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Prospects of integrated multi-omics-driven biomarkers for efficient hair loss therapy from systems biology perspective

Dilan Nisa Yilmaz [a], Ozge Onluturk Aydogan [a], Medi Kori [a], Busra Aydin [a], Md. Rezanur Rahman [b], Mohammad Ali Moni [c], Beste Turanli [a,*]

[a] Department of Bioengineering, Faculty of Engineering, Marmara University, Turkey
[b] Queensland Brain Institute, The University of Queensland, Brisbane, QLD 4072, Australia
[c] School of Health and Rehabilitation Sciences, Faculty of Health and Behavioral Sciences, The University of Queensland St Lucia, Australia

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ABSTRACT

The term "alopecia" is used for abnormal hair loss and it is a chronic dermatological condition observed in both genders and all races. Androgenetic alopecia (AGA) or male pattern baldness is the most common type of alopecia; however, it may be observed in females. Alopecia areata (AA) is the second most common non-scarring alopecia or hair loss around the world. Beyond the fact that alopecia is a disease itself, sometimes it might be one of the major side effects of many drugs including chemotherapeutics. Since healthy hair has been a symbol of well-being, youth, and vitality for centuries, the treatment of alopecia has essential importance to increasing life quality of the individuals that have faced hair loss. Regarding the progressively generated high-throughput data at various omics levels, systems biology has gained importance to better understand biologic processes by utilizing high-throughput data from multiple sources to develop models of biologic processes In this review, we overviewed AGA and AA via systems biology with the aid of omics technologies point of view to highlight not only the molecular mechanisms of the hair loss phenomenon but also potential preventive and therapeutic avenues. We discussed the findings in light of the multi-omics data integration that converges the future of uncovering personalized therapeutic options targeting hair loss.

1. Introduction

Hair has an essential effect on human appearance. Healthy hair has been a symbol of well-being, youth, and vitality for centuries. It also offers various functions, such as skin protection, sexual and social communication, producing sebum, apocrine sweat, pheromones, and stem cell resources (Buffoli et al., 2014). Thus, even though complete or partial hair loss for any reason is neither fatal nor painful, it may result in serious psychological consequences for the patient. While hair loss can be caused by numerous different reasons, the exact etiology behind the disease is hard to name and is generally unknown. The major causes of hair loss can be listed as androgen-related problems, infections, stress, and genetic disposal (Lin et al., 2016).

Humans have approximately 5 million hair follicles covering the whole body at birth. About 100,000 of these hair follicles places on humans' scalps, and no additional regeneration occurs after birth. Instead, existing hair follicles undergo the self-driven, continuous cyclic process to renew and grow (Welle and Wiener, 2016). The hair growth cycle has three main periods; anagen (growth) phase, catagen (transitional) phase, and telogen (resting) phase. The most active phase of hair growth is the anagen phase. It may last 2 to 3 years, but it can prolong to 6 years in some cases. Moreover, nearly 84 % of all scalp hairs are in the anagen phase. The catagen phase starts at the end of the anagen and, regardless of the hair type and location, generally lasts 1 to 3 weeks. The duration between the transitional and the onset of the new anagen phase is called the telogen phase. The duration may take few weeks to months according to the place of the hair on the human body. Approximately 10 % of all hair is in the telogen phase at any given moment. In a healthy person, the anagen-to-telogen ratio is 6 to 8:1 (Park et al., 2018; Messenger et al., 2010).

The term "alopecia" is used for abnormal hair loss and it is a chronic dermatological condition observed in both genders and all races. It is

Abbreviations: AGA, Androgenetic alopecia; AA, Alopecia areata; GWAS, Genome-wide association studies; DPCs, Mesenchyme-derived dermal papilla cells; FDA, Food and Drug Administration; BPH, Benign prostatic hyperplasia; SADBE, Squaric acid dibutyl ester; DNCB, Dinitrochlorobenzene; DPCP, Diphenyl-cyclopropenone.

* Corresponding author at: Dept. of Bioengineering, Faculty of Engineering, Marmara University, Goztepe, 34722 Istanbul, Turkey.
E-mail address: beste.turanli@marmara.edu.tr (B. Turanli).

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characterized by complete or partial hair loss, and it may affect the scalp or sometimes the body as well (Hunt and McHale, 2005). It can be associated with a wide range of reasons, including genetic heredity, autoimmune problems, infections, and environmental factors. It may occur temporarily or permanently; therefore, the treatments may save the hairy part left, but the hair will generally not regenerate. In addition to hereditary and hormonal problems, lifestyle alterations, such as immoderate intake of tobacco and alcohol, diet, improper care and even escalating stress levels are considered as strong triggers for alopecia. Alopecia can be divided into two main categories: with and without scarring. The most common form of non-scarring alopecia is androgenetic alopecia (AGA) and alopecia areata (AA).

1.1. Androgenetic alopecia

AGA or male pattern baldness is the most common type of alopecia in males; however, it may be observed in females. The incidence of AGA comprises approximately 50 % of the world's adult population (Whiting, 2001); 80 % of European men by the age of 80 are affected by baldness, while women's rate is nearly 30 % over the age of 30 (Norwood, 2001). Although individuals of all ethnic groups may be subject to AGA the incidence varies by race; Caucasian men tend to become bald more than men of African, Indian and Asian descent. (Stough et al., 2005). In AGA patients, the anagen duration decreases to months from years while the telogen phase remains constant, and this aberration causes the different anagen-to-telogen ratios as 0.1 to 3:1. This shortening eventually causes hair shedding and, thus, baldness (Kaufman, 2002). Therefore, diagnosis of AGA can be made by observing progressive miniaturization of the hair follicle, causing the differentiation of terminal hairs (pigmented and thick) to the vellus hair (short, fine, unpigmented) (Trueb, 2002) and alterations of the hair cycle duration (Otberg et al., 2007).

1.2. Alopecia areata

AA is the second most common non-scarring alopecia or hair loss around the world. Even though the exact prevalence is unknown, it is assumed that nearly 2 % of the world population are affected by AA during their lifetime (Gilhar et al., 2012). The pattern of the disease in the patient's body is very distinguishable. If there is small round or patchy bald lesions exist, the type of alopecia is named patchy alopecia areata and it generally occurs on the scalp or in the region of the beard. Total hair loss on the patient is called alopecia totalis and total loss of all body hair of the patient is classified as alopecia universalis. It is classified as an autoimmune disease caused by T cells attacking the HF and creating damage. Since the prevalence is increased between the family members, heredity is also taken into account as a risk factor (Pratt et al., 2017; Santos et al., 2015). Other forms of alopecia can be listed as chemotherapy-induced alopecia (anagen effluvium), cicatricial alopecia (scarring alopecia), and telogen effluvium. Except for the chemotherapy-induced alopecia, diagnosis of the other type of alopecia can take a long time since they are dependent on many different factors and the knowledge of the pathogenesis of the diseases is limited. Despite the exact cause is unclear, the genetic factors have been associated to some cases. Furthermore, the elevation of incomes in aesthetics field drive the demand of market and provided the development of new products for the treatment of alopecia. The last report on the global market size of alopecia denoted as USD 2.6 billion in 2019 while expecting increment for upcoming years. Particularly, increasing prevalence of AGA and AA is the key factor leading the market expansion all over the world (Alopecia market size, share, trends | Global Industry Report, 2027A).

Although there are great efforts to uncover novel and efficient hair loss therapy from both academical and industrial partners for decades, there is no reference that summarize omics-level signatures and current drug repositioning efforts for alopecia until now. Therefore, we aim to provide an overview of the recent omics-level biomarkers and existing or repurposed drugs to improve or personalize the current therapy options for AGA and AA which is the most common two types alopecia in the future (Fig. 1).

2. Different omics level signatures for alopecia

Although there are some drugs or compounds for the treatment of alopecia types and some cosmetic solutions to improve the visual appeal, there is no sure cure for it. Nearly all types of alopecia are based on multifactorial reasons and therefore, their solutions do not depend on one characteristic. As the systems biology approach can provide a holistic view to the understanding of the mechanism of different types of alopecia and thus, lead to the discovery of biomarkers as a target for drug developments, it has a great potential for the treatment of alopecia types.

The complexity of the human body is still one of the most studied challenges in life science research. With the help of the omics sciences, this complexity can be evaluated part by part and resolved by a layer-based system. In our case, omics data helps to visualize the treatment modalities by understanding the mechanism of the alopecia types from

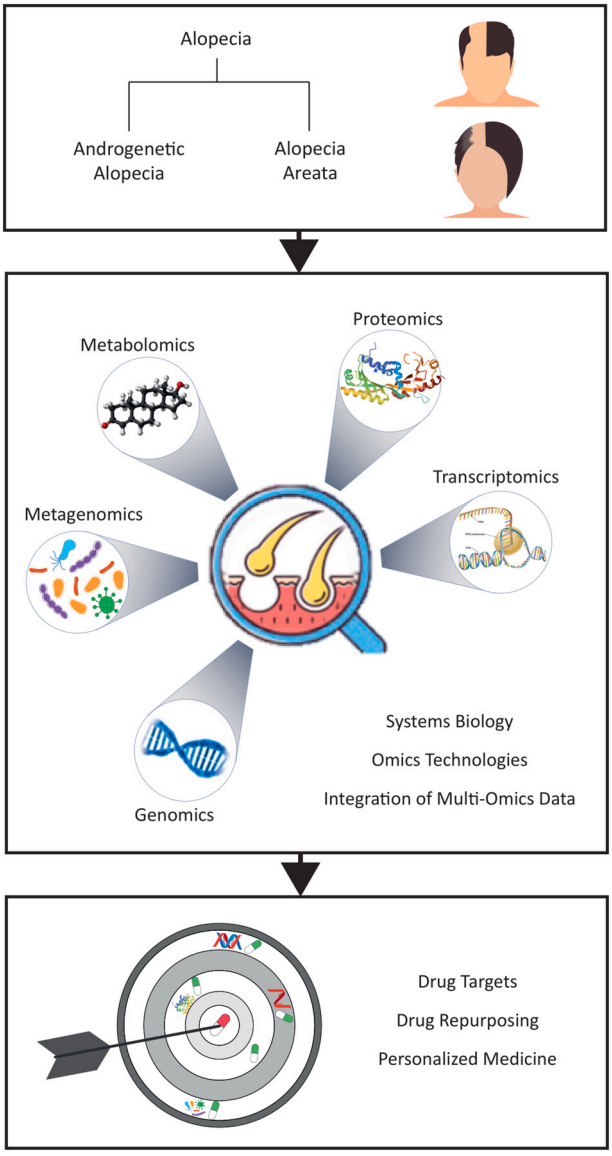

Fig. 1. The future of personalized alopecia treatment based on omics data integration.

the mRNA level to the microscopic level. In this way, we will have a comprehensive perspective for the estimation of future drug therapies supported by the omics data.

2.1. Genomic signatures of androgenetic alopecia

The researchers have been investigating the genetic reasons behind the AGA since Aristotle. Initial studies that were conducted on the genetic factors of AGA had focused on the sex hormone androgen since most of the cases have been seen on men and also, eunuchs which are castrated pre-pubertally do not develop AGA (Hamilton, 1942; Hamilton, 1951; Randall, 1994). Firstly, it was discovered that men with AGA have a higher amount of testosterone and 5α-dihydrotestosterone. Later on, the effects of type 2 5α-reductase on testosterone were understood, and thus, the genetic reasons behind the AGA were somewhat revealed (Randall, 2010; Kaufman et al., 1998).

One of the first AGA markers that discovered as a part of genome-wide association studies (GWAS) are two neighboring genes; Androgen Receptor (*AR*)/ectodysplasin A2 receptor (*EDA2R*) which is located in X chromosome (Hillmer et al., 2005; Pirastu et al., 2017; Richards et al., 2008). Although the involvement of the *AR/EDA2R* genes has undisputly effect in AGA, numbers of the loci and effect size create suspicion towards results. However, fine mappings studies by Brockschmidt et al. has revealed that the strongest association of AGA is related with the rs12558842 locus of X chromosome located in the upstream region of *AR* and *EDA2R* (Brockschmidt et al., 2010). After identifying the first marker, it takes a number of years to find additional loci for the AGA. The genetic complexity of the AGA was enlightened by further studies which revealed 11 major loci in total for understanding genetic susceptibility of the disease. Unlike the Xq12 locus, remaining regions are located in autosomal chromosomes. This can be considered as the explanation for the myth of the male AGA inherited from the maternal site (Heilmann-Heimbach et al., 2016). The strongest autosomal locus is the 20p11 discovered by the independent studies (Richards et al., 2008; Hillmer et al., 2008). In another GWAS study, genomic regions associated with AGA were detected. Interestingly, chromosome 17q21.31 associated with Parkinson's disease was also shown to be a susceptibility locus for the early onset of AGA (Li et al., 2012).

2.2. Genomic signatures of alopecia areata

Genome-wide association studies have been carried out to discover the genetic basis of AA. In the first GWAS study, more than 100 SNPs in eight different genomic regions was discovered. Most of these regions are involved in the immune functions and inflammatory mediation as well as the hair follicle cycle (Petukhova et al., 2010). The follow up study found out the genes that are encoded natural killer cell receptor D (NKG2D) and its ligand NKG2DL3 and therefore, the pathogenesis of the AA was enlightened (Jagielska et al., 2012). By the discovery of the two novel gene loci in 2015, 14 major genetic regions of the AA has uncovered (Betz et al., 2015). In another study, researchers conducted a GWAS study and evaluated about 1.2 million SNPs to find genomic loci associated with AA. They found novel associations at AA and also indicated common associations with type 1 diabetes and rheumatoid arthritis (Petukhova and Christiano, 2016).

Therefore, it can be understood that among different types of alopecia, the genetic reasons do not only depend on genomics biomarkers but also different levels of omics data (Table 1).

2.3. Coding and non-coding RNA signatures of androgenetic alopecia

Transcriptome studies on androgenetic alopecia were started by analysis of coding-RNA profiles. For microarray processes and gene characterizations, biopsy samples are generally isolated either from balding (vertex) and non-balding (occipital) parts of the AGA patients or from AGA patients to compare with a healthy control group. These clinical trials and studies have resulted in various potential biomarkers for prognosis and diagnosis of the AGA.

Functional annotations and annotation enrichments of transcriptomic data reveal that on the AGA cohorts, there are highly active immune and inflammatory responses. Moreover, it is understood that some of the important signaling pathways like WnT/β-catenin, transforming growth factor (TGF-β), bone morphogenic protein (BMP), and also, vitamin D synthesize pathway are inhibited by several related genes.

Table 1
Genomic regions and related genes for the alopecia types.

SNPs	Genetic region	Probable gene candidate	Alopecia type	Ref.
rs2497938/ rs12558842	Xq12	AR/EDA2R	AGA	(Hillmer et al., 2005; Brockschmidt et al., 2010)
rs6047844	20p11	PAX1, FOXA1	AGA	(Richards et al., 2008)
rs12565727	1p36	TARDBP	AGA	(Li et al., 2012)
rs9287638	2q37	HDAC4	AGA	(Li et al., 2012)
rs2073963	7q11.22	HDAC9	AGA	(Li et al., 2012)
rs6945541	7q21.1	AUTS2	AGA	(Li et al., 2012)
rs12373124	17q21.31	IMP5	AGA	(Li et al., 2012)
rs10502861	18q21	SETBP1	AGA	(Li et al., 2012)
rs10193725/ rs7349332	2q35	WNT6, WNT10A	AGA	(Heilmann et al., 2013)
rs7648585/ rs4679955	3q25.1	SUCNR1/ MBNL1	AGA	(Heilmann et al., 2013)
rs929626/ rs1081073	5q33.3	EBF1	AGA	(Heilmann et al., 2013)
rs9668810/ rs7975017	12p12.1	SSPN/ITPR2	AGA	(Heilmann et al., 2013)
rs2476601	1p13.2	PTPN22	AA	(Betz et al., 2015)
rs3789129	2q13	ACOXL, BCL2L11 (BIM)	AA	(Betz et al., 2015; Petukhova and Christiano, 2016)
rs231775	2q33.2	CD28, CTLA4, ICOS	AA	(Betz et al., 2015; Petukhova and Christiano, 2016)
rs7682481	4q27	IL21, IL2	AA	(Betz et al., 2015; Petukhova and Christiano, 2016)
rs848	5q31.1	IL13, 1L4	AA	(Betz et al., 2015; Petukhova and Christiano, 2016)
rs9275524	6p21.32	HLA-DQB1	AA	(Betz et al., 2015; Petukhova and Christiano, 2016)
rs12183587	6q25.1	RAET1L, ULBP3	AA	(Betz et al., 2015; Petukhova and Christiano, 2016)
rs10124366	9q31.1	STX17, NR4A3	AA	(Betz et al., 2015; Petukhova and Christiano, 2016)
rs3118470	10p15.1	IL15RA, IL2RA	AA	(Betz et al., 2015; Petukhova and Christiano, 2016)
rs574087	11q13	PRDX5	AA	(Betz et al., 2015; Petukhova and Christiano, 2016)
rs2155219	11q13.5	GARP (LRRC32)	AA	(Betz et al., 2015; Petukhova and Christiano, 2016)
rs2292239	12q13	IKZF4 (Eos), ERBB3	AA	(Betz et al., 2015; Petukhova and Christiano, 2016)
rs653178	12q24.12	SH2B3 (LNK), ATXN2	AA	(Betz et al., 2015; Petukhova and Christiano, 2016)
rs3862469	16p13.13	CIITA, CLEC16A, SOCS1	AA	(Betz et al., 2015)

Wnt/B-catenin pathway has a well-known effect on hair follicle regeneration, development, and morphogenesis. For example, the transition between the resting phase (telogen) to the active phase (anagen) of the hair follicle is carried out by the signals between WnT/β-catenin and BMP pathways. Therefore, any imbalanced situation on these pathways will directly affect hair growth. This makes the WnT/β-catenin signaling pathway a candidate risk factor of AGA. In the transcriptome studies, it is seen that SFRP2 (secreted frizzled-related protein 2) and DKK1 (dickkopf Wnt signaling pathway inhibitor 1) are the well-known inhibitors of the WnT/β-catenin signaling pathway are up-regulated in the HF of the patients of AGA (Heilmann et al., 2013). In another study, the BMP and activin membrane-bound inhibitor (BAMBI) is down-regulated. In the same study, the pro-opiomelanocortin (POMC) which the precursors of αmelanocyte-stimulating hormone (α-MSH) and adrenocorticotropic hormone (ACTH) are down-regulated at the mRNA and also protein level. Those hormones have several roles in hair growth activations and β-catenin stabilization (Premanand and Reena Rajkumari, 2018; Michel et al., 2017; Lu et al., 2016).

Transforming growth factors (TGF-β) are the cytokines that have a role in transition phase (catagen) induction in hair growth. The inhibition of this pathway can cause inhibition of catagen progression or even, initiation. In the study with cocultured DPCs, it has been seen that the TGF-β1 is up-regulated in the AGA cases and causes keratinocyte growth inhibition. Since the androgens can stimulate TGF-β1, the negative effects of it on the AGA cases are not that surprising (Welker et al., 1997; Shin et al., 2013). On the other hand, TGF-β2 is down-regulated with its activator integrin β6 (ITGB6) in AGA cases. These results can explain the delay of the catagen entry in the case of AGA (Michel et al., 2017; Tsuji et al., 2003).

Prostaglandins are the group of active lipids and have various effect on tissues such as inflammation and pain or homeostasis. Even though some members of the prostaglandin family such as PGE2 and PGF2α have positive effects on hair growth in mice, the recent study carried out by Garza et al. proved that the enzyme prostaglandin D2 synthase (PTGDS) and its product prostaglandin D2 (PGD2) are elevated in the mRNA and protein level in balding scalp. It is also found that the inhibition of hair growth by PGD2 requires its receptor G protein heterotrimeric guanine nucleotide–coupled receptor 44 (GPR44) (Garza et al., 2012) (Table 2).

Conclusively, it can be said that the transcriptomic reasons behind the AGA diverse between many factors and gene expressions, and therefore, it does not seem right to link its formation to a single cause.

2.4. Coding and non-coding RNA signatures of alopecia areata

In a study by Borcherding and coworkers (2020), single-cell RNA sequencing was performed in AA patients and normal subjects to gain transcriptomic insights into the disease process. They suggested that FOXP3, KLRK1 (NKG2D), ALAD, SLA, FABP5, and CTSB may play a role in humans AA (Borcherding et al., 2020). In another study, researchers investigated the differences in gene expression between AA and healthy individuals by performing RNA sequencing to find transcriptomic biomarkers. They demonstrated that the inflammation-associated genes IFNG, IL12B, CXCL11, IL13, and CCL18 and keratins such as KRT35, KRT83, and KRT81 were significantly differentially expressed when they compared the patients and normal samples (Glickman et al., 2021) (Table 2).

2.5. Proteomic and metabolomic signatures of androgenetic alopecia

Hair loss is a very important disease and sometimes side effects. As we cannot deny that the disease causes many psychological problems, its mechanism is still not fully elucidated. In this sense, -despite the developments in the state-of-the-art techniques-, the studies in the field of proteomics and metabolomics for studying alopecia are quite limited (Price et al., 2002; Rushton et al., 1991; Botchkarev and Kishimoto, 2003).

Table 2
Transcriptomic signatures of two alopecia types.

Alopecia type	Symbol	Chromosome	Description	Ref.
AGA	BAMBI	10	BMP and activin membrane bound inhibitor	(Petukhova and Christiano, 2016; Heilmann et al., 2013; Premanand and Reena Rajkumari, 2018)
	DKK1	10	Dickkopf WNT signaling pathway inhibitor 1	(Betz et al., 2015)
	ITGB6	2	Integrin Subunit Beta 6	(Welker et al., 1997)
	POMC	2	proopiomelanocortin	(Petukhova and Christiano, 2016; Heilmann et al., 2013; Premanand and Reena Rajkumari, 2018)
	PTGDS	9	Prostaglandin D2 Synthase	(Shin et al., 2013)
	SFRP2	4	Secreted frizzled related protein 2	(Betz et al., 2015)
	TGF-β1	19	Transforming growth factor beta 1	(Hardy, 1992)
	TGF-β2	1	Transforming growth factor beta 2	(Welker et al., 1997)
AA	ALAD	9	Aminolevulinate dehydratase	(Borcherding et al., 2020)
	CCL18	17	C-C motif chemokine ligand 18	(Glickman et al., 2021)
	CTSB	8	Cathepsin B	(Borcherding et al., 2020)
	CXCL11	4	C-X-C motif chemokine ligand 11	(Glickman et al., 2021)
	FABP5	8	Fatty acid binding protein 5	(Borcherding et al., 2020)
	FOXP3	X	Forkhead box P3	(Borcherding et al., 2020)
	IFNG	12	Interferon gamma	(Glickman et al., 2021)
	IL12B	5	Interleukin 12B	(Glickman et al., 2021)
	IL13	5	Interleukin 13	(Glickman et al., 2021)
	KLRK1 (NKG2D)	12	Killer cell lectin like receptor K1	(Borcherding et al., 2020)
	KRT35	17	Keratin 35	(Glickman et al., 2021)
	KRT81	12	Keratin 81	(Glickman et al., 2021)
	KRT83	12	Keratin 83	(Glickman et al., 2021)
	SLA	8	Src like adaptor	(Borcherding et al., 2020)

The mammalian hair follicle consists of different cell layers; mesenchyme-derived dermal papilla cells (DPCs) and dermal sheath cells, and epithelial cells. It is known that mesenchyme-derived DPCs have a key role in the growth and activity of the hair cycle process (Hardy, 1992). A study in 2013, investigated that is there any protein or that is differentially expressed in balding mesenchyme-derived DPCs compared to non-balding ones. At the end of their study, they found that some proteins which might be used as a marker for AGA etiology, are upregulated in balding DPCs by Western Blot and immunofluorescence

analysis and these proteins are ASS1, PAICS (ADE2), CKAP4, GSN, IQGAP1, PLEC1, and SKP1 (Moon et al., 2013).

In a meta-analysis in 2019, Syed Aun Muhammad and his colleagues created an interactive framework using different bioinformatic tools and systematic approaches to determine some biomarkers for clinical treatment. At the end of their study, they found some target and source protein interactions such as WIF1, SPON1, LYZ, GPRC5B, PTPRE, ZFP36L2, HBB, PHF15, LMCD1, KRT35, and VAV3 with APCDD1, WNT1, WNT3A, SHH, ESR1, TGFB1, and APP and also, they found some pathways that come forward consist of protein metabolism, signal transduction, WNT, BMP, EDA, NOTCH and SHH pathways. These proteins and pathways are especially related to hair growth and could cause some problems in the case of higher or lower expression (Muhammad et al., 2019) (Table 3).

Another important omics field for hair loss is metabolomics, especially the microbiome. Human hair and skin are a kind of host for various types of microorganisms (Grice and Segre, 2011; Kong, 2011). There are many studies about the human skin microbiome although the hair microbiome topic is very limited (Nakatsuji et al., 2013). Some studies showed that *Propionibacterium acnes* are related to hair casts and alopecia (Leyden et al., 1975; Wang et al., 2012). In 2019, a study put forth the first study which characterizes microbiome in healthy hair and AGA patients and connection with the progression of this disease. They reported that the presence of higher microorganism diversity in the lower parts of hair and Burkholderia is found at a high level on the middle part of the hair (Ho et al., 2019). It is known that dihydrotestosterone is a male hormone and an increased level of it is associated with pattern baldness (Adachi et al., 1970; McDonagh and Messenger, 1996). To clarify this topic, a research group worked to serve metabolic pathways of pattern baldness and the differences between patients and healthy people. They also identify the changes in hair metabolomic profiles according to sex. At the end of their studies, they suggested that pattern baldness is related to steroid hormone for both sexes but there is a difference for sexes, in males, androgen metabolism altered in although the estrogen metabolism altered in females (Lee et al., 2021). Another study aimed to clarify the interaction between finasteride treatment and dihydrotestosterone level in male pattern baldness. This study investigated differences in urinary metabolomics profiles. After all investigations, it has been seen that the androgens and estrogens levels were altered in the patient's urine with finasteride treatment and also dihydrotestosterone/testosterone ratio increased in the urine as an indicator of the therapeutic effect of this treatment (Lee et al., 2020).

2.6. Proteomic and metabolomic signatures of alopecia areata

A publication about the importance of proteome data that served as the first proteomics dataset for AA patients was published in 2018. In this study, researchers reported that α-tubulin, vimentin, HSP70, HSP90, ANXA2, and ENO1 were downregulated in AA patients compared with control biopsies. Moreover, this study suggests that the alterations at the protein level might be a potential reason for AA alongside the genetic background of a person and they indicated some potential and novel mechanisms or biological pathways that might consist of pathogenic mechanisms of AA (Thanomkitti et al., 2018). Another study in 2018 work to clarify proteome profile of healthy hair and results revealed that might be a clinical signature or novel biomarkers of hair for future that are keratins, multiple KAPs, and some host defense factor such as S100 proteins and histones (Adav et al., 2018). Before this study, in 2006 Young-Jin Lee and his colleagues also investigated the human hair proteome and they also found that keratin intermediate filaments have high abundancy and were methylated and demethylated (Lee et al., 2006). A more recent 2020 study examined serum levels of IFN-γ, IL -1β, IL −6 in AA patients, nonsegmental vitiligo patients, and normal controls. They found that serum concentrations of the three proteins were remarkably high when comparing AA patients with healthy controls (Tomaszewska et al., 2020) (Table 3).

In a study by Pinto and coworkers (2020), AA was investigated using metagenomics and metabolomics. To do this, the researchers collected urine samples from the subjects and determined differentially expressed

Table 3
Proteomic signatures of two alopecia types.

Alopecia Type	Symbol	Description	Ref.
AGA	APCDD1	APC down-regulated 1	(Hardy, 1992)
	APP	Amyloid beta precursor protein	(Hardy, 1992)
	ASS1	Argininosuccinate synthase 1	(Price et al., 2002)
	CKAP4	Cytoskeleton associated protein 4	(Price et al., 2002)
	ESRI	Estrogen Receptor 1	(Hardy, 1992)
	GPRC5B	G protein-coupled receptor class C group 5 member B	(Hardy, 1992)
	GSN	Gelsolin	(Price et al., 2002)
	HBB	Hemoglobin subunit beta	(Hardy, 1992)
	IQGAP1	IQ motif containing GTPase activating protein 1	(Price et al., 2002)
	KRT35	Keratin 35	(Hardy, 1992)
	LMCD1	LIM and cysteine rich domains 1	(Hardy, 1992)
	LYZ	Lysozyme	(Hardy, 1992)
	PAICS	Phosphoribosylaminoimidazole carboxylase and phosphoribosylaminoimidazolesuccinocarboxamide synthase	(Price et al., 2002)
	PHF15	Jade family PHD finger 2	(Hardy, 1992)
	PLEC1	Plectin	(Price et al., 2002)
	PTPRE	Protein tyrosine phosphatase receptor type E	(Hardy, 1992)
	SHH	Sonic hedgehog signaling molecule	(Hardy, 1992)
	SKP1	S-Phase Kinase Associated Protein 1	(Price et al., 2002)
	SPON1	Spondin 1	(Hardy, 1992)
	VAV3	Vav guanine nucleotide exchange factor 3	(Hardy, 1992)
	WIF1	Wnt inhibitory factor 1	(Hardy, 1992)
	WNT1	Wnt family member 1	(Hardy, 1992)
	WNT3A	Wnt family member 3A	(Hardy, 1992)
	ZFP36L2	ZFP36 ring finger protein like 2	(Hardy, 1992)
AA	ANXA2	Annexin A2	(Thanomkitti et al., 2018)
	HSP70	Heat shock protein family A (Hsp70) member 4	(Thanomkitti et al., 2018)
	HSP90	Heat shock protein 90 Alpha family class A member 1	(Thanomkitti et al., 2018)
	IFN-γ	Interferon gamma	(Tomaszewska et al., 2020)
	IL -1β	Interleukin 1 beta	(Tomaszewska et al., 2020)
	IL −6	Interleukin 6	(Tomaszewska et al., 2020)
	ENO1	Enolase 1	(Thanomkitti et al., 2018)

metabolites by comparing AA patients and healthy subjects. They demonstrated that the following metabolites, menthol, methanthiol, dihydrodehydro-beta-ionone, 2,5-dimethylfuran, and 1,2,3,4, tetrahydro-1,5,7-trimethylnapthalene, had remarkably different expressions (Pinto et al., 2019).

In the future, in the case of comparing these results that belong to both healthy and unhealthy hair proteome datasets, might offer to obtain more precise and more potential mechanism for the hair loss process.

All studies show that omics technologies have a great potential to clarify the networks in hair loss more precisely and help to discover more targeted, personalized, and exact treatments for this disease. Thanks to further studies, this disease might be prevented in the future.

3. Drugs that are currently used in the clinic for the treatment of alopecia

Management with alopecia includes different approaches. It can be changed with the history of the patients, the extent of the bald parts, patients' economic situation, and the type of alopecia. The first aim of the treatments is to stop hair follicle miniaturization, even reverse it. However, as there are no direct health effects of any kind of alopecia on patients, drug regulatory authorities expected that the drugs that will be used to cure alopecia should not cause any side effects. As a result, the FDA only approved 2 drugs except for surgical solutions. The rest is prescribed in an off-label approach (Table 4).

3.1. Minoxidil

The first approved drug for alopecia is Minoxidil (Rogaine) which is a vasodilator drug that opens the cell membrane's potassium channel. It is originally developed as an antihypertensive agent, but the patient has observed hypertrichosis as a side effect. Thus, it is repurposed as a treatment of Androgenetic Alopecia in the topical form and the FDA approved it used for AGA treatment in both genders in 1988 (Messenger and Rundegren, 2004).

Minoxidil's metabolism is based on the minoxidil sulfate conversion by the sulfotransferase enzyme located in the hair follicle rather directly affecting the hair cycle. It can be applied with a foam or lotion vehicle in a 2 to 5 % concentration for 12 and 24 weeks. The results show that the hair loss in the patient decreases significantly in both concentrations. Studies with the rats are suggested that the telogen phase, which is elongated in AGA, became shorter, and the duration of the anagen phase increased. The only downside of the Minoxidil is that its effect will be reused within the six months when the usage of it is stopped (Suchonwanit et al., 2019).

3.2. Finasteride

The second FDA-approved drug is Finasteride (Propecia), it was approved in the USA in 1997 at a dose of 1 mg/day for male typeAGA. It is developed by Merck directly for the AGA. It is an aza-steroid, synthetic drug with a high selectivity towards the type II 5α-reductase isoenzyme. By inhibiting this isoenzyme activity, it decreases the DHT concentrations on the scalp by approximately 60–70 %. Although the treatment is successful in men, its use on female type AGA seems to be less efficient (Lee et al., 2018).

In addition to that, since it is developed to reduce androgenic power, it shows some side effects on male patients such as erectile dysfunction, decreased sexual desire, and decreased ejaculated volume. While young patients show a higher response to the drug, the treatment needs to be last lifelong. In any break on the treatment, gradual hair loss will return within a year (Whiting et al., 1999).

3.3. Dutasteride

Along with the Finasteride, another azo-steroid drug exists in the pharmaceutical industry; Dutasteride (Avodart). The main difference between the two drugs is that Dutasteride is a dual inhibitor of both type I and type II 5α-reductase. It is only approved for benign prostatic hyperplasia (BPH) by the FDA but in some countries like South Korea or Japan, its usage for AGA is also approved in the dose of 0.5 mg/day. When compared with Finasteride, its efficacy is 100 times higher on inhibition of type I 5α-reductase and 3 times higher on type II 5α-reductase. However, like other inhibitors, the usage of it increases the risk of adverse sexual effects such as erectile dysfunction and decreased libido but the data are limited on its usage and side effects (Zhou et al., 2019).

3.4. Off-labeled treatments for androgenetic alopecia

Today, new exosome-based therapeutic strategies are coming to the fore, especially for AGA. In vitro, animal, and human studies have shown that exosomes derived from different cell types can induce hair growth and treat hair follicles. Although surgeons specializing in hair restoration agree with the hypothesis of the success of exosome treatment, the FDA warns of the side effects of exosome treatment (Gupta et al., 2020).

In addition to exosome therapy, platelet-rich plasma therapy (PRP) offers efficient solutions for AGA. PRP Therapy based on the use of the patient's own platelets has been shown to promote hair growth in AGA patients. Moreover, the studies reported that this therapy does not cause primary adverse effects in patients and is one of the effective off-label treatments for AGA (Cervantes et al., 2018).

Table 4
Medications that prescribed for AGA and AA.

Medication	Disease	Treatment approval	Type of the medication	Mechanism of action	Ref.
Minoxidil	AGA	FDA Approved	Topical	Unknown, possible vasodilatory	(Messenger and Rundegren, 2004)
Finasteride	AGA	FDA Approved	Oral	Type II 5α-reductase inhibitor	(Whiting et al., 1999)
Finasteride	AGA	Not approved/Off-label	Topical	Type II 5α-reductase inhibitor	(Lee et al., 2018)
Dutasteride	AGA	Approved in Mexico and South Korea	Oral	5α-reductase inhibitor	(Zhou et al., 2019)
Exosome therapy	AGA	Not approved/Off-label	Topical	Intracellular shuttling	(Gupta et al., 2020)
Platelet-rich plasma therapy	AGA	Not approved/Off-label	Topical	Activates cell membrane receptors	(Cervantes et al., 2018)
Stromal vascular fraction therapy	AGA	Not approved/Off-label	Topical	Used anti-inflammatory and antiandrogenic effects	(Kim et al., 2021)
Transplantation of multipotent stem cells	AGA	Not approved/off-label	Topical	Can differentiate into distinct types of cells	(Egger et al., 2020)
Squaric Acid Dibutyl Ester (SADBE)	AA	Not approved/off-label	Topical	Reducing immune response	(Mahasaksiri et al., 2021; Singh and Lavanya, 2010)
Dinitrochlorobenzene (DNCB)	AA	Not approved/off-label	Topical	Reducing immune response	(Mahasaksiri et al., 2021; Singh and Lavanya, 2010)
Diphenyl-cyclopropenone (DPCP)	AA	Not approved/off-label	Topical	Reducing immune response	(Mahasaksiri et al., 2021; Singh and Lavanya, 2010)

A, stromal vascular fraction (SVF) therapy, a type of stem cell therapy, also shows promising results, especially in AGA patients. A recent study reported that the hair density of patients who received SVF therapy increased significantly within 6 months (Kim et al., 2021).

Besides these strategies, transplantation of multipotent stem cells such as adipose tissue, bone marrow, or umbilical cord blood is the most accepted strategy by the authorities, especially in AGA patients (Egger et al., 2020).

3.5. Off-labeled treatments for alopecia areata

For AA patients, there is neither accepted treatment therapy exists in the field nor approved drugs. As a matter of fact that treatment of alopecia areata requires immunotherapeutic agents, management of the disease requires two types of it; immunosuppression and immune deviation. The most commonly used treatment is corticosteroids as immunosuppression for decreasing the CD4 and CD8 T-cell ratio and therefore, decreasing hair shedding. It is applied in topical form like many skin diseases. Furthermore, treatment options can be varied with sensitizing agents such as squaric acid dibutyl ester (SADBE), dinitrochlorobenzene (DNCB), and diphenyl-cyclopropenone (DPCP) on patients, especially those who have recalcitrant and repeated AA.

While three of the options are widely used, DNBC has been verified as mutagenic by the Ames test. Thus, DNBC is no longer the first option for AA treatment. On the other hand, Squaric acid dibutyl ester (SADBE) was found to be a contact allergen in 1979 and since then used in AA treatment. It is a more expensive compound than others since it does not cause any cross-react with chemicals and is found in the natural environment. However, it may cause severe side effects such as the burning of the patients' skins and it is very unstable in the acetone solution. The most common and well studies immunotherapeutic agent is DPCP with no mutagenic effect on adult patients. It is the first choice of treatment therapy of AA recommended by the British Association of Dermatologists (Gensure, 2018). While it is cheaper than the SADBE, it is also more stable and there are no reported side effects (Mahasaksiri et al., 2021; Singh and Lavanya, 2010; Wang et al., 2018).

4. Multi-omics evaluation of the alopecia that converges to future therapeutics

The biological high-throughput data and the scientific branches to organize it have gained importance in the past decades. One of these scientific branches, systems biology, leverages omics data from various biological levels (genomics, transcriptomics, metabolomics etc.) has evolved rapidly. Particularly, omics data integration approaches have revealed not only unprecedented insights into disease mechanisms but also uncovered candidate novel genes, pathways, drug targets (Turanli et al., 2021a; Sevimoglu et al., 2018; Gov et al., 2017a; Kori et al., 2019; Kori and Arga, 2018). Therefore, there is a critical shift from a traditional view of dealing with disease specific individual genes to a network view, where a large number of biological molecules coordinately interacts with each other regarding to many factors including physiological, individual or environmental factors (Turanli et al., 2019; Turanli et al., 2017a).

To harness the strengths of data-driven networks, genome wide association studies (GWAS), the gene expression profilings and either metabolomics or proteomics can be overlapped to create integrative network for alopecia as well as other diseases (Karagoz et al., 2015; Calimlioglu et al., 2015; Gov et al., 2017b).

Moreover, predictions for drug development can be facilitated by the use of systems biology. The identification of biological targets and new promising drugs can be achieved by using either computational or experimental methods for drug repositioning by collecting clinical data at different omics levels and analyzing them within systematic and integrative pipelines (Turanli et al., 2021b; Turanli et al., 2017b).

As knowledge coming from different omics levels will enlighten the disease molecular mechanisms, the evaluation of disease progression or calling the most appropriate treatment regimens might be possible in a more precise and individualized way, converging to the personalization of health services. These efforts can be extended via the construction of a specific disease screening panel composed of multi-omics signatures of alopecia. Due to having high sensitivity and specificity with only a single signature is not easy, providing a group of multi-omics signature will enhance more efficient therapeutic modalities (Fig. 1). Such a monitoring/screening panel might elevate individualized medicine practice in the field.

Communications and signaling transductions across hair follicles and skin microbiome is another question to be answered. This type of relationship can only be revealed when data integration reaches organism-wise systems level. Although the construction of skin microbiome networks has been attempted (Pinto et al., 2019), such efforts have to be further expanded to shed a light on the relationship with hair loss and to develop more efficient methodologies.

5. Conclusion

Alopecia or hair loss is a global health problem that affects both men and women around the world. Beyond the fact that alopecia is a disease itself, sometimes it might be one of major side effects of many drugs including chemotherapeutics. Since healthy hair has been a symbol of well-being, youth, and vitality for centuries, the treatment of alopecia has essential importance to increasing life quality of the individuals that have faced hair loss. Moreover, alopecia has an expanded global market size in every year. Although its pathology and its treatment are nearly understood, there is no method that can regenerate the lost hair naturally or reverse the whole process. This deficit, which the medical field has not solved yet, is filled by cosmetic companies by finding temporary or permanent solutions to cover physical problems of alopecia patients. Even visual solutions such as cover bald parts such as wigs, hair powder and sprays have an inevitable market size, while no need to mention about popularity of the hair transplantation.

In order to provide an updated vision of the key insights in alopecia, we have reviewed specifically systems biology studies for unraveling future therapy options with the aid of multi-omics data integration approaches. Although major mechanisms responsible for hair loss are described in this review, the influence of additional factors in the disease remains undefined. That is why integration of different omics studies may provide new opportunities to reveal disease mechanism by seeing the whole picture. Parallel to the improvement of the molecular biology and systems biology methods, more specific and sensitive biomarkers will lead to personalized therapies. Although different omics studies from non-coding genes to metabolites showed promising results which may be translated into clinic in the foreseeable future, there is an urgent need of validation in larger populations.

While all omics efforts may help researchers to discover new therapeutics, it can be foreseen that drug repositioning can be achieved rather than drug discovery because of its advantages. The less aggressive and more effective drugs may be redirected for hair loss problem or combination therapy options can be declared regarding computational drug repositioning approaches. Synthetic biology companies of the future may produce personal care products for individuals based on their requirement to uncover hair loss. Designing bioengineered cosmetic products might be more effective and also environmentally friendly than traditionally sourced products.

Consent for publication

Not applicable.

Declaration of competing interest

The authors declare that there is no conflict of interest.

Data availability

No data was used for the research described in the article.

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References

Adachi, K., Takayasu, S., Takashima, I., Kondo, S., 1970. Human Hair Follicles: Metabolism And Control Mechanisms, Vol. 21.

Adav, S.S., Subbaiaih, R.S., Kerk, S.K., Lee, A.Y., Lai, H.Y., Ng, K.W., Sze, S.K., Schmidtchen, A., 2018. Studies on the proteome of human hair - identification of histones and deamidated keratins. Sci. Rep. 8, 1–11. https://doi.org/10.1038/s41598-018-20041-9.

Alopecia market size, share, trends | Global Industry Report 2027. Available online. https://www.grandviewresearch.com/industry-analysis/alopecia-market. (Accessed 28 May 2021).

Betz, R.C., Petukhova, L., Ripke, S., Huang, H., Menelaou, A., Redler, S., Becker, T., Heilmann, S., Yamany, T., Duvic, M., et al., 2015. Genome-wide meta-analysis in alopecia areata resolves HLA associations and reveals two new susceptibility loci. Nat. Commun. 6, 1–8. https://doi.org/10.1038/ncomms6966.

Borcherding, N., Crotts, S.B., Ortolan, L.S., Henderson, N., Bormann, N.L., Jabbari, A., 2020. A transcriptomic map of murine and human alopecia areata. JCIInsight 5. https://doi.org/10.1172/JCI.INSIGHT.137424.

Botchkarev, V.A., Kishimoto, J., 2003. Molecular control of epithelial-mesenchymal interactions during hair follicle cycling. In: Proceedings of the Journal of Investigative Dermatology Symposium Proceedings, Vol. 8. Blackwell Publishing Inc., pp. 46–55

Brockschmidt, F.F., Hillmer, A.M., Eigelshoven, S., Hanneken, S., Heilmann, S., Barth, S., Herold, C., Becker, T., Kruse, R., Nöthen, M.M., 2010. Fine mapping of the human AR/EDA2R locus in androgenetic alopecia. Br. J. Dermatol. 162, 899–903. https://doi.org/10.1111/j.1365-2133.2010.09649.x.

Buffoli, B., Rinaldi, F., Labanca, M., Sorbellini, E., Trink, A., Guanziroli, E., Rezzani, R., Rodella, L.F., 2014. The human hair: from anatomy to physiology. Int. J. Dermatol. 53, 331–341. https://doi.org/10.1111/ijd.12362.

Calimlioglu, B., Karagoz, K., Sevimoglu, T., Kilic, E., Gov, E., Arga, K.Y., 2015. Tissue-specific molecular biomarker signatures of type 2 diabetes: an integrative analysis of transcriptomics and protein-protein interaction data. OMICS 19, 563–573. https://doi.org/10.1089/omi.2015.0088.

Cervantes, J., Perper, M., Wong, L.L., Eber, A.E., Fricke, A.C.V., Wikramanayake, T.C., Jimenez, J.J., 2018. Effectiveness of platelet-rich plasma for androgenetic alopecia: a review of the literature. Ski. Appendage Disord. 4, 1–11. https://doi.org/10.1159/000477671.

Egger, A., Tomic-Canic, M., Tosti, A., Frost, P., 2020. Advances in stem cell-based therapy for hair loss. CellR4 Repair Replace. Regen. Reprogram. 8.

Garza, L.A., Liu, Y., Yang, Z., Alagesan, B., Lawson, J.A., Norberg, S.M., Loy, D.E., Zhao, T., Blatt, H.B., Stanton, D.C., et al., 2012. Prostaglandin D 2 inhibits hair growth and is elevated in bald scalp of men with androgenetic alopecia. Sci. Transl. Med. 4 https://doi.org/10.1126/scitranslmed.3003122.

Gensure, R., 2018. Pharmacological treatment of alopecia. In: Alopecia. InTech.

Gilhar, A., Etzioni, A., Paus, R., 2012. Alopecia areata. N. Engl. J. Med. 366, 1515–1525. https://doi.org/10.1056/NEJMra1103442.

Glickman, J.W., Dubin, C., Dahabreh, D., Han, J., Del Duca, E., Estrada, Y.D., Zhang, N., Kimmel, G.W., Singer, G., Krueger, J.G., et al., 2021. An integrated scalp and blood biomarker approach suggests the systemic nature of alopecia areata. Allergy 76, 3053–3065. https://doi.org/10.1111/ALL.14814.

Gov, E., Kori, M., Arga, K.Y., 2017. RNA-based ovarian cancer research from 'a gene to systems biomedicine' perspective. Syst. Biol. Reprod. Med. 63, 219–238. https://doi.org/10.1080/19396368.2017.1330368.

Gov, E., Kori, M., Arga, K.Y., 2017. Multiomics analysis of tumor microenvironment reveals Gata2 and miRNA-124-3p as potential novel biomarkers in ovarian cancer. OMICS 21, 603–615. https://doi.org/10.1089/omi.2017.0115.

Grice, E.A., Segre, J.A., 2011. The skin microbiome. Nat. Rev. Microbiol. 9, 244–253. https://doi.org/10.1038/nrmicro2537.

Gupta, A.K., Renaud, H.J., Halaas, Y., Rapaport, J.A., 2020. Exosomes: a new effective non-surgical therapy for androgenetic alopecia? Skinmed 18, 96–100.

Hamilton, J.B., 1942. Male hormone stimulation is a prerequisite and incitant in common baldness1. J. Invest. Dermatol. 5, 473–474. https://doi.org/10.1038/jid.1942.62.

Hamilton, J.B., 1951. Male pattern hair loss in man: types and incidence. Ann. N. Y. Acad. Sci. 53, 708–728. https://doi.org/10.1111/j.1749-6632.1951.tb31971.x.

Hardy, M.H., 1992. The secret life of the hair follicle. Trends Genet. 8, 55–61. https://doi.org/10.1016/0168-9525(92)90350-D.

Heilmann, S., Kiefer, A.K., Fricker, N., Drichel, D., Hillmer, A.M., Herold, C., Tung, J.Y., Eriksson, N., Redler, S., Betz, R.C., et al., 2013. Androgenetic alopecia: identification of four genetic risk loci and evidence for the contribution of WNT signaling to its etiology. J. Invest. Dermatol. 133, 1489–1496. https://doi.org/10.1038/jid.2013.43.

Heilmann-Heimbach, S., Hochfeld, L.M., Paus, R., Nöthen, M.M., 2016. Hunting the genes in male-pattern alopecia: how important are they, how close are we and what will they tell us? Exp. Dermatol. 25, 251–257. https://doi.org/10.1111/exd.12965.

Hillmer, A.M., Hanneken, S., Ritzmann, S., Becker, T., Freudenberg, J., Brockschmidt, F. F., Flaquer, A., Freudenberg-Hua, Y., Jamra, R.A., Metzen, C., et al., 2005. Genetic variation in the human androgen receptor gene is the major determinant of common early-onset androgenetic alopecia. Am. J. Hum. Genet. 77, 140–148. https://doi.org/10.1086/431425.

Hillmer, A.M., Brockschmidt, F.F., Hanneken, S., Eigelshoven, S., Steffens, M., Flaquer, A., Herms, S., Becker, T., Kortüm, A.K., Nyholt, D.R., et al., 2008. Susceptibility variants for male-pattern baldness on chromosome 20p11. Nat. Genet. 40, 1279–1281. https://doi.org/10.1038/ng.228.

Ho, B.S.Y., Ho, E.X.P., Chu, C.W., Ramasamy, S., Bigliardi-Qi, M., de Sessions, P.F., Bigliardi, P.L., 2019. Microbiome in the hair follicle of androgenetic alopecia patients. PLoS One 14, e0216330. https://doi.org/10.1371/JOURNAL.PONE.0216330.

Hunt, N., McHale, S., 2005. The psychological impact of alopecia. Br. Med. J. 331, 951–953. https://doi.org/10.1136/bmj.331.7522.951.

Jagielska, D., Redler, S., Brockschmidt, F.F., Herold, C., Pasternack, S.M., Garcia Bartels, N., Hanneken, S., Eigelshoven, S., Refke, M., Barth, S., et al., 2012. Follow-up study of the first genome-wide association scan in alopecia areata: IL13 and KIAA0350 as susceptibility loci supported with genome-wide significance. J. Invest. Dermatol. 132, 2192–2197. https://doi.org/10.1038/jid.2012.129.

Karagoz, K., Sinha, R., Arga, K.Y., 2015. Triple negative breast cancer: a multi-omics network discovery strategy for candidate targets and driving pathways. OMICS 19, 115–130. https://doi.org/10.1089/omi.2014.0135.

Kaufman, K.D., 2002. Androgens and alopecia. Mol. Cell. Endocrinol. 198, 89–95. https://doi.org/10.1016/S0303-7207(02)00372-6.

Kaufman, K.D., Olsen, E.A., Whiting, D., Savin, R., DeVillez, R., Bergfeld, W., Price, V.H., Van Neste, D., Roberts, J.L., Hordinsky, M., et al., 1998. Finasteride in the treatment of men with androgenetic alopecia. J. Am. Acad. Dermatol. 39, 578–589. https://doi.org/10.1016/S0190-9622(98)70007-6.

Kim, S.J., Kim, M.J., Lee, Y.J., Lee, J.C., Kim, J.H., Kim, D.H., Do, Y.H., Choi, J.W., Chung, S.I., Do, B.R., 2021. Innovative method of alopecia treatment by autologous adipose-derived SVF. Stem Cell Res. Ther. 12, 1–9. https://doi.org/10.1186/S13287-021-02557-6/FIGURES/4.

Kong, H.H., 2011. Skin microbiome: genomics-based insights into the diversity and role of skin microbes. Trends Mol. Med. 17, 320–328. https://doi.org/10.1016/j.molmed.2011.01.013.

Kori, M., Arga, K.Y., 2018. Potential biomarkers and therapeutic targets in cervical cancer: insights from the meta-analysis of transcriptomics data within network biomedicine perspective. PLoS One 13, e0200717. https://doi.org/10.1371/JOURNAL.PONE.0200717.

Kori, M., Gov, E., Arga, K.Y., 2019. In: Novel genomic biomarker candidates for cervical cancer as identified by differential co-expression networkanalysis, 23, pp. 261–273. https://doi.org/10.1089/OMI.2019.0025 https://home.liebertpub.com/omi. https://home.liebertpub.com/omi.

Lee, Y.J., Rice, R.H., Lee, Y.M., 2006. Proteome analysis of human hair shaft: from protein identification to posttranslational modification. Mol. Cell. Proteomics 5, 789–800. https://doi.org/10.1074/mcp.M500278-MCP200.

Lee, S.W., Juhasz, M., Mobasher, P., Ekelem, C., Mesinkovska, N.A., 2018. A systematic review of topical finasteride in the treatment of androgenetic alopecia in men and women. J. Drugs Dermatol. 17, 457–463.

Lee, Y.R., Im, E., Kim, H., Lew, B.L., Sim, W.Y., Lee, J., Oh, H.Bin, Paeng, K.J., Hong, J., Chung, B.C., 2020. Untargeted metabolomics and steroid signatures in urine of male pattern baldness patients after finasteride treatment for a year. Metabolites 10, 131. https://doi.org/10.3390/metabo10040131.

Lee, Y.R., Lew, B.L., Sim, W.Y., Hong, J., Chung, B.C., 2021. Alterations in pattern baldness according to sex: hair metabolomics approach. Metabolites 11, 178. https://doi.org/10.3390/metabo11030178.

Leyden, J.J., McGinley, K.J., Mills, O.H., Kligman, A.M., 1975. Propionibacterium levels in patients with and without acne vulgaris. J. Invest. Dermatol. 65, 382–384. https://doi.org/10.1111/1523-1747.ep12607634.

Li, R., Brockschmidt, F.F., Kiefer, A.K., Stefansson, H., Nyholt, D.R., Song, K., Vermeulen, S.H., Kanoni, S., Glass, D., Medland, S.E., et al., 2012. Six novel susceptibility loci for early-onset androgenetic alopecia and their unexpected association with common diseases. PLoS Genet. 8, e1002746 https://doi.org/10.1371/journal.pgen.1002746.

Lin, R.L., Garibyan, L., Kimball, A.B., Drake, L.A., 2016. Systemic causes of hair loss. Ann. Med. 48, 393–402. https://doi.org/10.1080/07853890.2016.1180426.

Lu, G.Q., Wu, Z.B., Chu, X.Y., Bi, Z.G., Fan, W.X., 2016. An investigation of crosstalk between Wnt/β-catenin and transforming growth factor-β signaling in androgenetic alopecia. Medicine (Baltimore) 95. https://doi.org/10.1097/MD.0000000000004297.

Mahasaksiri, T., Kositkuljorn, C., Anuntrangsee, T., Suchonwanit, P., 2021. Application of topical immunotherapy in the treatment of alopecia areata: a review and update. Drug Des. Dev. Ther. 15, 1285–1298. https://doi.org/10.2147/DDDT.S297858.

McDonagh, A.J.G., Messenger, A.G., 1996. The pathogenesis of alopecia areata. Dermatol. Clin. 14, 661–670. https://doi.org/10.1016/S0733-8635(05)70392-2.

Messenger, A.G., Rundegren, J., 2004. Minoxidil: mechanisms of action on hair growth. Br. J. Dermatol. 150, 186–194. https://doi.org/10.1111/j.1365-2133.2004.05785.x.

Messenger, A.G., De Berker, D.A.R., Sinclair, R.D., 2010. Disorders of hair. In: Rook's Textbook of Dermatology, , Eighth editionVol. 4. Wiley-Blackwell, pp. 3329–3428. ISBN 9781405161695.

Michel, L., Reygagne, P., Benech, P., Jean-Louis, F., Scalvino, S., Ly Ka So, S., Hamidou, Z., Bianovici, S., Pouch, J., Ducos, B., et al., 2017. Study of gene expression alteration in male androgenetic alopecia: evidence of predominant molecular signalling pathways. Br. J. Dermatol. 177, 1322–1336. https://doi.org/10.1111/bjd.15577.

Moon, P.G., Kwack, M.H., Lee, J.E., Cho, Y.E., Park, J.H., Hwang, D., Kim, M.K., Kim, J. C., Sung, Y.K., Baek, M.C., 2013. Proteomic analysis of balding and non-balding mesenchyme-derived dermal papilla cells from androgenetic alopecia patients using on-line two-dimensional reversed phase-reversed phase LC-MS/MS. J. Proteome 85, 174–191. https://doi.org/10.1016/j.jprot.2013.04.004.

Muhammad, S.A., Fatima, N., Paracha, R.Z., Ali, A., Chen, J.Y., 2019. A systematic simulation-based meta-analytical framework for prediction of physiological biomarkers in alopecia. J. Biol. Res. 26, 1–16. https://doi.org/10.1186/s40709-019-0094-x.

Nakatsuji, T., Chiang, H.I., Jiang, S.B., Nagarajan, H., Zengler, K., Gallo, R.L., 2013. The microbiome extends to subepidermal compartments of normal skin. Nat. Commun. 4, 1431. https://doi.org/10.1038/ncomms2441.

Norwood, O.T., 2001. Incidence of female androgenetic alopecia (female pattern alopecia). Dermatol.Surg. 27, 53–54. https://doi.org/10.1046/j.1524-4725.2001.00124.x.

Otberg, N., Finner, A.M., Shapiro, J., 2007. Androgenetic alopecia. Endocrinol. Metab. Clin. N. Am. 36, 379–398. https://doi.org/10.1016/j.ecl.2007.03.004.

Park, A.M., Khan, S., Rawnsley, J., 2018. Hair biology: growth and pigmentation. Facial Plast. Surg. Clin. N.Am. 26, 415–424. https://doi.org/10.1016/j.fsc.2018.06.003.

Petukhova, L., Christiano, A.M., 2016. Functional interpretation of genome-wide association study evidence in alopecia areata. J. Invest. Dermatol. 136, 314–317. https://doi.org/10.1038/JID.2015.402.

Petukhova, L., Duvic, M., Hordinsky, M., Norris, D., Price, V., Shimomura, Y., Kim, H., Singh, P., Lee, A., Chen, W.V., et al., 2010. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. Nature 466, 113–117. https://doi.org/10.1038/nature09114.

Pinto, D., Sorbellini, E., Marzani, B., Rucco, M., Giuliani, G., Rinaldi, F., 2019. Scalp bacterial shift in Alopecia areata. PLoS One 14. https://doi.org/10.1371/journal.pone.0215206.

Pirastu, N., Joshi, P.K., De Vries, P.S., Cornelis, M.C., McKeigue, P.M., Keum, N., Franceschini, N., Colombo, M., Giovannucci, E.L., Spiliopoulou, A., et al., 2017. GWAS for male-pattern baldness identifies 71 susceptibility loci explaining 38% of the risk. Nat. Commun. 8, 1–10. https://doi.org/10.1038/s41467-017-01490-8.

Pratt, C.H., King, L.E., Messenger, A.G., Christiano, A.M., Sundberg, J.P., 2017. Alopecia areata. Nat. Rev. Dis. Primers 3, 1–17. https://doi.org/10.1038/nrdp.2017.11.

Premanand, A., Reena Rajkumari, B., 2018. Androgen modulation of Wnt/β-catenin signaling in androgenetic alopecia. Arch. Dermatol. Res. 310, 391–399. https://doi.org/10.1007/s00403-018-1826-8.

Price, V.H., Menefee, E., Sanchez, M., Ruane, P., Kaufman, K.D., 2002. Changes in hair weight and hair count in men with androgenetic alopecia after treatment with finasteride, 1 mg, daily. J. Am. Acad. Dermatol. 46, 517–523. https://doi.org/10.1067/mjd.2002.120537.

Randall, V.A., 1994. Androgens and human hair growth. Clin. Endocrinol. 40, 439–457. https://doi.org/10.1111/j.1365-2265.1994.tb02483.x.

Randall, V.A., 2010. Molecular basis of androgenetic alopecia. In: Aging Hair. Springer, Berlin Heidelberg, pp. 9–24. ISBN 9783642026355.

Richards, J.B., Yuan, X., Geller, F., Waterworth, D., Bataille, V., Glass, D., Song, K., Waeber, G., Vollenweider, P., Aben, K.K.H., et al., 2008. Male-pattern baldness susceptibility locus at 20p11. Nat. Genet. 40, 1282–1284. https://doi.org/10.1038/ng.255.

Rushton, D.H., Ramsay, I.D., Norris, M.J., Gilkes, J.J.H., 1991. Natural progression of male pattern baldness in young men. Clin. Exp. Dermatol. 16, 188–192. https://doi.org/10.1111/j.1365-2230.1991.tb00343.x.

Santos, Z., Avci, P., Hamblin, M.R., 2015. Drug discovery for alopecia: gone today, hair tomorrow. Expert Opin. Drug Discov. 10, 269–292. https://doi.org/10.1517/17460441.2015.1009892.

Sevimoglu, T., Turanli, B., Bereketoglu, C., Arga, K.Y., Karadag, A.S., 2018. Systems biomarkers in psoriasis: integrative evaluation of computational and experimental data at transcript and protein levels. Gene 647, 157–163. https://doi.org/10.1016/j.gene.2018.01.033.

Shin, H., Yoo, H.G., Inui, S., Itami, S., Kim, I.G., Cho, A.R., Lee, D.H., Park, W.S., Kwon, O., Cho, K.H., et al., 2013. Induction of transforming growth factor-beta 1 by androgen is mediated by reactive oxygen species in hair follicle dermal papilla cells. BMB Rep. 46, 460–464. https://doi.org/10.5483/BMBRep.2013.46.9.228.

Singh, G., Lavanya, M.S., 2010. Topical immunotherapy in alopecia areata. Int. J. Trichology 2, 36–39. https://doi.org/10.4103/0974-7753.66911.

Stough, D., Stenn, K., Haber, R., Parsley, W.M., Vogel, J.E., Whiting, D.A., Washenik, K., 2005. Psychological effect, pathophysiology, and management of androgenetic alopecia in men. Mayo Clin. Proc. 80, 1316–1322. https://doi.org/10.4065/80.10.1316.

Suchonwanit, P., Thammarucha, S., Leerunyakul, K., 2019. Minoxidil and its use in hair disorders: a review. Drug Des. Dev. Ther. 13, 2777–2786. https://doi.org/10.2147/DDDT.S214907.

Thanomkitti, K., Kanlaya, R., Fong-Ngern, K., Kapincharanon, C., Sueksakit, K., Chanchaem, P., Thuangtong, R., Thongboonkerd, V., 2018. Differential proteomics of lesional vs. non-lesional biopsies revealed non-immune mechanisms of alopecia areata. Sci. Rep. 8, 1–13. https://doi.org/10.1038/s41598-017-18282-1.

Tomaszewska, K., Kozłowska, M., Kaszuba, A., Lesiak, A., Narbutt, J., Zalewska-Janowska, A., 2020. Increased serum levels of IFN- γ, IL-1 β, and IL-6 in patients with alopecia areata and nonsegmental vitiligo. Oxidative Med. Cell. Longev. 2020 https://doi.org/10.1155/2020/5693572.

Trueb, R.M., 2002. Molecular mechanisms of androgenetic alopecia. Exp. Gerontol. 37, 981–990.

Tsuji, Y., Denda, S., Soma, T., Raftery, L., Momoi, T., Hibino, T., 2003. A potential suppressor of TGF-β delays catagen progression in hair follicles. In: Proceedings of the Journal of Investigative Dermatology Symposium Proceedings, Vol. 8. Blackwell Publishing Inc., pp. 65–68

Turanli, B., Gulfidan, G., Arga, K.Y., 2017. Systems biomedicine: from genome scale molecular networks to efficacious biomarkers and therapeutic targets. In: Res. Sci. Art 21st Century Turkey, 2, pp. 2380–2388.

Turanli, B., Gulfidan, G., Arga, K.Y., 2017. Transcriptomic-guided drug repositioning supported by a new bioinformatics search tool: GeneXpharma. OMICS 21, 584–591. https://doi.org/10.1089/omi.2017.0127.

Turanli, B., Karagoz, K., Gulfidan, G., Sinha, R., Mardinoglu, A., Arga, K.Y., 2019. A network-based cancer drug discovery: from integrated multi-omics approaches to precision medicine. Curr. Pharm. Des. 24, 3778–3790. https://doi.org/10.2174/1381612824666181106095959.

Turanli, B., Yildirim, E., Gulfidan, G., Arga, K.Y., Sinha, R., 2021. Current state of "omics" biomarkers in pancreatic cancer. J. Pers. Med. 11, 1–24. https://doi.org/10.3390/jpm11020127.

Turanli, B., Altay, O., Borén, J., Turkez, H., Nielsen, J., Uhlen, M., Arga, K.Y., Mardinoglu, A., 2021. Systems biology based drug repositioning for development of cancer therapy. Semin. Cancer Biol. 68, 47–58.

Wang, E., Lee, J.S.S., Hee, T.H., 2012. Is Propionibacterium acnes associated with hair casts and alopecia. Int. J. Trichology 4, 93–97. https://doi.org/10.4103/0974-7753.96907.

Wang, E.C.E., Dai, Z., Christiano, A.M., 2018. Novel therapies for alopecia areata: the era of rational drug development. J. Allergy Clin. Immunol. 141, 499–504. https://doi.org/10.1016/j.jaci.2017.10.028.

Welker, P., Foitzik, K., Bulfone-Paus, S., Henz, B.M., Paus, R., 1997. Hair cycle-dependent changes in the gene expression and protein content of transforming factor β1 and β3 in murine skin. Arch. Dermatol. Res. 289, 554–557. https://doi.org/10.1007/s004030050239.

Welle, M.M., Wiener, D.J., 2016. The hair follicle: a comparative review of canine hair follicle anatomy and physiology. Toxicol. Pathol. 44, 564–574. https://doi.org/10.1177/0192623316631843.

Whiting, D.A., 2001. Possible mechanisms of miniaturization during androgenetic alopecia or pattern hair loss. J. Am. Acad. Dermatol. 45, 81–86. https://doi.org/10.1067/mjd.2001.117428.

Whiting, D.A., Waldstreicher, J., Sanchez, M., Kaufman, K.D., 1999. Measuring reversal of hair miniaturization in androgenetic alopecia by follicular counts in horizontal sections of serial scalp biopsies: results of finasteride 1 mg treatment of men and postmenopausal women. J. Investig. Dermatol.Symp. Proc. 4, 282–284. https://doi.org/10.1038/sj.jidsp.5640230.

Zhou, Z., Song, S., Gao, Z., Wu, J., Ma, J., Cui, Y., 2019. The efficacy and safety of dutasteride compared with finasteride in treating men with androgenetic alopecia: a systematic review and meta-analysis. Clin. Interv. Aging 14, 399–406. https://doi.org/10.2147/CIA.S192435.