaturization leads to the transformation of terminal hair follicles into vellus-like follicles, causing the hair to become finer and shorter with each cycle [7].

The normal hair cycle consists of three phases: the anagen phase (growth), the catagen phase (regression), and the telogen phase (resting). During AGA, the anagen phase shortens, while the telogen phase prolongs, resulting in a reduction in the length and thickness of the hair. This cycle of progressively shorter anagen phases and prolonged telogen phases leads to visible hair thinning and, eventually, baldness. The process is influenced by genetic and hormonal factors, particularly the conversion of testosterone to dihydrotestosterone (DHT), which plays a key role in the miniaturization of hair follicles [8].

AGA is highly prevalent, affecting 30% to 50% of men by the age of 50. The condition varies significantly across different populations, with Caucasians having the highest prevalence rates. In Caucasian men, the prevalence of AGA increases with age, affecting approximately 30% of men in their 30s, 40% in their 40s, and 50% in their 50s. The condition is believed to be polygenic and multifactorial, involving a combination of genetic predisposition and environmental influences [9].

Several genetic loci have been identified in association with AGA, including the androgen receptor gene on the X chromosome, which has been linked to the condition's hereditary nature. Additionally, AGA has been associated with various metabolic and cardiovascular conditions, including obesity, insulin resistance, and hypertension. These associations suggest a complex interplay between genetic susceptibility, metabolic health, and the development of AGA, making it a subject of ongoing research in the fields of dermatology and endocrinology [10].

The following table provides a concise overview of the various diagnostic tools and methods used to evaluate AGA, helping to differentiate it from other types of hair loss and identifying its underlying causes.

Table 1: Diagnostic Methods for Androgenetic Alopecia (AGA) [11]

Diagnostic Method	Description
History	A thorough history helps to rule out other causes of hair loss, such as telogen effluvium. Typically involves chronic hair loss with thinning over the frontal, parietal, or vertex areas. Other aspects include systemic diseases, medication history, family history, diet, and lifestyle factors like traction, smoking, and UV exposure. In females, hormonal dysfunction is assessed.
General Scalp	The scalp usually appears normal in AGA. Clinical examination aims to identify

and Hair Examination	whether the hair loss is patterned. Factors such as seborrheic dermatitis and photo-damage, which can aggravate AGA, are also evaluated.
Pull Test	A simple method to assess hair loss severity. About 60 hairs are gently pulled, and the number of hairs obtained determines if the test is positive or negative. A negative test indicates normal shedding, while a positive test suggests active shedding, often indicating other diagnoses like telogen effluvium in AGA patients.
Trichoscopy	A non-invasive method for diagnosing and monitoring scalp and hair diseases using a dermoscope. In AGA, it shows hair diameter variability >20%, yellow dots, single-hair follicular units, and peripilar hyperpigmentation. Major and minor trichoscopic criteria help diagnose AGA with high specificity, especially in female patients.
Trichogram and Photo-trichogram	Trichograms differentiate between hair loss types by examining hair roots after plucking. Phototrichogram (PTG) are non-invasive and involve serial close-up photographs of specific areas to assess hair growth rate, density, and shaft thickness. Variants include contrast-enhanced PTG and automated PTG (Trichoscan).
Hair Wash Test	A test to distinguish between AGA and telogen effluvium (TE) by counting telogen hairs after washing the scalp following a five-day period without washing. The method has limitations, including hair breakage and time consumption, particularly in patients with curly hair.
Laboratory Investigations	Recommended in cases of unclear diagnosis, these tests help consider differential diagnoses. Hormone tests are generally of little use for AGA, but other factors like excessive vitamin A supplementation, which may induce hair loss, are checked.
Scalp Biopsy	Not routinely recommended due to its invasive nature. Typically involves taking a biopsy from the center of the most affected areas. Horizontal and transverse sectioning provides an overview of follicle number, density, and morphology. A terminal-to-vellus hair ratio of less than 3:1 is indicative of AGA.

❖ Pathophysiology of Androgenetic Alopecia (AGA)

Overview of Hair Cycle

Hair growth is a continuous process characterized by four distinct phases: anagen (growth), catagen (regression), telogen (rest), and exogen (shedding). Each hair follicle cycles independently, undergoing ten to thirty cycles in a lifetime. The human scalp typically contains around 100,000 hair follicles, and normal shedding involves the loss of 100 to 150 telogen hairs per day. The balance between these phases maintains a relatively stable and healthy hair density. In AGA, however, this balance is disrupted, leading to progressive hair thinning and follicular miniaturization [12].

Follicular Miniaturization in AGA

AGA is primarily marked by follicular miniaturization, which involves the progressive reduction in hair follicle size. This process is hypothesized to begin during the early catagen stage when hair follicles are more vulnerable to external forces. The bald areas in AGA patients exhibit lower proliferation rates, increased DNA damage, and higher rates of apoptosis, particularly during the catagen regression phase. Apoptosis, while a natural part of the hair cycle, may contribute to the miniaturization of hair follicles in AGA, leading to the characteristic thinning and hair loss [13].

Genetic Factors in AGA Pathogenesis

AGA follows a polygenic inheritance model, which accounts for its high prevalence and the wide variety of phenotypic expressions. Genome-wide association studies (GWAS) have identified numerous genetic loci associated with AGA, including the androgen receptor (AR) gene on the X chromosome and the ectodysplasin A2 receptor (EDAR2) gene. These genes are involved in androgen metabolism and hair follicle regulation. Interestingly, some susceptibility loci, such as those on chromosome 20p11 and chromosome 7p21.1, do not directly involve the androgen pathway but still significantly contribute to AGA's genetic predisposition [3].

Role of Androgens and Androgen Receptor in AGA

Androgens, particularly testosterone and its more potent form dihydrotestosterone (DHT), play a critical role in AGA pathogenesis. Androgens are synthesized and metabolized in the skin and hair follicles through various enzymes, including steroid 5α-reductase (SRD5A), which converts testosterone to DHT. The presence of androgen receptors (ARs) in hair follicles, particularly in the dermal papilla cells, mediates the effects of androgens. These interactions result in hair

follicle miniaturization and the early onset of the catagen phase, leading to the progressive hair thinning seen in AGA [14].

Dermal Papilla Cells (DPC) and AGA Pathogenesis

The dermal papilla cells (DPC) at the base of the hair follicle are essential in regulating hair growth. DPCs mediate the effects of androgens on hair follicles by releasing growth factors and signaling molecules that influence the surrounding epithelial cells. In AGA, DPCs from balding areas exhibit higher levels of androgen receptors and altered growth factor production, leading to hair follicle miniaturization and the inhibition of hair growth. The interplay between DPCs and epithelial cells, mediated by growth factors like TGF-β1, plays a crucial role in the progression of AGA [15].

Growth Factors and Other Hormonal Influences in AGA

Several growth factors and hormones influence the pathogenesis of AGA. Insulin-like growth factor 1 (IGF-1) is crucial in regulating the hair cycle, while estrogen receptor alpha (ESR1) in the dermal papilla influences androgen signaling in hair follicles. Additionally, melatonin, parathyroid hormone (PTH), prolactin (PRL), corticotropin-releasing hormone (CRH), and melanocortins have all been implicated in the complex hormonal regulation of hair growth and miniaturization in AGA. These factors may act synergistically or antagonistically with androgens, further complicating the molecular mechanisms underlying AGA [16].

- **FTO Gene Polymorphism & Metabolic Syndrome**

The Fat Mass and Obesity Associated (FTO) Gene

The FTO gene, or Fat Mass and Obesity Associated gene, is a genetic variant linked to an increased risk of obesity and related metabolic conditions. This gene plays a crucial role in the complex interplay of genetics and environmental factors that contribute to metabolic syndrome. Research has shown that individuals with specific variations in the FTO gene have a higher incidence of obesity, which is often accompanied by metabolic syndrome, a cluster of conditions that increase the risk of heart disease, stroke, and diabetes [17].

Location and Structure of the FTO Gene

The FTO gene is located on the long arm of chromosome 16, specifically in the 16q12.2 region. This gene spans over 400 kilobases and consists of 9 exons and 8 introns. The FTO protein, produced by this gene, has a double-stranded beta-helix fold and a structure that includes ferrous iron (Fe(II)) and alpha-ketoglutarate-dependent activity at the N terminus. The stability of the N-terminal domain (NTD) of the FTO protein is essential for its function, which primarily involves the demethylation of RNA [18].

The FTO Protein and Its Mechanism of Action

The FTO protein is an alpha-ketoglutarate-dependent oxygenase, distinguished from others in its family by the presence of a unique loop containing the K216 residue (lysine). This protein selectively demethylates specific RNA substrates, influencing gene expression by modifying RNA transcripts during transcription. FTO's regulatory role extends to various signaling pathways, such as the mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) pathways, which are crucial for energy homeostasis and metabolic processes [18].

Functions of the FTO Protein

The FTO protein is found in several tissues, including adipose tissue, the pancreas, liver, and salivary glands. In adipose tissue, it regulates fat mass and adipogenesis, while in the pancreas, it is critical for beta-cell function and insulin secretion, potentially linking FTO activity to glucose intolerance. Multiple genome-wide association studies (GWAS) have identified genetic variants in the FTO gene that are strongly associated with obesity and high body mass index (BMI). These findings suggest that the FTO gene plays a significant role in controlling food intake, body fat content, and overall energy balance [19].

FTO Gene Polymorphism

Genetic polymorphism refers to the variation in DNA sequences that occur in a population at a frequency of 1% or higher. In the context of the FTO gene, polymorphisms, particularly single nucleotide polymorphisms (SNPs), have been identified as key factors associated with obesity risk. One notable SNP, the rs9939609 (T>A) variant, is located in the first intron of the FTO gene and has been linked to a 20-30% increased risk of obesity. This variant is also associated with metabolic abnormalities, such as altered lipid profiles, including lower levels of high-density lipoprotein cholesterol (HDL-C) and higher levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) [20, 21].

Interaction Between FTO Polymorphism and Adjacent Genes

The FTO gene is situated among several neighbouring genes, including RBL2, AKTIP, and RPGRIP1L upstream, and IRX3, IRX5, and IRX6 downstream. These adjacent genes are implicated in the development of metabolic

syndrome (MetS) and related metabolic changes. The interaction between FTO polymorphisms and these neighbouring genes may further influence the risk of MetS, suggesting that the genetic effects of FTO extend beyond obesity to a broader range of metabolic dysfunctions. This complex genetic interplay highlights the multifaceted role of the FTO gene in metabolic health and disease [22].

❖ **The Metabolic Syndrome**

Definition and Components of Metabolic Syndrome

Metabolic syndrome is a cluster of conditions that increase the risk of heart disease, stroke, and type 2 diabetes (T2D). The World Health Organization (WHO) in 1999 defined metabolic syndrome primarily based on the presence of insulin resistance (IR), which could manifest as impaired glucose tolerance (IGT), high plasma insulin levels, or T2D. A positive diagnosis also requires the presence of at least two other risk factors: central obesity (waist-to-hip ratio >0.9 for men or >0.85 for women, or a body mass index [BMI] >30), hypertension (systolic blood pressure >140 mmHg and/or diastolic pressure >90 mmHg), Dyslipidemia (triglycerides ≥1.7 mM and/or HDL <0.9 mM for men or <1.0 mM for women), or microalbuminuria. The European Group for the Study of Insulin Resistance (EGIR) later refined this definition by emphasizing central obesity and omitting microalbuminuria [23].

The Relation Between Metabolic Syndrome and Androgenetic Alopecia Pathogenesis

Androgenetic alopecia (AGA), traditionally viewed as a cosmetic issue, has been increasingly associated with metabolic abnormalities. AGA is linked to several metabolic disorders, including cardiovascular disease, hypertension, and obesity, indicating a broader systemic involvement. The relationship between AGA and metabolic syndrome suggests that adipokines, which are cytokines produced by adipose tissue, may play a role in the pathogenesis of AGA. However, the precise mechanisms and the role of adipokines in AGA remain underexplored [24].

Insulin Resistance and Its Impact on AGA

Insulin resistance (IR) is a key feature of metabolic syndrome and is characterized by reduced sensitivity of cells to insulin, leading to impaired glucose uptake and elevated blood insulin levels. IR contributes to obesity, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), and cardiovascular diseases. Hyperinsulinemia, which results from IR, can decrease the levels of sex hormone-binding globulin (SHBG), leading to an increase in free androgens. These androgens can exacerbate AGA by promoting follicular miniaturization and hair loss. Additionally, leptin, a hormone linked to IR and obesity, may also play a role in AGA by influencing hair follicle growth and inflammation [25].

The Role of Leptin and Adiponectin in AGA

Leptin, encoded by the LEP gene on chromosome 7, is primarily produced by white adipose tissue and has been implicated in hair follicle growth regulation. Leptin receptors (LEPR) are found in the dermal papilla and outer epithelial layer of hair follicles, suggesting a direct impact on hair growth. Elevated leptin levels, common in obesity and IR, are associated with increased inflammation and may correlate with the severity of AGA. On the other hand, adiponectin, another adipose-derived hormone, has insulin-sensitizing and anti-inflammatory properties. The adiponectin/leptin (Adpn/Lep) ratio is considered a better predictor of metabolic syndrome risk than adiponectin or leptin alone, and lower Adpn/Lep ratios are observed in patients with AGA, correlating with disease severity [26].

The Proposed Mechanism of Scalp Adipose Metabolism in AGA

A proposed mechanism linking scalp adipose tissue metabolism to AGA pathogenesis involves the downregulation of peroxisome proliferator-activated receptor gamma (PPARγ) signaling, leading to reduced adipogenesis and thinning of the scalp adipose layer. This reduction creates a gap between miniaturized hair follicles and the adipose layer, diminishing the influence of adipocyte-derived growth factors such as hepatocyte growth factor (HGF) and platelet-derived growth factor (PDGFA) on hair follicle stem cells. This unfavourable environment hampers hair growth and regeneration, contributing to the progression of AGA [27].

The Relation Between FTO rs9939609 Polymorphism and Metabolic Syndrome

Among the various polymorphisms of the FTO gene, the rs9939609 variant has been extensively studied for its association with metabolic syndrome and its components. This variant, located within intron 1 of FTO, is linked to increased obesity risk, abnormal lipid profiles, and insulin resistance. The rs9939609 polymorphism may affect metabolic syndrome susceptibility by altering the expression and function of the FTO gene, disrupting RNA methylation, and influencing appetite regulation. Furthermore, the rs9939609 variant has been associated with hypertension, dyslipidemia, and fasting blood sugar levels,

making it a critical factor in understanding the genetic basis of metabolic syndrome [28].

❖ **Future Directions and Clinical Implications**

The exploration of FTO gene polymorphisms in the context of androgenetic alopecia (AGA) opens up several avenues for future research. Further studies are needed to elucidate the precise molecular mechanisms by which FTO variants influence hair follicle biology and contribute to AGA. This research could involve larger, more diverse cohorts to confirm the association between FTO polymorphisms and AGA across different populations. Additionally, investigating the interaction between FTO variants and other genetic loci implicated in AGA, as well as their relationship with metabolic syndrome components, could provide a more comprehensive understanding of the condition. Clinically, these findings could pave the way for personalized treatment strategies targeting metabolic pathways in AGA patients. For instance, therapies that modulate FTO activity or address insulin resistance could be developed to mitigate the progression of hair loss in individuals with specific genetic predispositions.

Conclusions

In conclusion, the FTO gene, widely recognized for its role in obesity and metabolic syndrome, may also play a significant role in the pathogenesis of androgenetic alopecia. The evidence suggests that FTO polymorphisms, particularly the rs9939609 variant, could contribute to the development and severity of AGA by influencing androgen levels, adipose tissue distribution, and metabolic processes. While the exact mechanisms remain to be fully understood, the potential link between FTO gene variants and AGA highlights the importance of considering metabolic factors in the management of hair loss. Continued research in this area is essential to fully unravel the genetic and metabolic underpinnings of AGA, with the ultimate goal of developing more effective, personalized therapeutic approaches.

References

[1] M.S. Nestor, G. Ablon, A. Gade, H. Han, D.L. Fischer. Treatment options for androgenetic alopecia: Efficacy, side effects, compliance, financial considerations, and ethics. J Cosmet Dermatol;vol, 20:pp, 3759-81. 2021

[2] R. Cuevas-Diaz Duran, E. Martinez-Ledesma, M. Garcia-Garcia, D. Bajo Gauzin, A. Sarro-Ramírez, C. Gonzalez-Carrillo, et al. The Biology and Genomics of Human Hair Follicles: A Focus on Androgenetic Alopecia. International Journal of Molecular Sciences;vol, 25:pp, 2542. 2024

[3] R. Cuevas-Diaz Duran, E. Martinez-Ledesma, M. Garcia-Garcia, D. Bajo Gauzin, A. Sarro-Ramírez, C. Gonzalez-Carrillo, et al. The Biology and Genomics of Human Hair Follicles: A Focus on Androgenetic Alopecia. Int J Mol Sci;vol, 25. 2024

[4] C. Huang, W. Chen, X. Wang. Studies on the fat mass and obesity-associated (FTO) gene and its impact on obesity-associated diseases. Genes Dis;vol, 10:pp, 2351-65. 2023

[5] K.A. Fawcett, I. Barroso. The genetics of obesity: FTO leads the way. Trends Genet;vol, 26:pp, 266-74. 2010

[6] P. Czajkowski, E. Adamska-Patruno, W. Bauer, J. Fiedorczuk, U. Krasowska, M. Moroz, et al. The Impact of FTO Genetic Variants on Obesity and Its Metabolic Consequences is Dependent on Daily Macronutrient Intake. Nutrients;vol, 12. 2020

[7] S. Devjani, O. Ezemma, K.J. Kelley, E. Stratton, M. Senna. Androgenetic Alopecia: Therapy Update. Drugs;vol, 83:pp, 701-15. 2023

[8] D. Thor, A. Pagani, J. Bukowiecki, K.S. Houschyar, S.T. Kølle, S.P. Wyles, et al. A Novel Hair Restoration Technology Counteracts Androgenic Hair Loss and Promotes Hair Growth in A Blinded Clinical Trial. J Clin Med;vol, 12. 2023

[9] O.A. Al Najjar, M.A. Alkhars, S.F. Al Molhim, M.S. AlAjmi, A.A. Alhafith, M.A. Al Najjar, et al. The Impact of Androgenic Alopecia on the Quality of Life of Male Individuals: A Cross-Sectional Study. Cureus;vol, 15: pp, e47760. 2023

[10] I.P. Sadasivam, R. Sambandam, D. Kaliyaperumal, J.E. Dileep. Androgenetic Alopecia in Men: An Update On Genetics. Indian J Dermatol;vol, 69:pp, 282. 2024

[11] Y. Wang, W. Ding, M. Yao, Y. Li, M. Wang, L. Wang, et al. Diagnostic and grading criteria for androgenetic alopecia using dermoscopy. Skin Res Technol;vol, 30:pp, e13649. 2024

[12] N. Natarelli, N. Gahoonia, R.K. Sivamani. Integrative and Mechanistic Approach to the Hair Growth Cycle and Hair Loss. J Clin Med;vol, 12.pp, 2023

[13] R. Abdin, Y. Zhang, J.J. Jimenez. Treatment of Androgenetic Alopecia Using PRP to Target Dysregulated

Mechanisms and Pathways. Front Med (Lausanne);vol, 9:pp, 843127. 2022

[14] J.J. Lai, P. Chang, K.P. Lai, L. Chen, C. Chang. The role of androgen and androgen receptor in skin-related disorders. Arch Dermatol Res;vol, 304:pp, 499-510. 2012

[15] Y. Zhang, J. Huang, D. Fu, Z. Liu, H. Wang, J. Wang, et al. Transcriptome Analysis Reveals an Inhibitory Effect of Dihydrotestosterone-Treated 2D- and 3D-Cultured Dermal Papilla Cells on Hair Follicle Growth. Front Cell Dev Biol;vol, 9:pp, 724310. 2021

[16] F. Rinaldi, A. Trink, G. Mondadori, G. Giuliani, D. Pinto. The Menopausal Transition: Is the Hair Follicle "Going through Menopause"? Biomedicines;vol, 11. 2023

[17] M.E. Hess, J.C. Brüning. The fat mass and obesity-associated (FTO) gene: Obesity and beyond? Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease;vol, 1842:pp. 2039-47. 2014

[18] A.M. Popović, A. Huđek Turković, K. Žuna, V. Bačun-Družina, I. Rubelj, M. Matovinović. FTO Gene Polymorphisms at the Crossroads of Metabolic Pathways of Obesity and Epigenetic Influences. Food Technol Biotechnol;vol, 61:pp, 14-26. 2023

[19] K. Ferenc, T. Pilžys, D. Garbicz, M. Marcinkowski, O. Skorobogatov, M. Dylewska, et al. Intracellular and tissue specific expression of FTO protein in pig: changes with age, energy intake and metabolic status. Sci Rep;vol,10:pp, 13029. 2020

[20] S. Xiao, X. Zeng, L. Quan, J. Zhu. Correlation between polymorphism of FTO gene and type 2 diabetes mellitus in Uygur people from northwest China. Int J Clin Exp Med;vol, 8:pp,9744-50. 2015

[21] A. Chama-Avilés, K.L. Flores-Viveros, J.A. Cabrera-Ayala, A. Aguilar-Galarza, W. García-Muñoz, L. Haddad-Talancón, et al. Identification and Association of Single Nucleotide Polymorphisms of the FTO Gene with Indicators of Overweight and Obesity in a Young Mexican Population. Genes (Basel);vol, 14. 2023

[22] Y. Song, H. Wade, B. Zhang, W. Xu, R. Wu, S. Li, et al. Polymorphisms of Fat Mass and Obesity-Associated Gene in the Pathogenesis of Child and Adolescent Metabolic Syndrome. Nutrients;vol, 15. 2023

[23] C.K. Roberts, A.L. Hevener, R.J. Barnard. Metabolic syndrome and insulin resistance: underlying causes and modification by exercise training. Compr Physiol;vol, 3:pp.1-58. 2013

[24] L.P. Liu, M.A. Wariboko, X. Hu, Z.H. Wang, Q. Wu, Y.M. Li. Factors associated with early-onset androgenetic alopecia: A scoping review. PLoS One;vol, 19:pp, e0299212. 2024

[25] X. Zhao, X. An, C. Yang, W. Sun, H. Ji, F. Lian. The crucial role and mechanism of insulin resistance in metabolic disease. Front Endocrinol (Lausanne);14:1149239. 2023

[26] K. Dopytalska, A. Baranowska-Bik, M. Roszkiewicz, W. Bik, I. Walecka. The role of leptin in selected skin diseases. Lipids in Health and Disease; vol,19: pp,215. 2020

[27] C.J.G. Cruz, Y.K. Hong, W.J.F. Aala, R.Y. Tsai, P.L. Chung, Y.S. Tsai, et al. Adipose transcriptome in the scalp of androgenetic alopecia. Front Med (Lausanne);vol,10:pp,1195656. 2023

[28] R. Molina-Luque, N. Ulloa, M. Romero-Saldaña, M. Zilic, A. Gleisner, F. Lanuza, et al. Association between the FTO SNP rs9939609 and Metabolic Syndrome in Chilean Children. Nutrients;vol,13. 2021