Genes involved in hair follicle cycle of cashmere goat

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Abstract

The hair follicle (HF) is central to most economically important fiber growth in livestock. However, the changes in expression of genes that drive these processes remain incompletely characterised. As model animal of hair biology, cashmere goat might help deciphering genes involved in primary and secondary HF of skin. We used RNA-seq to study gene expression profiles of HF including anagen, catagen and telogen in Nei Mongol Cashmere Goat (NMCG), which will increase our understanding of HF biology and contribute to the development of strategies to improve cashmere. Exome data from 7 secondary HFs and 11 primary HFs in NMCGs was mined. 22,176 annotated genes in reference genome were evaluated, 7481 of which were shown to be expressed in HFs. Join together, 1923 of 7481 were expressed in all HFs, 3219 and 2339 of which were co-expressed in primary and secondary HFs exclusively. GO analysis showed that GO: (0044464, 0003824, 0032501, 0032502) were associated gene sets. High expressed gene in secondary and primary HFs are mainly involved in 14 GO categories which included in above mentioned GO items. High expressed genes in two type HFs of 1923 are mainly located in CHI 7, 18 and 19 ($p<0.01$). Genes located in 4.6~4.9 Mb of CHI1 might be one gene cluster which has important function in HF development. Six SNPs related to hair follicle based on ~30K polymorphism loci different from reference, were functionally identified in CHI 1 and 19 respectively. Compare to secondary HF, primary HF expresses more genes to deal with stimulations from all-environment. Additionally, 13 HF specific expressed genes were identified according to comparative transcriptome (28) analysis.

Keywords: RNA-seq, hair follicle, goat, comparative transcriptome

Introduction

In mammals, hair follicles undergo recurrent cycling of controlled growth (anagen), regression (catagen), and relative quiescence (telogen) with a defined periodicity. Characterizing gene expression in hair follicles can help to elucidate the hair growth cycle by delineating the genes and pathways involved in follicular growth and degeneration. Evolutionarily conserved hair follicle cycling is thought to provide mechanisms for controlling the length of hair in specific body sites, and to allow the periodic shedding of fur

in response to seasonal changes in mammals. Although components of numerous molecular pathways, including TGFβ/BMP family members and their antagonists, FGFs and steroid hormone receptors, have been implicated in the control of hair follicle cycling, the underlying mechanisms regulating its timing remain elusive. Cashmere goat is the good model to decipher hair follicle biology due to its second hair follicle undergo a very different cycling from primary hair follicle.

Taking a genomics approach to study gene expression during hair follicle cycling, scientists working in mouse discovered that, in addition to circadian fluctuation, CLOCK–regulated genes are also modulated in phase with the hair growth cycle (Kevin et al, 2009). While circadian clock mechanisms have been implicated in a variety of diurnal biological processes, the findings indicate that circadian clock genes may be utilized to modulate the progression of non-diurnal cyclic processes also. Comparing to mouse, more cashmere goat works focused on candidate genes which discovered in other mammals, due to lack of reference genome of goat. MicroRNAs (miRNAs) are non-coding conserved short nucleotides that exhibit a unique function as translational suppressors towards a wide realm of mRNAs. To date, a specific set of miRNAs has been characterized by our team as hair related regulators based on their expression levels and/or target mRNA functions; however, a comprehensive view of the changes in miRNA expression regulated by pivotal cellular signaling mechanisms remains elusive due to lack of robust miRNA-mRNA interaction mining in mammal. To discover hair follicle related gene in goat is the first task faced by cashmere goat researchers.

The objectives of this study were to determine whether intact RNA could be extracted from a small number of plucked, unstaged hair follicles in sufficient quantity to conduct transcriptome study, and to conduct global gene expression profiling. To this end, RNA was extracted from individual unstaged follicle plucked from the back side skin of cashmere goats. Taken together, our results suggest that a unique subset of mRNAs could have an integrating effect on upstream pivotal transcriptional regulators influencing decisions regarding proper cellular responses.

Material and Methods

To uncover the genome-wide landscape of gene expression during hair follicle cycling, we performed whole transcriptome analysis for 12 primary hair follicles and 12 secondary hair follicles. RNA-seq analysis was successfully realized on total RNA from 7 secondary hair follicles and 11 primary hair follicles which plucked from Nei Mongol Cashmere Goats back skin (Sung et al, 2006; Fu et al, 2012). All the 22,176 annotated genes in reference genome (Dong et al, 2012) were evaluated, 7481 of which were shown to be expressed in hair follicles.

Results

One third of annotated goat reference genes are periodically expressed in phase with the hair growth cycle

Join all RNA-Seq of hair follicles, 1923 of 7481 were expressed in all hair follicles, 3219 and 2339 of which were co-expressed in primary and secondary hair follicles exclusively (Figure 1).

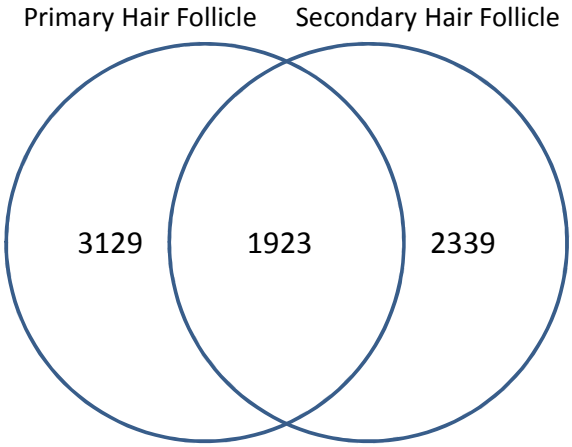

Figure 1. *Venn diagram of expressed genes of two different hair follicle in cashmere goat skin*

Remarkably, this genome-wide landscape grouped together many of the key genes previously shown to be functionally important during hair follicle morphogenesis and/or cycling, such as genes which found in mice and goats before: hair follicle density (Lef1, Msx1, Msx2, Sox18, Trps1), structure (KAPs, KPs, Dlx3, Foxn1, Foxq1, Hoxc13, Notch1, Ovol1, Runx1), morphogenesis (Ctnnb1, Cutl1, Gli2, Lef1, Msx2, Smad7), and cycling (Hr, Msx2, Stat3, Vdr). GO analysis showed that GO: (0044464, 0003824, 0032501, 0032502) were associated with the three different expressed gene sets (Figure 2). Among the 1923 co-expressed genes, high expressed gene in secondary and primary hair follicles are mainly involved in 14 GO categories which included in above mentioned GO items (Figure 2).

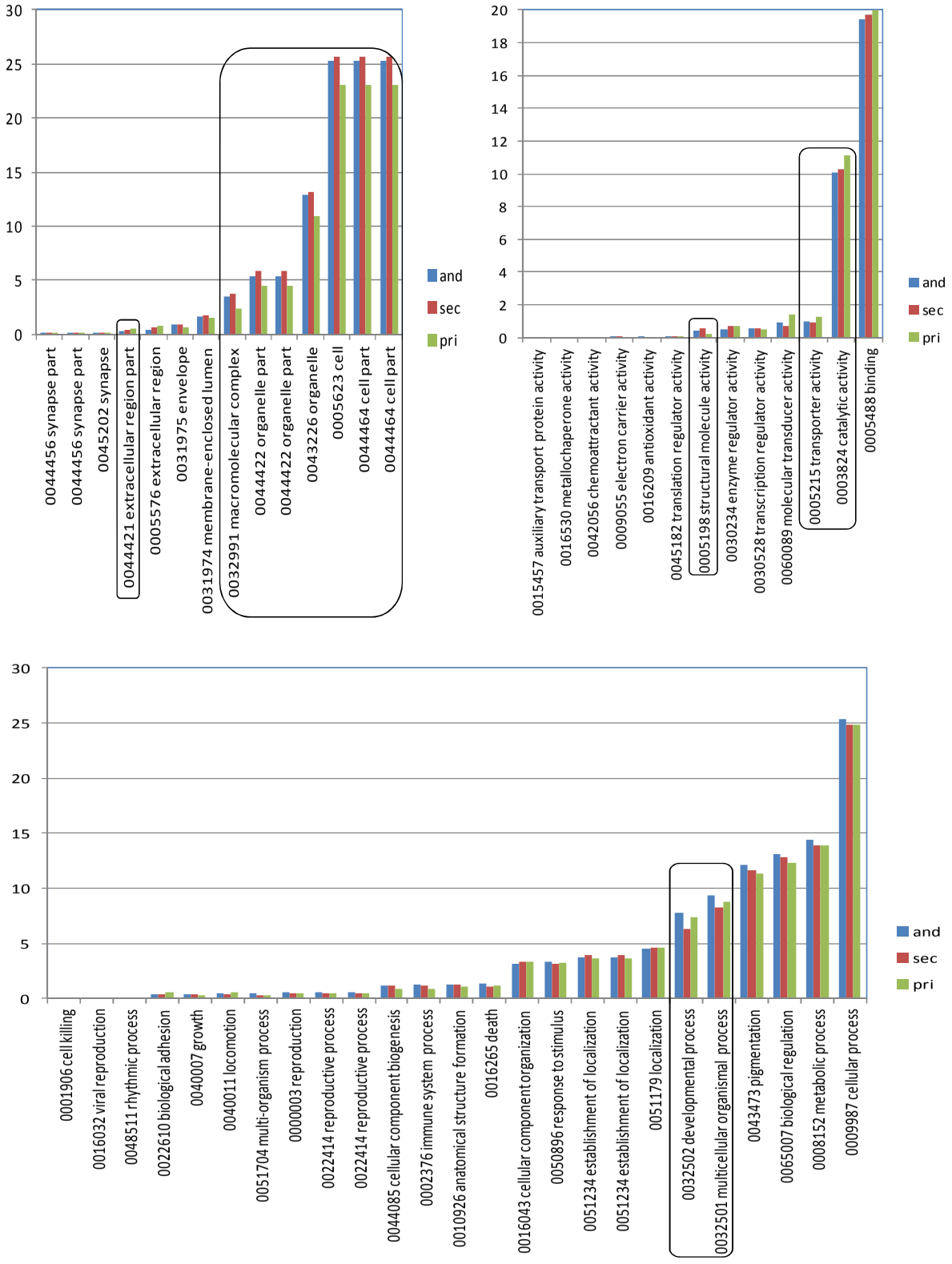

Figure 2. *Gene Ontology annotation of co-expressed and specific expressed gene in primary and secondary hair follicle (left: cc,right: mf, bottom: bp)*

Distinct functional groups of genes are activated at different phases of hair follicle cycling

To identify genes which are activated (highly expressed) at specific hair follicle, we performed statistical differential analysis of hair follicle dependent-regulated genes by comparing the expression from one to the other. We then searched for significantly enriched Gene Ontology (GO) Biological Process categories within the different sets of genes upregulated at specific hair follicle. Among the genes upregulated at primary hair follicle is a significantly overrepresented number of biological regulation process genes, as well as other genes that are required during development and proliferation (Figure 3). Many of the other enriched functional categories are also expected based on our current knowledge of hair follicle biology, validating the value of this approach. In addition to identifying several pathways known to be involved in hair follicle regulation, our enrichment analysis identified functional categories that were unexpected, potentially providing novel insights into regulation of hair follicle cycling. For instance, we found significantly enriched group of genes annotated with the function of immune system process and pigmentation, suggesting that many active molecular processes are occurring during different hair follicle cycling. Hair follicle specific expressed genes based on 28 transcriptome of goat are shown in Table 1. These data show that primary hair follicle expresses more genes to deal with stimulations than secondary hair follicle, although they are widely expressed within hair follicles throughout hair follicle cycling.

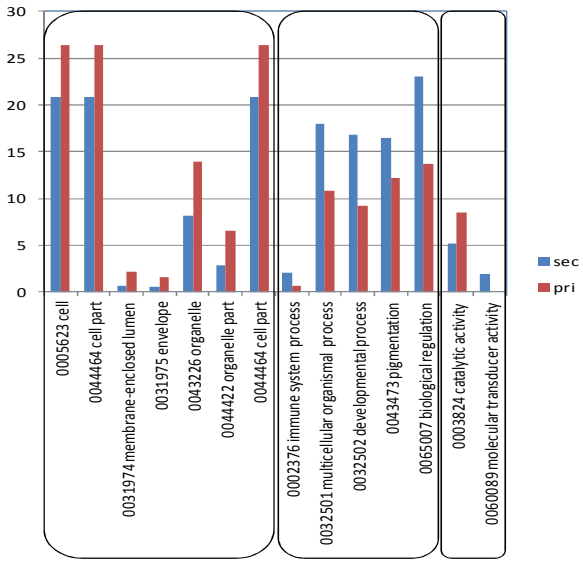

***Figure 3**: Gene ontology enrichment analysis of high expressed genes in both hair follicles (left: cc, middle: bp, right: mf)*

Table 1: *Hair follicle specific expressed genes based on 28 transcriptome of goat*

No.	Corresponding Homolog
1	ENSBTAP00000004707
2	ENSBTAP00000006318
3	ENSBTAP00000014138
4	ENSBTAP00000018403
5	ENSBTAP00000023511
6	ENSBTAP00000044431
7	ENSP00000243056
8	ENSP00000339238
9	ENSP00000341584
10	ENSP00000347635
11	ENSP00000353742
12	ENSP00000364609
13	ENSP00000367891

Identification of conserved expressed genes during hair follicle cycling from expression profiles

To investigate the molecular control of hair follicle, we profiled conserved (co-expressed in both hair follicles) mRNA expression in hair follicle of goat back side skin at multiple time points in un-phased hair growth cycle. To detect genes with conserved expression (regardless fold changes) over multiple hair growth cycles, we constructed a Boolean model within background components. The background component includes a mixture model of shared periodic expression profiles and allows deviation from perfect periodicity due to initial hair follicle morphogenesis. Given this model structure and observed data, we used Boolean inference techniques to motif of GRN for each of the hair follicles. Based on Boolean network analysis, high expressed genes in two type hair follicles of 1923 are mainly located in chromosome 7, 18 and 19 ($p<0.01$) as shown in Table 2. The 1923 genes were more enriched expressed in primary hair follicles than secondary hair follicles ($p=0.062$). Genes located in 4.6~4.9 Mb of chromosome 1 might be one gene cluster which has similar function in hair follicle development. Co-expressed genes are enriched in gene cluster and might act as an attractor or basin in hair follicle gene regulation network.

Table 2. *Chromosome distribution of genes which highly expressed in both hair follicles*

Chr	Secondary Hair Follicles							Primary Hair Follicles											Sum
1	7	7	12	6	4	9	6	27	9	35	11	11	32	31	12	38	7	5	269
2	31	28	42	30	30	37	33	75	25	80	28	29	66	63	24	84	31	33	769
3	27	16	30	19	30	31	30	63	31	71	23	25	71	74	34	77	24	29	705
4	18	18	28	17	28	23	24	45	20	50	15	15	48	44	16	57	16	21	503
5	40	27	40	32	45	40	38	65	32	71	23	20	69	62	22	74	31	37	768
6	15	11	18	11	15	13	14	38	14	41	10	15	37	36	18	42	14	14	376
7	70	50	86	44	80	83	81	121	37	132	32	19	112	108	32	134	52	65	1338
8	27	15	27	15	30	24	22	48	22	52	15	12	49	49	23	58	15	22	525
9	5	8	12	8	8	8	9	26	10	27	10	11	22	24	12	30	10	9	249
10	32	24	41	30	38	31	43	80	30	86	33	28	78	78	31	94	33	38	848
11	29	30	37	31	34	31	35	80	28	79	37	20	67	66	20	82	33	34	773
12	3	5	9	6	9	10	10	19	8	19	11	7	19	19	6	21	8	9	198
13	46	35	39	28	47	46	44	74	24	78	28	15	69	68	17	89	26	37	810
14	11	13	16	14	11	15	15	35	17	39	9	9	31	33	16	41	12	15	352
15	10	7	13	8	12	17	11	25	8	24	8	9	23	23	9	28	6	9	250
16	44	35	56	37	42	40	34	90	30	95	28	23	79	75	24	102	30	34	898
17	33	20	30	27	32	33	29	50	20	54	18	13	45	48	15	56	28	30	581
18	59	29	71	35	69	67	66	107	41	106	34	28	98	91	33	111	40	59	1144
19	55	41	61	48	62	57	55	104	38	113	28	21	92	90	30	114	49	49	1107
20	2	3	4	4	4	4	3	12	4	14	2	4	9	10	6	14	3	2	104
21	23	19	24	16	23	19	20	50	21	49	13	14	41	40	20	52	22	25	491
22	42	30	44	24	45	39	40	82	26	82	25	16	76	74	16	89	29	38	817
23	45	32	50	33	39	41	41	64	23	72	18	10	62	60	20	78	32	31	751
24	11	12	16	7	8	11	9	38	15	38	11	13	29	31	11	44	10	13	327
25	34	31	33	29	31	30	34	53	13	51	19	11	44	40	7	56	28	31	575
26	6	9	11	10	7	10	8	26	8	26	10	10	25	19	8	30	7	6	236
27	6	4	4	3	4	3	4	8	1	10	3	3	8	8	2	10	4	2	87
28	10	12	10	13	11	8	14	36	15	42	18	16	36	39	17	42	13	13	365
29	31	14	35	21	41	36	36	49	22	56	13	9	52	45	15	60	20	29	584
X	11	11	18	11	4	10	16	31	15	38	15	17	35	36	18	42	13	13	354
UN	17	12	17	12	15	15	14	23	6	23	5	3	16	15	7	21	14	12	247
Sum	800	608	934	629	858	841	838	1644	613	1753	553	456	1540	1499	541	1870	660	764	17401

Discussion

Skin and appendages such as hair follicles are attractive candidates for gene therapy targets because they are easily accessible and can be removed and genetically manipulated in culture. Hair follicles are of special interest because our understanding of hair follicle biology and pathophysiology has progressed significantly in recent years, and we now have a much better understanding of how genes, encoding transcription factors, growth factors, and cytokines regulate both hair follicle development and the cycles of hair follicle growth. As our understanding of the polygenic basis for a number of fiber traits, gene-based selection might also be designed to provide more promising performance than current classic estimated breeding value for cashmere. This work will promote some of the recent progress in gene delivery to hair follicles (Manabu et al, 2003) and gene based selection can cause phenotypic changes in hair follicles and cashmere traits. Additional targets include RORs (Rora, Rorb, and Rorc), which are members of a subfamily of orphan nuclear receptors that bind to ROR response elements (RREs) to transcriptionally activate, but also they are thought to mediate many of its physiological effects. RNA-seq analysis will benefit to construct the whole map of the GRN in hair follicle biology.

Gene expression profiling has become an increasingly important tool for: understanding how

cells and tissues function under normal conditions; elucidating molecular mechanisms associated with aging and trait development and progression; and characterizing the responses to stimulations come from environment. Several groups have used microarray and quantitative realtime polymerase chain reaction (qRT-PCR) to characterize gene expression profiles in hair follicles and skin. Most of this work has been focused on identifying hair follicle cycle-associated genes and elucidating the mechanisms of epithelial stem cell differentiation and proliferation. The ultimate aim of such studies is to understand hair growth in order to provide potential targets for the treatment of hair loss in human and genetic markers for improve fiber traits in animal. The average quantifiable yield of RNA/follicle was ~100ng. Ribosomal ratios were lower than normally expected, but investigation indicated the RNA was intact. The samples were amplified in the follow up whole transcriptome procedure. However, if gene expression profiling of hair follicles is to be used routinely as a tool for clinical analysis, research, or forensic studies, it is important to develop simple, robust methods for the collection, storage, transportation, and analysis of samples.

In summary, our findings demonstrate a novel role for hair follicle gene in modulating the progression of the hair growth cycle, a cyclic biological process that has a much longer duration than the diurnal period. Changes in the stability of conserved expressed gene in both hair follicles can offset mRNA changes, and this can potentially explain the different hair follicle cycle. Another possible explanation is that the mRNAs of core hair follicles are fluctuating less dramatically between the different hair cycle phases. However, we were unable to test whether the protein level changes similarly to the transcript during hair follicle cycling. In future investigations, we plan to study the levels and localization of transcripts and proteins throughout the hair growth cycle.

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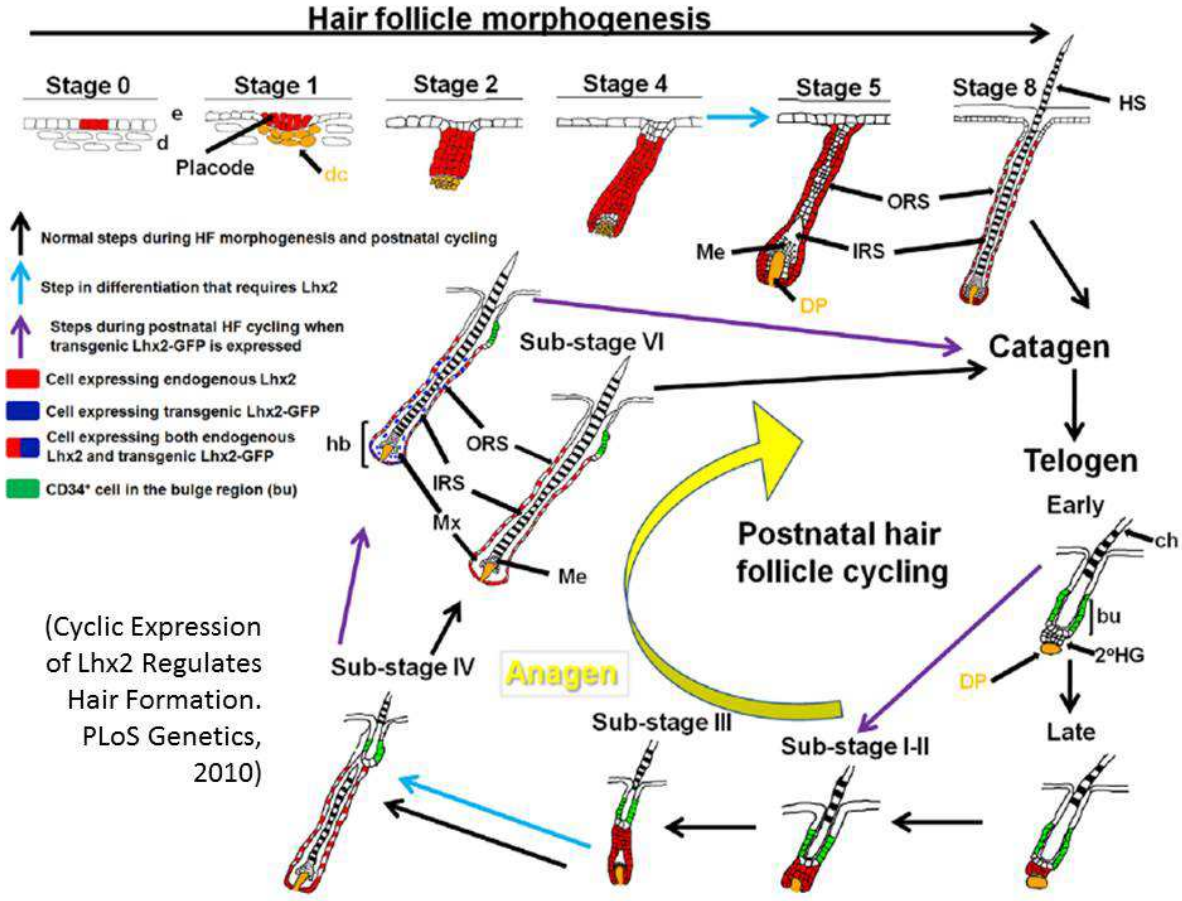
Introduction

- Hair is important for temperature regulation, physical protection, sensory activity, seasonal camouflage, and social interactions. Hair is formed in hair follicles, which are complex mini-organs in the skin that are specialized for this purpose. All hair follicles are formed during fetal development, then new hair is generated in the hair follicle by continually undergoing phases of active growth (anagen), regression/recession (catagen), and inactivity /rest (telogen) throughout life.
- The length of the hair is determined by the duration of the growth phase; for example, the growth phase for scalp hair can proceed for a number of years, while the growth phase for eyebrows last a few months.
- Hair follicle cycle of down hair and guard hair is different in cashmere goat. After the growth phase, hair formation ceases, and the follicle recedes and enters a period of rest. After a period of rest, a new growth period starts, and the old hair is ejected and lost from the body. The reason for this complex regulation of hair growth is not understood, but it has been suggested that it makes it possible to adjust hair growth to the season.

- Lhx2 is a gene that is important for the regulation of hair growth.
  - Leif Carlsson's research team identifies the transcription factor Lhx2 as an important regulator of hair formation. The Lhx2 gene is active during the hair follicle's growth phase and is turned off during the resting period. The scientists have been able to show that Lhx2 is functionally involved in the formation of hair, as hair follicles in which Lhx2 has been inactivated cannot produce hair. Moreover, the activation of the Lhx2 gene in hair follicles has been shown to activate the growth phase and hence the formation of hair.
  - Lhx2 is primarily expressed outside the so-called bulge region of the hair follicle, where the follicle's stem cells are found. Moreover, transgenic expression of Lhx2 after birth is sufficient to activate the growth phase and stimulate hair growth.



(Cyclic Expression of Lhx2 Regulates Hair Formation. PLoS Genetics, 2010)

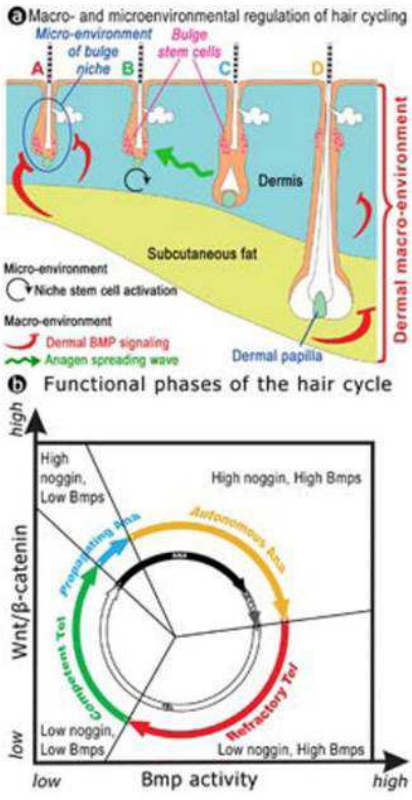
- The mammalian hair follicle is a complex 'mini-organ' thought to form only during development; loss of an adult follicle is considered permanent. However, the possibility that hair follicles develop de novo following wounding was raised in studies on rabbits, mice and even humans fifty years ago. Subsequently, these observations were generally discounted because definitive evidence for follicular neogenesis was not presented. After wounding, hair follicles form de novo in genetically normal adult mice. The regenerated hair follicles establish a stem cell population, express known molecular markers of follicle differentiation, produce a hair shaft and progress through all stages of the hair follicle cycle. Lineage analysis demonstrated that the nascent follicles arise from epithelial cells outside of the hair follicle stem cell niche, suggesting that epidermal cells in the wound assume a hair follicle stem cell phenotype. Inhibition of Wnt signalling after re-epithelialization completely abrogates this wounding-induced folliculogenesis, whereas overexpression of Wnt ligand in the epidermis increases the number of regenerated hair follicles. These remarkable regenerative capabilities of the adult support the notion that wounding induces an embryonic phenotype in skin, and that this provides a window for manipulation of hair follicle neogenesis by Wnt proteins. These findings suggest treatments for wounds, hair loss and other degenerative skin disorders.

(Wnt-dependent de novo hair follicle regeneration in adult mouse skin after wounding. Nature. 2007)

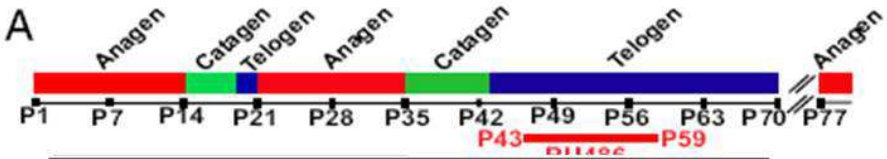
- Hair follicles form during embryonic development and, after birth, undergo recurrent cycling of growth, regression, and relative quiescence. As a functional mini-organ, the hair follicle develops in an environment with dynamic and alternating changes of diverse molecular signals. Over the past decades, genetically engineered mouse models have been used to study hair follicle morphogenesis and significant advances have been made toward the identification of key signaling pathways and the regulatory genes involved. In contrast, much less is understood in signals regulating hair follicle regeneration. Like hair follicle development, hair follicle regeneration probably relies on populations of stem cells that undergo a highly coordinated and stepwise program of differentiation to produce the completed structure.

(Dynamic Signals for Hair Follicle Development and Regeneration. Stem Cells and Development. 2012)

- Canonical WNT signals play an important role in hair follicle development. In addition to being crucial for epidermal appendage initiation, they control the interfollicular spacing pattern and contribute to the spatial orientation and largely parallel alignment of hair follicles. However, owing to the complexity of canonical WNT signalling and its interconnections with other pathways, many details of hair follicle formation await further clarification.



(Cyclic dermal BMP signalling regulates stem cell activation during hair regeneration. Nature. 2008)

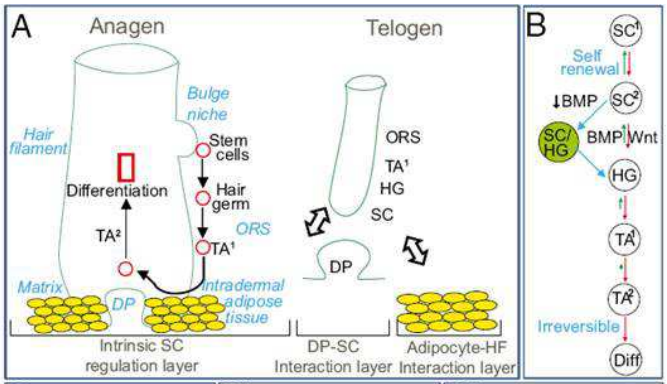


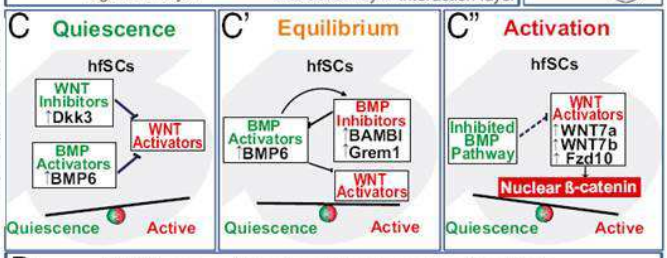
M — Hair Germ Signature

	Down-regulated genes	Up-regulated genes
Cell Cycle	Arrest: Pmp22(-9x), Nbl1(-6x; -2x), Gas1(-3x);Sesn1(-2x)	Progression: Gsg2(30x), Mki67(14x) Cks2(11x), Ccnb1-rs1(9x), Ccnb1(9x; 2x), Ccna2(8x), Cdc2a(5x), Ccnl1(4x) Ccnb2(4x), Ccnd2(4x), Wee(4x), Ccnl2(3x), Csnk2a2(3x), Ccnd1(2x)
Signaling	FGF18(-239x; -6x), Sfrp(-73x; -2x), BMP6(-37x; 3x), Grem1(-18x; -3x), Fzd2(-15x; -4x; -2x; -2x), Ppa2a(-15x; -2x; -2x), Dkk3(-9x; -3x; -3x), Sema3e(-7x), Fzd7(-5x), Lgr5(-5x; -9x; -5x), Ltbp2(-4x; -11x), Ltbp3(-3x; -3x), Ltbp4(-3x), Fzd3(-3x; -2x; -2x), Fst(-2x)	Areg(223x; 5x), Ptgs1(90x), Wnt5a (49x), S100A8(49x; 6x), S100A9(34x; 5x), Wnt16(26x; 2x), Clca1(21x), Clca2(11x), HbEGF(20x; 7x; 4x), Lrp4(7x), Map4K5(6x), Ptgs2(5x), Map3K12(5x), Hmgn3(3x), Axin2(3x), Wnt10a(2x), Wnt4a(2x)
Transcription Factors	Id2(-52x; -9x; -2x), Lhx2(-9x), NFATc1(-8x; 2x), Sox9(-6x), Id3(-5x; -3x), Id4(-5x), Vdr(-3x), Tcf3(-3x), Nfib(-2x)	Sox6(37x), Ovo1(24x), Ap2y(16x), Sox7(6x), Sox4(5x), Cox5a(3x), Mybl2(3x), Fosb(3x; 3x), Skp2(3x), Klf5(3x), Gata(3x)
ECM / Cell Adhesion	CD34(-776x; -5x), Col6a1(-26x; -3x), Ecm1(-9x; -2x), Pnf2(-5x), cdh13(-4x), S100A6(-3x), Macf1(ACF7)(-2x)	Cdh4(6x), Col16a1(4x), Col20a1 (3x; -6x; -3x), Col4a5(2x)

Overlapping cKO^{RU}/HG down-regulated gene
Oppositely regulated cKO^{RU}/HG gene
Overlapping cKO^{RU}/HG up-regulated gene
Overlapping Wnt/HG up-regulated gene
Overlapping cKO^{RU} / Wnt HG up-regulated gene

Competitive balance of intrabulge BMP/Wnt signaling reveals a robust gene network ruling stem cell homeostasis and cyclic activation. PNAS. 2013





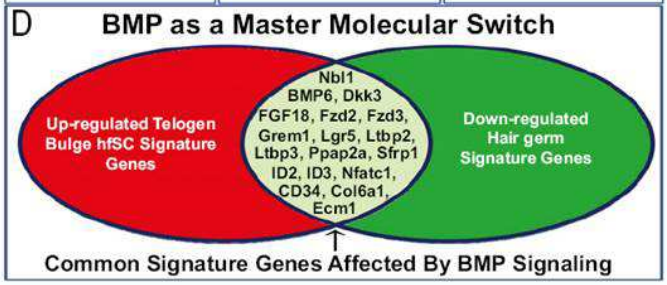
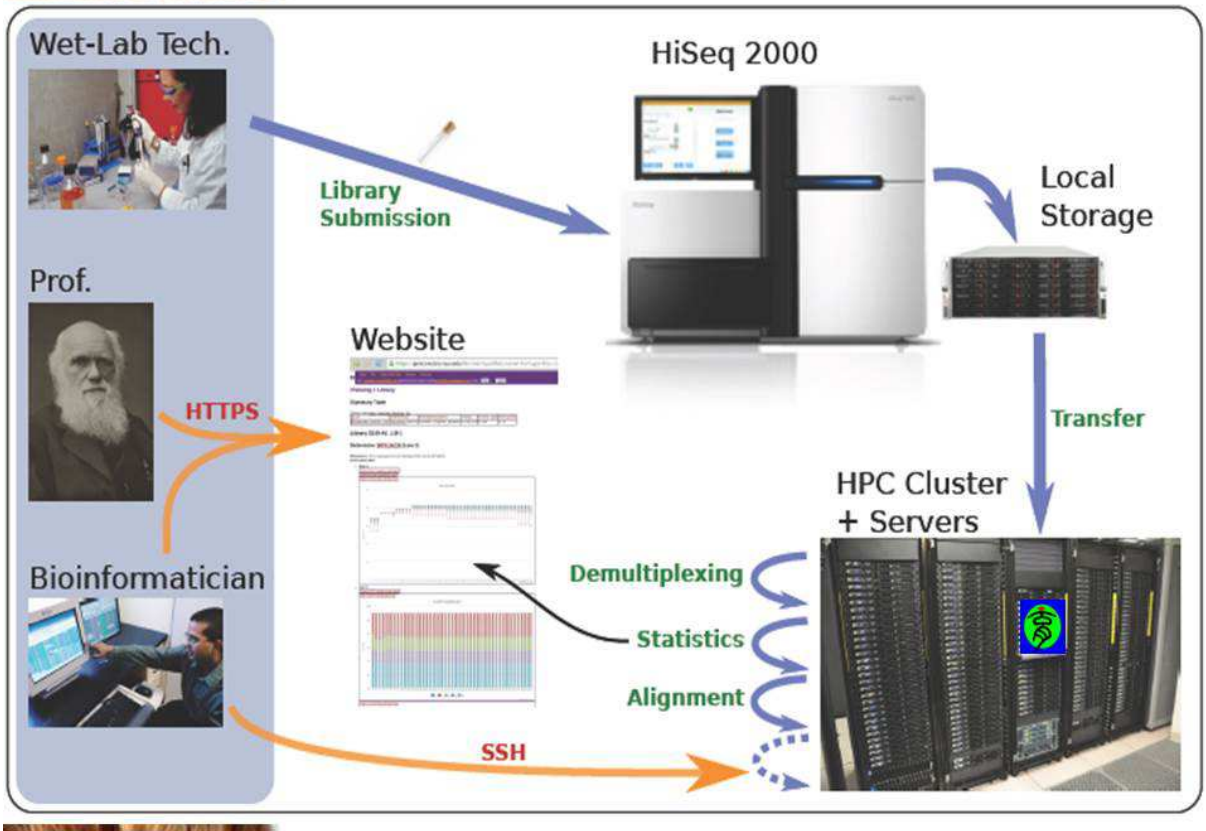


Fig. 5. Model of intrinsic mechanism of ligand–receptor-dependent cross talk between BMP and Wnt signaling in hfSC homeostasis regulation. (*A*) An intrinsic SC regulation layer acts as a third hierarchical layer regulating hfSC homeostasis along with the DP–SC interaction layer and HF–adipocyte interaction layer. (*B*) Schematic of transient activated hfSCs after BMP inhibition reflects a new SC/HG status that shares properties between SC and HG states and may be very temporary in vivo. (*C–C''*) Proposed hypothesis of intrinsic constant competitive cycling between activator (Wnt) and inhibitor (BMP) activities in bulge hfSCs. (*D*) Common signature genes between bulge and HG affected by BMP signaling, which works as a master switch. Diff, differentiated cells; HG, hair germ; SC, stem cell; TA, transit amplifying.

RNA-Seq of Hair follicle

- The hair follicle (HF) is central to most economically important fiber growth in livestock. However, the changes in expression of genes that drive these processes remain incompletely characterised. As model animal of hair biology, cashmere goat might help deciphering genes involved in primary and secondary HF of skin. We used RNA-seq to study gene expression profiles of HF including anagen, catagen and telogen in Nei Mongol Cashmere Goat (NMCG), which will increase our understanding of HF biology and contribute to the development of strategies to improve cashmere.



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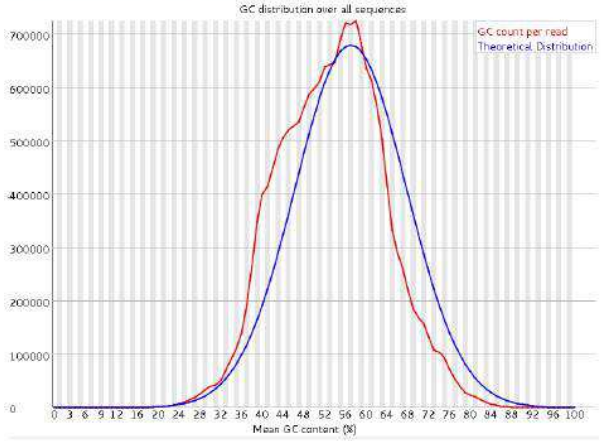

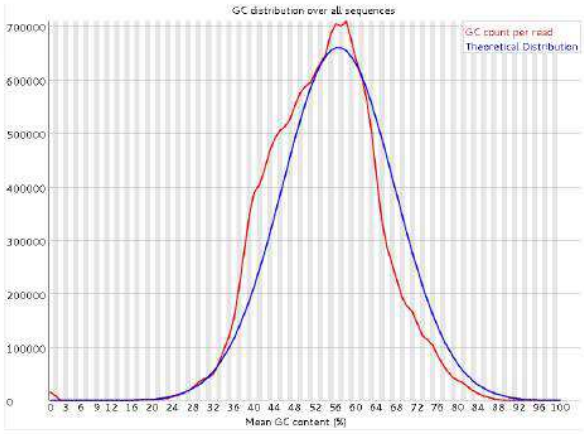

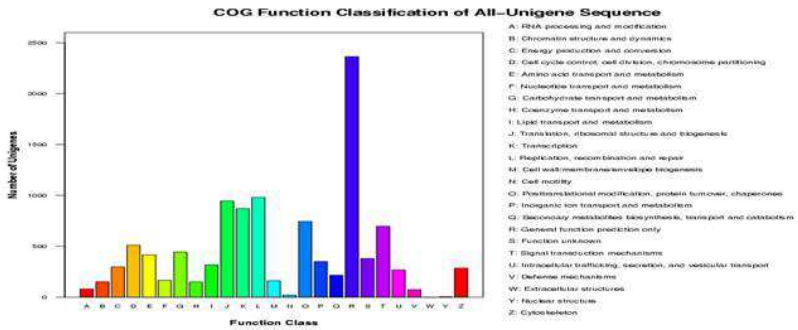

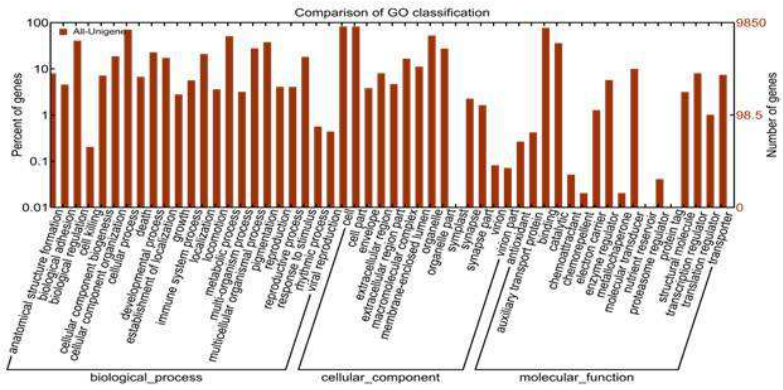

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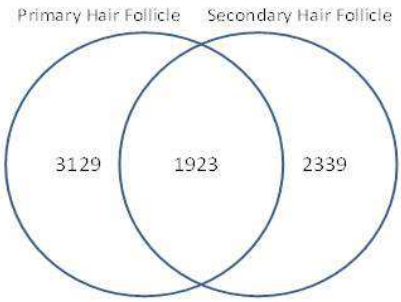
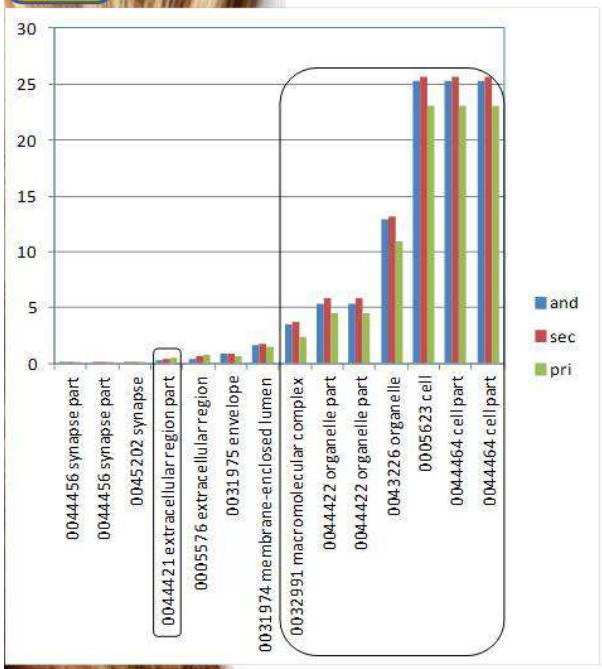
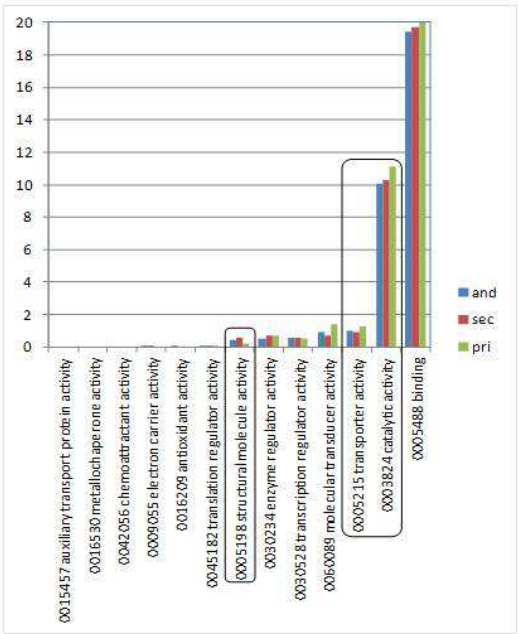
2

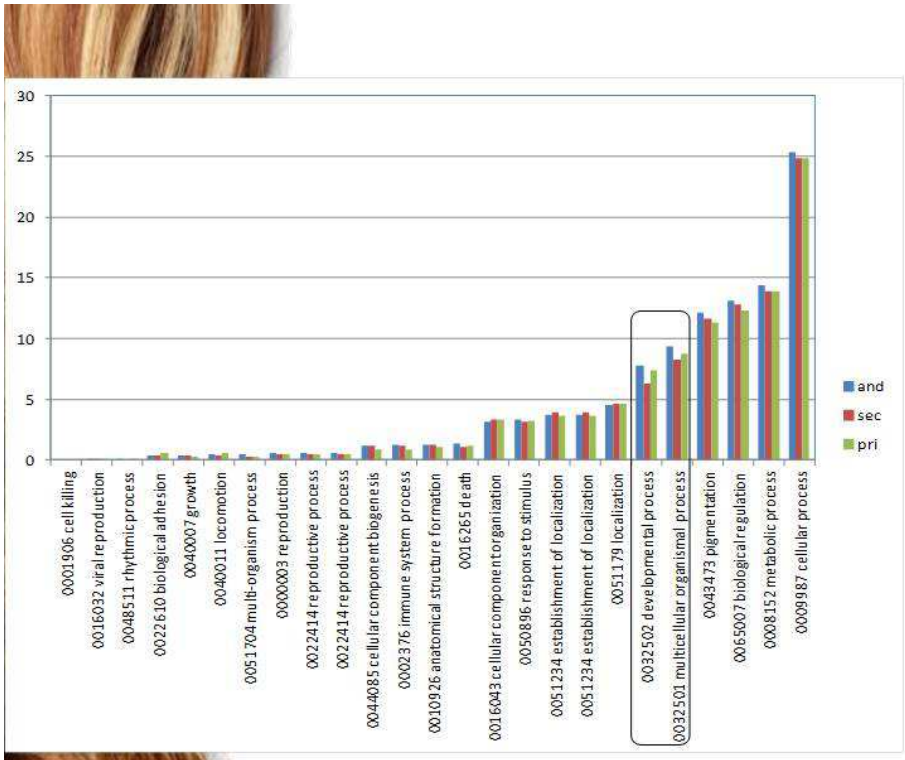


- Exome data from 7 secondary HFs and 11 primary HFs in NMCGs was mined. 22,176 annotated genes in reference genome were evaluated, 7481 of which were shown to be expressed in HFs. Join together, 1923 of 7481 were expressed in all HFs, 3219 and 2339 of which were co-expressed in primary and secondary HFs exclusively. GO analysis showed that GO: (0044464, 0003824, 0032501, 0032502) were associated gene sets. High expressed gene in secondary and primary HFs are mainly involved in 14 GO categories which included in above mentioned GO items.

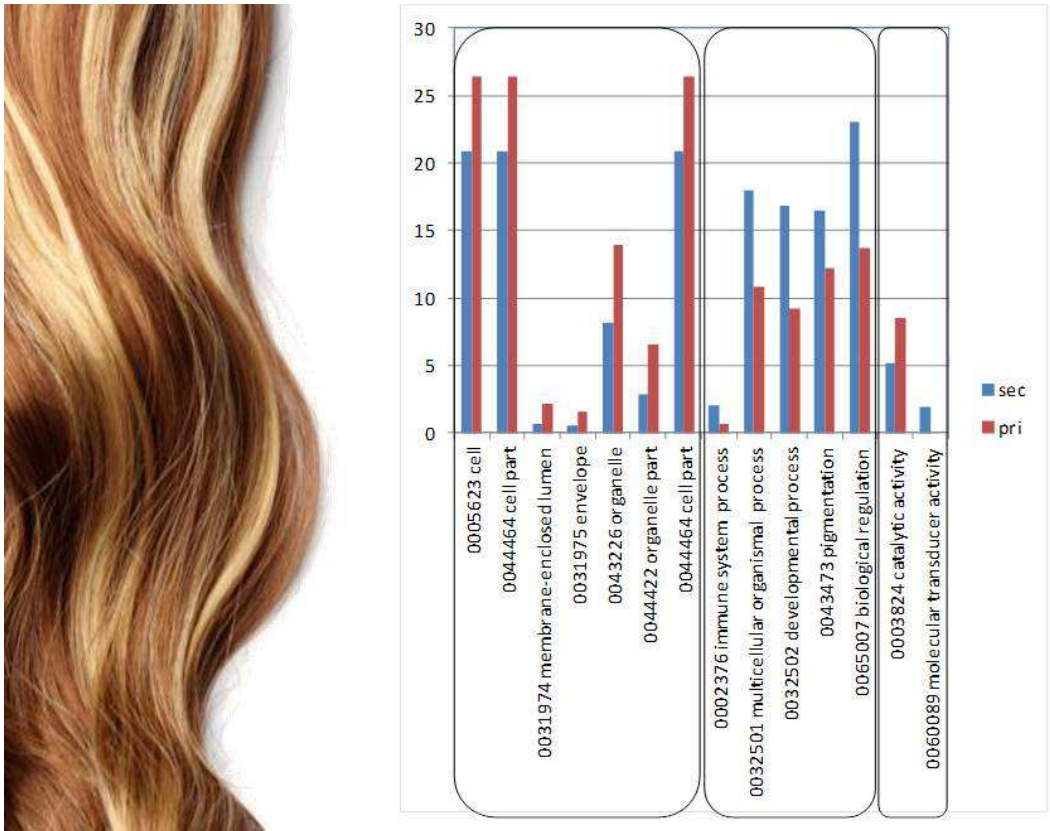
3







Gene Ontology annotation of co-expressed and specific expressed gene in primary and secondary hair follicle
(left: cc,right: mf, bottom: bp)



Gene Ontology annotation of high expressed gene in primary and secondary hair follicle (left: cc, middle: bp, right: mf)

4

High expressed genes in two type HFs of 1923 are mainly located in CHI 7, 18 and 19 (p<0.01).

Chr	Secondary Hair Follicles							Primary Hair Follicles											Sum
1	7	7	12	6	4	9	6	27	9	38	11	11	32	31	12	38	7	8	269
2	31	28	42	30	30	37	33	78	28	80	28	29	66	63	24	84	31	53	769
3	27	16	30	19	30	31	30	63	31	71	25	28	71	74	34	77	24	29	708
4	18	18	28	17	28	25	24	48	20	60	16	18	48	44	16	57	16	21	603
5	40	27	40	32	46	40	38	68	32	71	25	20	69	62	22	74	31	57	768
6	16	11	18	11	16	13	14	38	14	41	10	16	37	36	18	42	14	14	376
7	70	60	86	44	80	85	81	121	57	132	52	19	112	108	52	134	52	66	1338
8	27	18	27	16	30	24	22	48	22	52	16	12	49	49	23	88	16	22	626
9	8	8	12	8	8	8	9	26	10	27	10	11	22	24	12	30	10	9	249
10	32	24	41	30	38	31	43	80	30	86	33	28	78	78	31	94	33	38	848
11	29	30	37	31	34	31	35	80	28	79	37	20	67	66	20	82	33	34	773
12	3	6	9	6	9	10	10	19	8	19	11	7	19	19	6	21	8	9	198
13	46	35	39	28	47	46	44	74	24	78	28	16	69	68	17	89	26	37	810
14	11	13	16	14	11	18	18	36	17	39	9	9	31	33	16	41	12	15	362
15	10	7	13	8	12	17	11	26	8	24	8	9	23	23	9	28	6	9	260
16	44	35	56	37	42	40	34	90	30	98	28	23	79	76	24	102	30	34	898
17	33	20	30	27	32	33	29	80	20	84	18	13	46	48	16	86	28	30	681
18	69	29	71	38	69	67	66	107	41	106	34	28	98	91	33	111	40	69	1144
19	65	41	61	48	62	67	66	104	38	115	28	21	92	90	30	114	49	49	1107
20	2	3	4	4	4	4	5	12	4	14	2	4	9	10	6	14	5	2	104
21	23	19	24	16	23	19	20	50	21	49	13	14	41	40	20	62	22	28	491
22	42	30	44	24	46	39	40	82	26	82	28	16	76	74	16	89	29	38	817
23	48	32	50	35	39	41	41	64	23	72	18	10	62	60	20	78	32	31	781
24	11	12	16	7	8	11	9	38	16	38	11	13	29	31	11	44	10	13	327
25	34	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	56	28	31	878
26	6	9	11	10	7	10	8	26	8	26	10	10	26	19	8	30	7	6	236
27	6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	2	10	4	2	87
28	10	12	[illegible]	[illegible]	11	8	14	36	15	42	18	16	36	39	17	42	15	13	365
29	31	[illegible]	[illegible]	[illegible]	41	36	36	49	22	56	13	9	62	46	18	60	20	29	584
X	11	11	18	11	4	10	16	31	15	38	16	17	35	36	18	42	15	13	364
UN	17	12	17	12	18	18	14	23	6	23	8	3	16	15	7	21	14	12	247
Sum	800	608	904	629	888	841	858	1644	615	1785	885	486	1640	1499	841	1870	660	764	17401

The 1923 genes were more enriched expressed in primary hair follicles than secondary hair follicles (p=0.062).

5

Co-expressed genes are enriched in gene cluster and might act as an attractor or basin in hair follicle gene regulation network.

- Genes located in 4.6~4.9 Mb of CHI1 might be one gene cluster which has important function in HF development.
- Six SNPs related to hair follicle based on ~30K polymorphism loci different from reference, were functionally identified in CHI 1 and 19 respectively.
- Compare to secondary HF, primary HF expresses more genes to deal with stimulations from all-environment.
- Additionally, 13 HF specific expressed genes were identified according to comparative transcriptome (28) analysis.

Hair specific expressed gene list

ENSBTAP00000004707
ENSBTAP00000006318
ENSBTAP00000014138
ENSBTAP00000018403
ENSBTAP00000023511
ENSBTAP00000044431
ENSP00000243056
ENSP00000339238
ENSP00000341584
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ENSP00000364609
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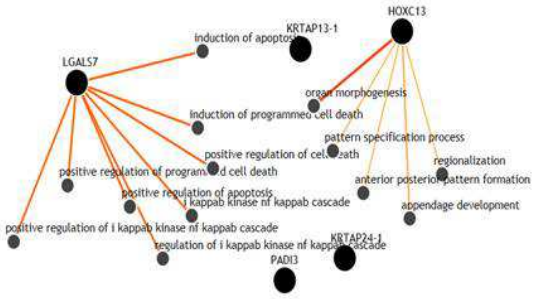
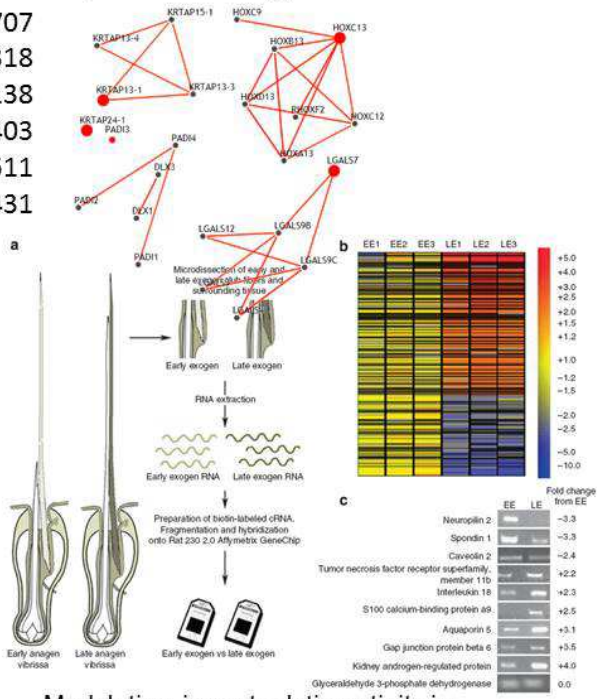
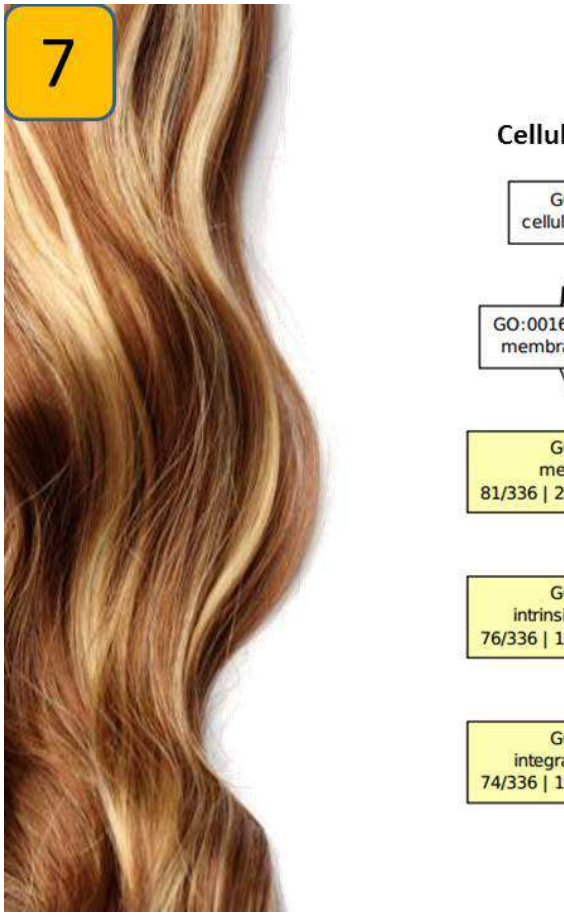
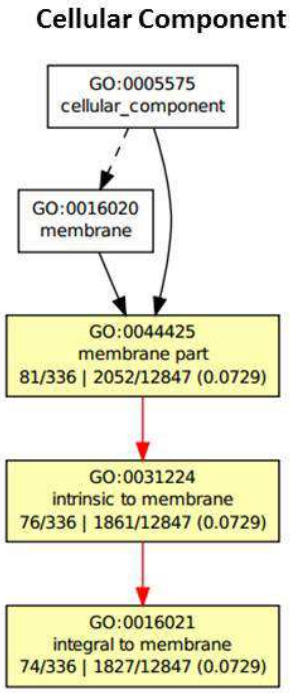
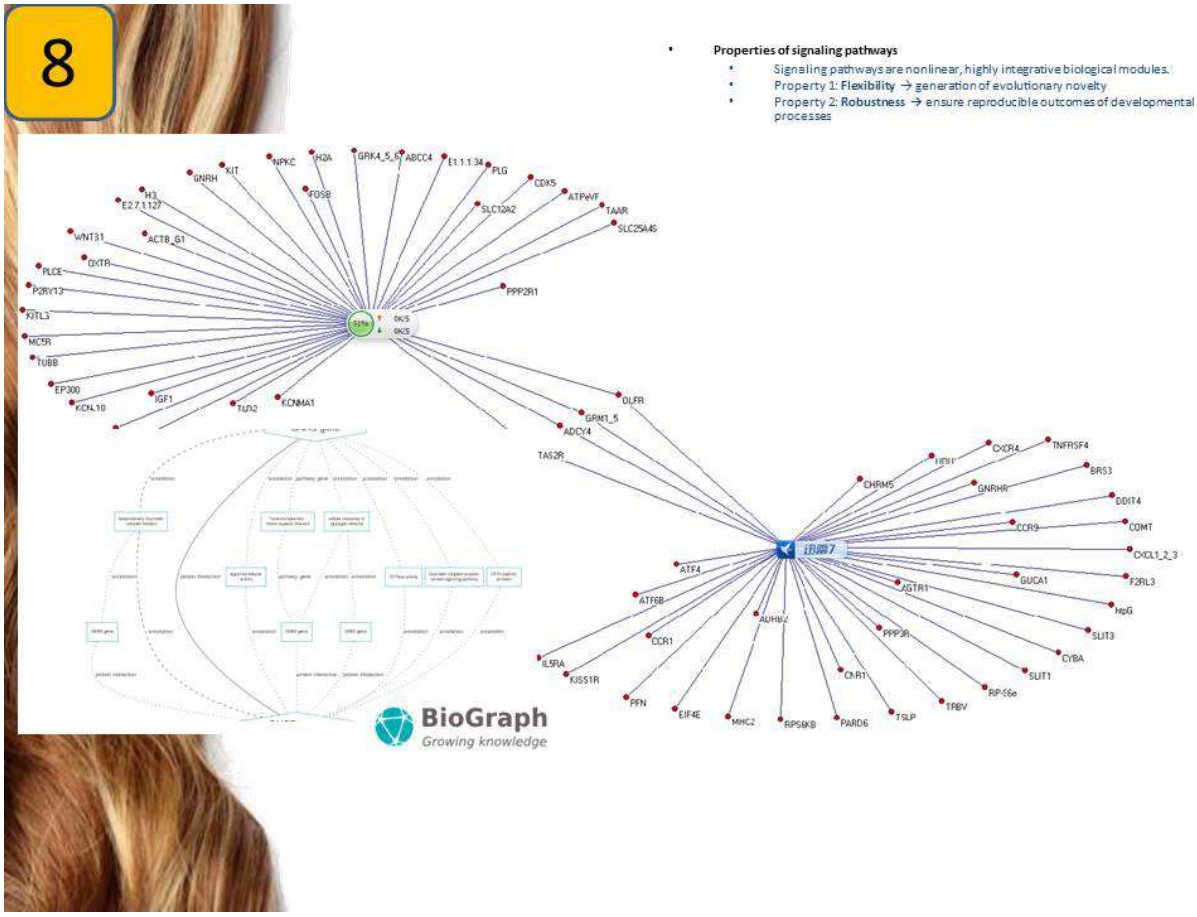


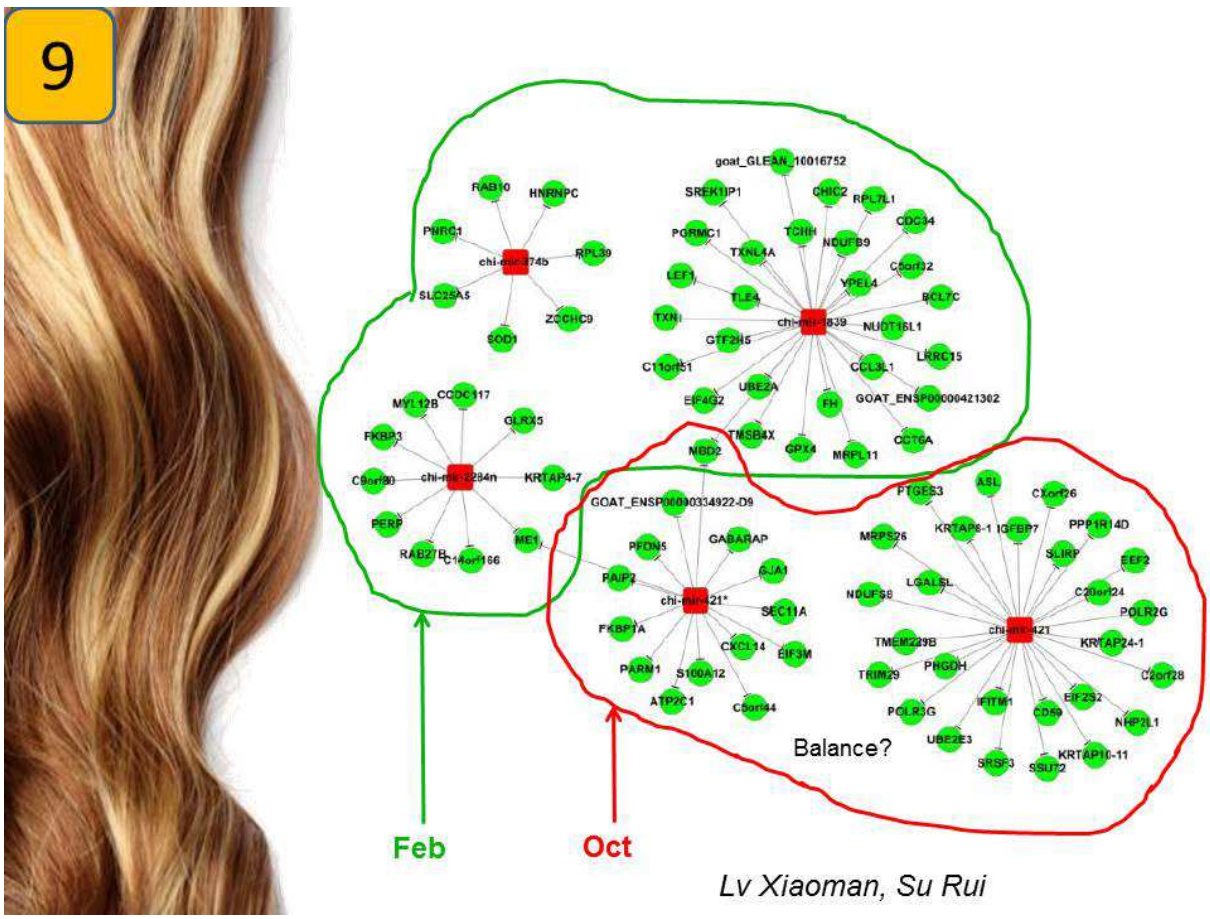


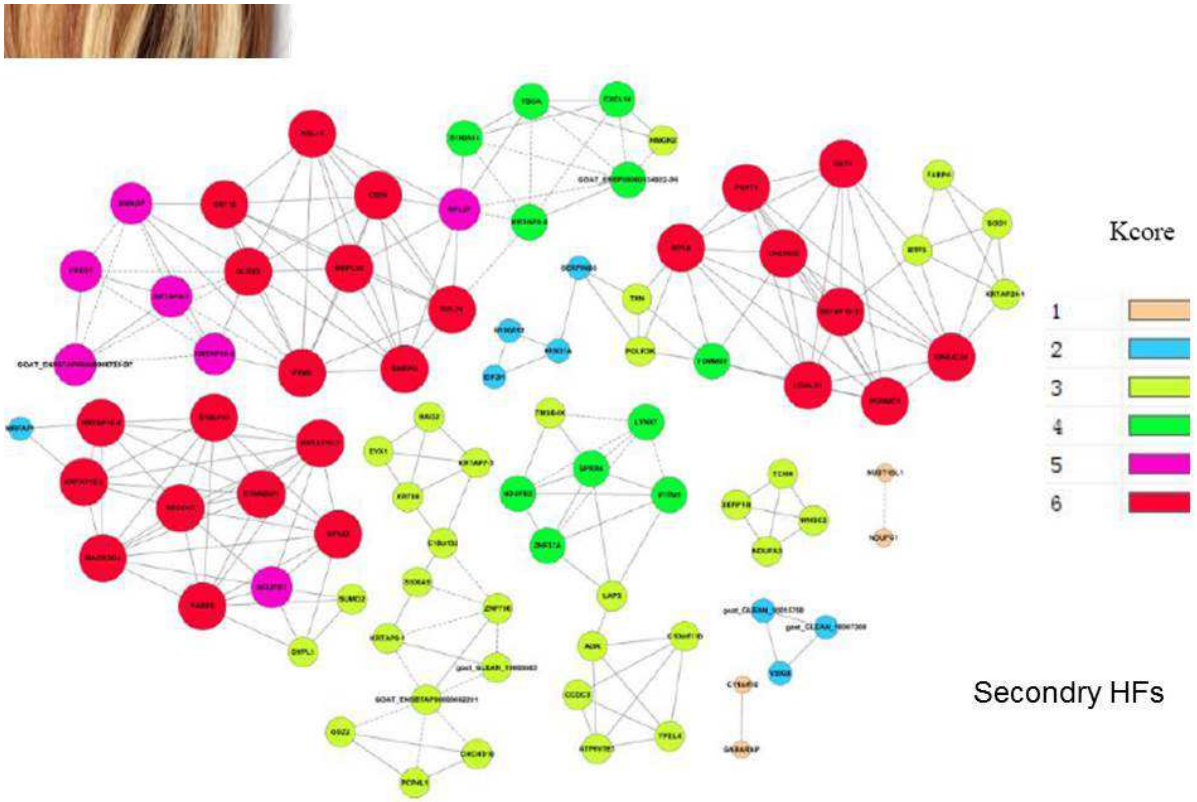
Modulation in proteolytic activity is identified as a hallmark of exogen by transcriptional profiling of hair follicles. J Invest Dermatol. 2011



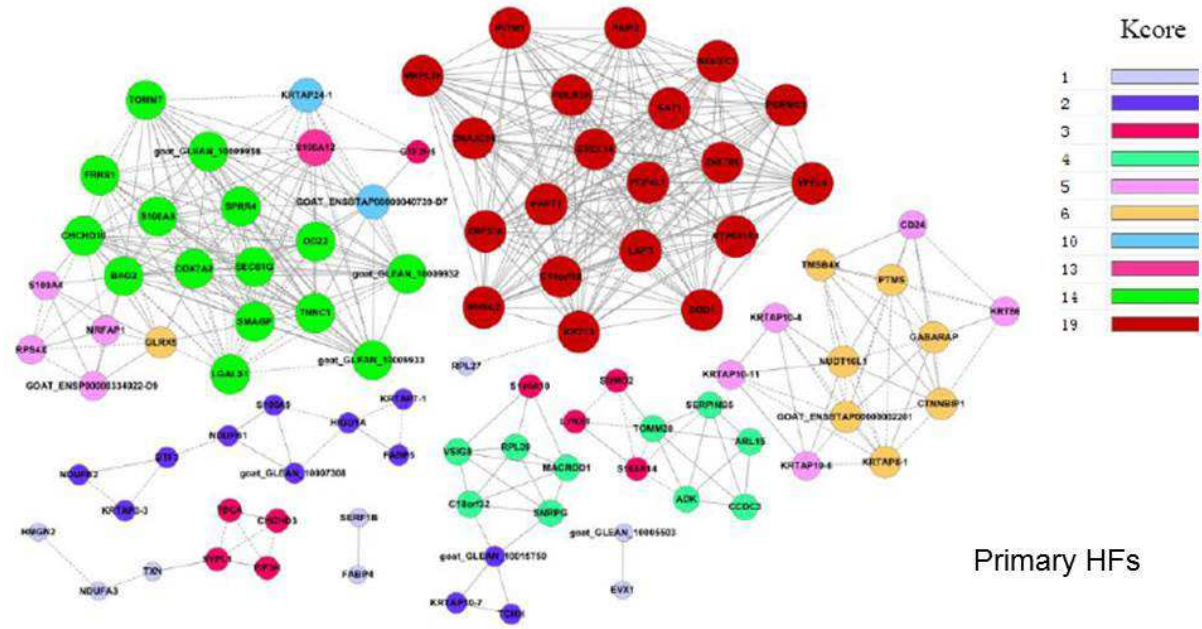



8
Properties of signaling pathways
Signaling pathways are nonlinear, highly integrative biological modules.
Property 1: Flexibility → generation of evolutionary novelty
Property 2: Robustness → ensure reproducible outcomes of developmental processes
BioGraph
Growing knowledge


9
Balance?
Feb
Oct
Lv Xiaoman, Su Rui



Zhao Dechao, Su Rui

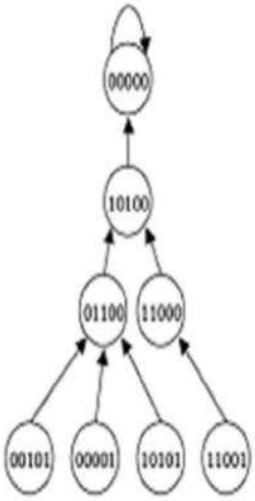


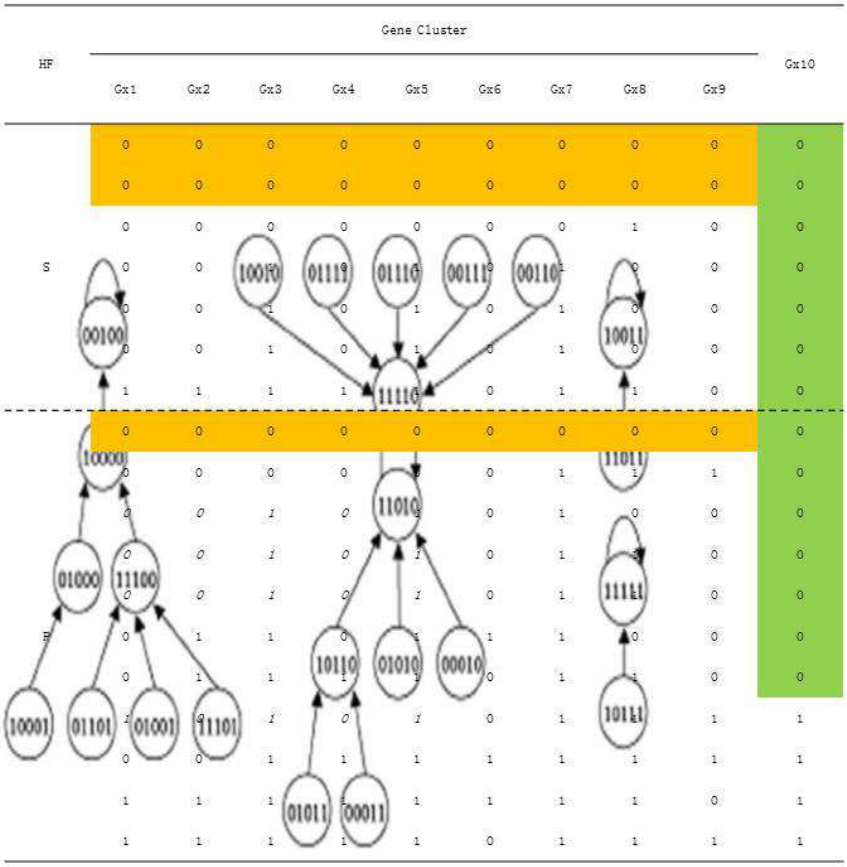
Zhao Dechao, Su Rui

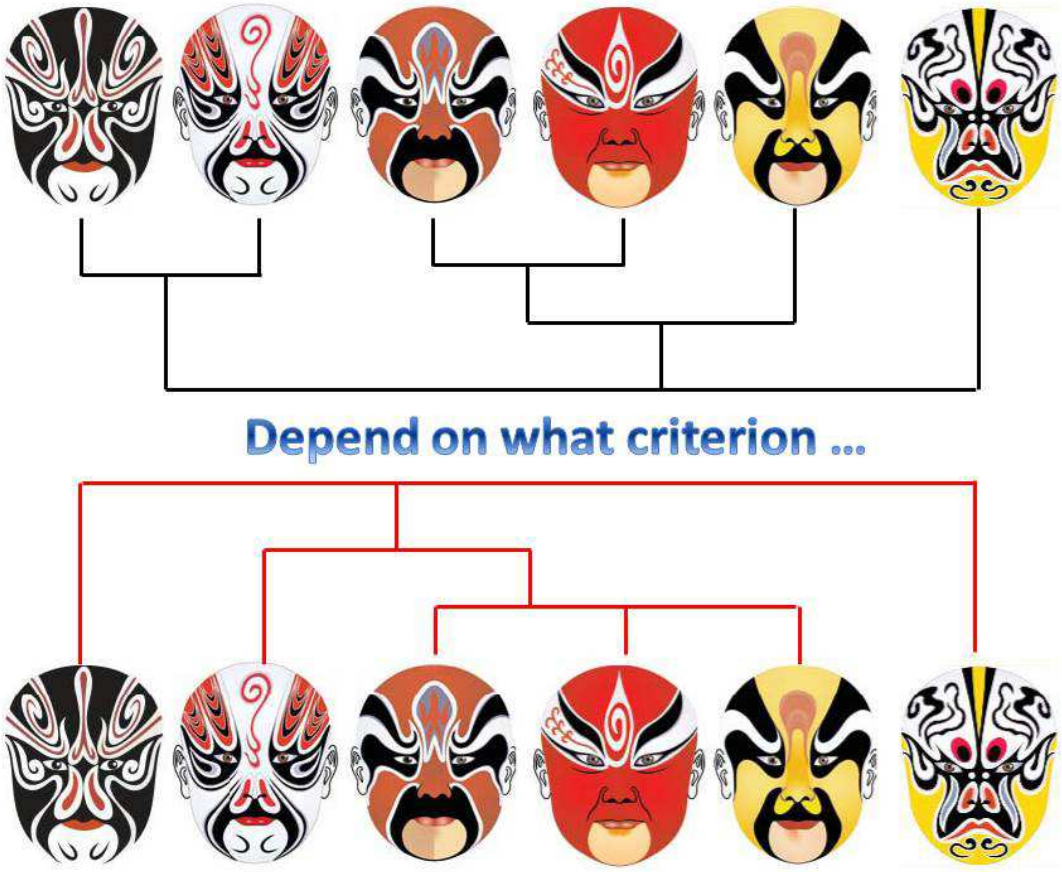
Effects of FGF5 gene on fibre traits of Inner Mongolian cashmere goats

- One PCR-SSCP Study
- GMO-Knock out
- Melatonin Up-regulate FGF5

FGF2?
Let-7 ?







In 1954, Chase published a review of hair cycling in which he detailed hair growth in the mouse and integrated hair biology with the biology of his day. In this research we have used Chase as our model and tried to put the adult hair follicle growth cycle in perspective. We have tried to sketch the adult hair follicle cycle, as we know it today and what needs to be known. Above all, we hope that this work will serve as an introduction to basic biologists who are looking for a defined biological system that illustrates many of the challenges of modern biology: cell differentiation, epithelial-mesenchymal interactions, stem cell biology, pattern formation, apoptosis, cell and organ growth cycles, and pigmentation. The most important theme in studying the cycling hair follicle is that the follicle is a regenerating system. By traversing the phases of the cycle (growth, regression, resting, shedding, then growth again), the follicle demonstrates the unusual ability to completely regenerate itself. The basis for this regeneration rests in the unique follicular epithelial and mesenchymal components and their interactions. Recently, some of the molecular signals making up these interactions have been defined. They involve gene families also found in other regenerating systems such as fibroblast growth factor, transforming growth factor-beta, Wnt pathway, Sonic hedgehog, neurotrophins, and homeobox. For the immediate future, our challenge is to define the molecular basis for hair follicle growth control, to regenerate a mature hair follicle in vitro from defined populations, and to offer real solutions to our patients' problems, and to benfit fiber animal producers.


Thanks
regenerate yourself
ADAPTmap
FEED THE FUTURE
nextgen
3SR