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## **Substrate softness promotes terminal differentiation of human keratinocytes without altering their ability to proliferate back into a rigid environment**

Choua Ya<sup>1,2</sup>, Mariana Carrancá<sup>1</sup>, Dominique Sigauco-Roussel<sup>1</sup>, Philippe Faure<sup>3</sup>, Bérengère Fromy<sup>1†</sup>, Romain Debret<sup>1†\*</sup>

<sup>1</sup> CNRS, University Lyon 1, UMR 5305, Laboratory of Tissue Biology and Therapeutic Engineering, IBCP, 7 Passage du Vercors, 69367 Lyon Cedex 07, France.

<sup>2</sup> Isispharma, 29 Rue Maurice Flandin, 69003 Lyon, France.

<sup>3</sup> Alpol Cosmétique, 140 Rue Pasteur, 01500 Château-Gaillard, France.

† co-last authors

\* Corresponding author: Romain Debret  
LBTI, UMR5305 CNRS/UCBL  
7, passage du Vercors  
F-69367 LYON cedex 7  
[romain.debret@ibcp.fr](mailto:romain.debret@ibcp.fr)

## **Abstract**

Substrate stiffness is a key regulator of cell behavior. To investigate how mechanical properties of cell microenvironment affect the human keratinocyte, primary cells were seeded on polyacrylamide hydrogels of different compliances (soft: 4 kPa, medium: 14 kPa, rigid: 45 kPa) in comparison with glass coverslip (> GPa). Keratinocyte spreading and proliferation were strongly decreased on the softest hydrogel, while no significant difference was observed between medium, rigid hydrogels and glass coverslip, and cells viability was comparable in all conditions after 72h. We then performed a RNA-seq to compare the transcriptomes from keratinocytes cultured for 72h on the softest hydrogel or on coverslips. The cells on the soft hydrogel showed a strong increase in the expression of late differentiation marker genes from the epidermal differentiation complex (1q21) and the antioxidant machinery. In parallel, these cells displayed a significant loss of expression of the matrix receptors (integrin  $\alpha 6$  and  $\beta 1$ ) and of the EGF receptor. However, when these cells were replated on a plastic culture plate (> GPa), they were able to re-engage the proliferation machinery with a strong colony formation efficiency. Overall, using low-calcium differentiation monolayers at confluence, the lesser the rigidity, the stronger the markers of late differentiation are expressed while the inverse is observed regarding the markers of early differentiation. In conclusion, below a certain rigidity, human keratinocytes undergo genome reprogramming indicating terminal differentiation that can switch back to proliferation in contact with a stiffer environment.

**Keywords**

Mechanical properties, keratinocytes, differentiation, proliferation, transcriptome profiling

## Introduction

In the epidermis, the balance between keratinocyte proliferation in the basal layer and terminal differentiation and shedding in the upper layers maintain normal tissue homeostasis [3]. The keratinocytes are interconnected via intercellular junctions and lie on a basal membrane at the interface of the epidermis and the dermis, the underlying extracellular matrix (ECM)-rich connective tissue. Mechanical, biophysical and biochemical factors regulate the keratinocyte function. Indeed, physical interactions are detected by the keratinocytes through mechanotransduction mechanisms transforming mechanical loads into biochemical cascades and have been involved in the regulation of keratinocyte proliferation, differentiation, morphology, and migration [27]. There has been extensive research into the measurement of the skin's elastic modulus via a multitude of *in vitro* and *in vivo* techniques with various values depending on the method used (see [6,11] for comprehensive reviews). *In vivo*, the mechanical measurements obtained are generally attributed to those of the dermis because of its thickness with respect to the epidermis, with a rigidity of 5 and 10 kPa as measured by indentation [30]. The dermis is a connective tissue composed mainly of fibroblasts responsible for the synthesis of an ECM rich in collagen fibers, elastic fibers, glycosaminoglycans and the fundamental substance. Mechanically speaking, the dermis gives the skin its strength, firmness, elasticity and viscosity. Studies have attempted to measure the mechanical properties of the different histological layers of the skin but high interconnections between the different layers rendered the discrimination challenging.

The mechanical properties of the skin can be altered by physiological phenomena such as aging or wounding [9,30], or by pathological phenomena with consequences on the epidermal homeostasis [10]. During chronological aging, the expression level of ECM constituents, such as type I and III collagens [23] and elastin [7], decrease, while the synthesis and the activities of matrix metalloproteases increase [24]. Together, these alterations lead to age-related reduction of skin elastic modulus as reported in humans [30]. During the wound healing process, the composition and structure of the ECM are continuously modified during the formation of granulation tissue and remodeling [8], inducing drastic changes in the mechanical properties of the dermis. Indeed, the rigidity of the granulation tissue increased from 18 kPa at 7 days after wounding to 50 kPa at 12 days [9]. This increase is required for the initiation of keratinocyte migration. Persistent abnormal alterations in the mechanical properties of ECM would therefore contribute to healing defects such as chronic or hypertrophic wounds [12].

*In vitro* studies showed that keratinocytes are able to respond to the rigidity of the support. Studies on the HaCaT cell line have indeed shown that the rigidity of the support promotes proliferation and migration, leading to an increase in re-epithelization, whereas cell differentiation is inhibited [25]. The substrate stiffening promotes proliferation by activation of the EGF signaling pathway, as reported using primary human keratinocytes [13]. In addition, the rigidity of the substrate regulated the formation of adhesion junctions via activation of the Jun N-terminal kinase pathway [29]. Finally, stiffness affects the morphology of cells resulting in a decrease in cell spread and focal adhesions [22]. The changes in the dermal stiffness could thus explain the phenotypic disturbances observed in keratinocytes leading to an alteration of epidermal homeostasis.

However, data on the impact of skin stiffness on epidermal differentiation are still very sparse, particularly using primary human cells. In this study, we aimed to investigate how mechanical properties

of the microenvironment affect primary human keratinocyte phenotype. For this purpose, we used primary human keratinocytes grown on substrates of different compliances.

## Materials and methods

### Ethical considerations

Infant foreskins were collected according to the Declaration of Helsinki Principles. A written informed consent was obtained from infants' parents according to French bioethical law of 2004.

### Cell culture

The human epidermal keratinocyte cultures were obtained from child foreskin biopsies after enzymatic treatment [1]. Briefly, the biopsies were cut in small pieces and immersed overnight at 4°C in a solution containing trypsin (Gibco, Life Technologies, Carlsbad, CA, USA) and dispase (Dispase II; Roche Diagnostics, Mannheim, Germany). Then, the dermis and epidermis were separated and the epidermis was incubated for 20 min at 37°C with trypsin and 0,05% EDTA. The cells were resuspended and filtered through a 70 µm cell stainer (BD Biosciences) to remove the remaining aggregates. After extraction, keratinocytes were cultured in KGM2 medium (Keratinocyte Growth Medium 2, Promocell, Heidelberg, Germany) comprising 0.06 mM CaCl<sub>2</sub> and supplemented with 100 µg/ml of primocin at 37°C and 5% CO<sub>2</sub>. Cells were amplified on plastic dishes prior seeding on the different substrates for experimental assessments. To induce keratinocyte differentiation, at confluence, cells were cultured in KGM2 without growth factor supplement. The cells were used at early passage (passage 1 and 2) in subsequent experiments. All cell-based *in vitro* experiments were repeated in triplicate.

### Generation of polyacrylamide hydrogels

The hydrogels were synthesized according to the principle described previously by Tse and Engler [2]. Briefly, 18 mm diameter coverslips were activated with 70 mM NaOH solution and heated at 80°C. This step was repeated with milliQ water until NaOH forms a thin semi-transparent film. The coverslips were treated for 5 min with APES (3-Aminopropyltriethoxysilane, Sigma) and thoroughly rinsed. Then, 0.5% glutaraldehyde (Sigma) was added onto the coverslips for 30 min and dried few minutes at room temperature. In parallel, 24x60 mm glass slides were chlorosilanated with DCDMS (dichlorodimethylsilane, Sigma) for 5 min, gently rinsed, and dried 30 min at room temperature.

Polyacrylamide gels with different modulus of elasticity values were produced by mixing acrylamide/bis-acrylamide solutions at final percentages (p/v) of 3/0.1, 4/0.225 and 10/0.225 for Soft, Medium and Rigid hydrogels respectively. The polymerization is initiated with APS (ammonium persulfate, Sigma) and TEMED (N,N,N',N'-tetramethylethane-1,2-diamine, Sigma). The polyacrylamide solution is immediately pipetted onto the chlorosilanated slide and covered by the functionalized coverslip. After the completed polymerization, the top coverslip with the attached polyacrylamide gel is slowly peeled off and rinsed to take out DCDMS on gel surface.

To facilitate keratinocyte attachment, a heterobifunctional crosslinker, sulfo-SANPAH (sulfosuccinimidyl6(4-azido-2-nitrophenyl-amino)hexanoate, ThermoFisher Scientific), is used to crosslink extracellular matrix molecules onto the surface of the gel. 0.2 mg/mL sulfo-SANPAH solution is added to gel surface, placed 3 inches under an ultraviolet lamp, irradiated for 10 min and rinsed with water. Then, 100 µg/mL of rat tail collagen I solution (ThermoFisher Scientific) is added on the gel and

incubated for 2 h at room temperature under a 50 rpm agitation. Hydrogels were rinsed in PBS (phosphate buffered saline), placed in 12-well plates and immersed in culture media at 37°C one night prior to cell seeding.

### **Mechanical characterization of polyacrylamide hydrogels**

Viscoelastic properties of polyacrylamide gels (12mm diameter and ~1.2mm thick) were determined by Dynamical Mechanic Analysis (DMA 242 E Artemis, NEZSTCH, Germany). Samples were subject to compression tests under liquid immersion (PBS) water bath at room temperature. Strain-sweep measurements were performed to determine the elastic limit or linear domain of the gels. The tan delta, complex modulus ( $E^*$ ) as well as storage ( $E'$ ) and loss modulus ( $E''$ ) were determined from dynamic stress curves obtained for an amplitude of 55  $\mu\text{m}$ , a frequency of 1Hz and 10% constraint.

### **Immunofluorescence**

Keratinocytes were plated on a glass coverslip or polyacrylamide gels in 12-well plates for 24 h to analyze cell morphology, or for 72 h to observe differentiation markers. Then, the cell were fixed in 4 % paraformaldehyde for 10 min.

To visualize focal adhesion and actin cytoskeleton, cells were permeabilized with 0.1% Triton X-100 for 10 min, blocked with 5 % of goat serum in PBS for 1 h at room temperature and incubated with anti-talin antibody (clone 8D4, Sigma) overnight at 4°C. Secondary Alexa-488 anti-mouse (Invitrogen) was incubated 1 h at room temperature. Actin network was stained with TRITC-phalloidin for 5 min at room temperature. Differentiation markers were immuno-detected with anti-K10 (Ab76318, Abcam, 1:500) or anti-involucrin (Ab53112, Abcam, 1:500) for 2 h at room temperature. Secondary Alexa-563 anti-rabbit (Invitrogen) was incubated 1 h at room temperature.

All stainings were incubated with DAPI (4,6-diamidino-2-phenylindole) to visualize DNA and mounted with Permafluor™ Aqueous Mounting Medium (Labvision, Thermo Fisher Scientific). All images were acquired with a Nikon TiE inverted fluorescent microscope.

### **Cell proliferation and viability assay**

Cells ( $5 \times 10^3$  per substrate) were seeded on glass coverslip or polyacrylamide hydrogels. Cells were fixed at 24h, 48h and 72h with 4 % paraformaldehyde for 10 min and stained with DAPI for 5 min. Cell proliferation was determined by nuclei count using ImageJ software. All experiments were repeated at least 3 times in triplicate.

To assess keratinocyte viability, cells were cultured on glass coverslip or on hydrogels for 3 days. Cells were then stained with LIVE/DEAD™ Cell Imaging Kit (Invitrogen), as described by the manufacturer's protocol. Green living cells and red dead cells were counted and the ratio of living cells/dead cells was expressed as a percentage of cell viability.

### **mRNA extraction and qRT-PCR**

Total RNA was extracted from cells at indicated times using RNeasy mini kit (Qiagen, Valencia, CA) according to the manufacturer's instructions. Reverse transcription was performed using PrimeScript™ RT Reagent Kit (Takara, Tokyo, Japan). qRT-PCR was performed on a Mx3000P real-time PCR system (Stratagene, San Diego, CA, USA) using SYBR® Premix Ex Taq™ II (TaKaRa). Amplification was started at 95 °C for 30 s as the first step, followed by 40 successive cycles of PCR: at 95 °C for 5 s, at 60 °C for 30 s and at 72 °C for 30 s. Primers specific for RPL13 (ribosomal housekeeping gene), MKI67 (proliferation marker), KRT1 and KRT10 (early differentiation marker), IVL, TGM1, FLG and CDSN (late differentiation markers), ITGA6 and ITGB1 (cell adhesion), CDKN1A and CDKN2A (cell cycle progression), EREG and EGFR (epidermal growth factor signaling), MT1H, AKR1B10 and AKR1C2 (oxidative machinery) were used.

### **Western blot**

To analyze protein expression, cells were washed briefly in PBS and lysed on ice in the RIPA buffer (50 mM Tris-HCl, pH 8, 150 mM NaCl, 1% Nonidet P-40, 0.1% sodium deoxycholate, 0.1% SDS, 1 mM orthovanadate and protease inhibitor cocktail (Thermo Fischer scientific). Lysates were centrifuged for 10 min at 14000 g at 4°C to eliminate cell debris. Proteins were separated by SDS-PAGE followed by transfer to polyvinylidene fluoride membrane (EMD-Millipore, Billerica, MA). Membrane was blocked with 5 % non-fat milk in Tris buffered saline (TBS) buffer containing 0.1% Tween-20, and incubated with rabbit anti-involucrin (SY5) antibody (SC-21748, Santa Cruz, 1:1000) and mouse anti-actin (C4, MAB1501, Sigma-Aldrich, 1:5000), overnight at 4°C. Membrane was incubated with secondary antibodies for 1 h at room temperature: goat anti-rabbit IgG (H+L)-HRP conjugate (170-6510, Biorad, 1:10000) and goat anti-mouse IgG (H+L)-HRP conjugate (170-6516, Biorad, 1:10000). Antibody binding was detected by the enhanced chemiluminescence system (Thermo Fischer Scientific), using the Fusion Fx system (Vilbert Lourmat).

### **RNA sequencing**

Cells were cultured on glass substrate and soft hydrogel for 3 days and total RNA was extracted using RNeasy mini kit (Qiagen). RNA quantity and purity were verified using 2200 TapeStation system (Agilent Technologies). Library preparation was performed using mRNA-Seq Library Prep Kit Lexogen following manufacturer's instructions. Libraries were validated on TapeStation – HSD1000 ScreenTape® Dosage. Barcoded libraries were pooled together (three per run) on an equimolar basis and run using PI chips on an Ion Torrent™ PGM sequencer using HiQ chemistry. Library preparation and sequencing were achieved by the IGFL sequencing platform (Lyon, France).

### **Bioinformatic analyses**

Reads were aligned to the human reference genome hg19 using the Ion Torrent RNASeqAnalysis plugin. Two consecutive alignments were achieved through the STAR and Bowtie2 programs to generate the BAM files. Reads over genes were determined using the R/Bioconductor “Rsubread” software package to create a counts matrix [15]. Differential gene expression analysis was performed using R/Bioconductor “limma” and “edgeR” software packages [18,20,21]. Smear plot and heat map

were generated from limma-voom normalized values in R [14]. Genes with a differential expression FDR  $\leq 0.05$  were considered significant. Two sets of significant genes, upregulated or downregulated, were subjected to Gene Ontology (GO) analysis using GOrilla tool [5] and enrichment analysis of the 5 top molecular functions are represented.

### **Clonogenic assay**

Primary keratinocytes were plated on soft hydrogel or glass coverslip for 3 days then clonogenic assay was realized on three generations with plastic culture plate. For each generation, the cells were trypsinized, re-suspended in the media and counted. The cells were re-seeded (500 cells/well) in 6-well plates and incubated for 10 days. On the tenth day, cells were trypsinized, counted and re-seeded (500 cells/well) in a new 6-well plates. In parallel, cells were fixed with 4% paraformaldehyde solution for 10 min and the colonies were stained with 0.1% cristal violet for 1 hour. The wells were rinsed three times with PBS and cells were lysed with 2% SDS solution. The absorbance (570 nm) was readed with Tecan Infinite 1000M. All experiments were performed in triplicate.

### **Statistical analysis**

All data were presented as mean  $\pm$  SD for three independent experiments. Statistical significance ( $p < 0.05$ ) was determined by performing either unpaired T-test when comparing two groups or one way or two way analysis of variance (ANOVA) followed by a Bonferroni post-test when comparing multiple groups. All analyses were performed with GraphPad Prism5 software.

## Results

To investigate human keratinocyte behavior in response to substrate stiffness, we used polyacrylamide hydrogels (PAH) of different compliances and functionalized with type I collagen coating to allow cell adhesion. The three different PAH preparations displayed  $E^*$  of  $3.91 \pm 1.4$  kPa (Soft),  $14.63 \pm 3.7$  kPa (Medium) and  $44.98 \pm 3.6$  kPa (Rigid), respectively (Fig. 1a). 24 hours post-seeding, the morphology of freshly isolated human keratinocytes was modified by the substrate stiffness (Fig. 1b). On Soft PAH, cell shape remained round with a thin distribution of the actin cytoskeleton at the plasma membrane, while no clear focal adhesion point was observed. On Medium and Rigid PAH, cells were much more spread as illustrated by a wider distribution of actin and the presence of well-defined focal adhesion points. Glass coverslip condition was characterized by the formation of stress fibers across the cytoplasm and well-defined focal adhesion points at the cell periphery leading to a polygonal cell shape. Since cells were present in all conditions, their proliferation was assessed by cell counting during three days (Fig. 1c). No significant difference was observed between Medium PAH, Rigid PAH and glass coverslip conditions. In contrast, no proliferation was noted on the Soft substrate. Cell viability was then assessed in all conditions after three days and no significant difference was observed (Fig. 1d). These results show that the human keratinocyte gradually adapts to the substrate rigidity on which it adheres. On the softest substrate, although the cells were in the proliferative phase during the isolation and amplification process on plastic ( $> \text{GPa}$ ), the keratinocyte appears in a "quiescence-like" state, suggesting a very quick change of keratinocyte phenotype in response to the low compliance (below 15 kPa).

To investigate the particular "quiescence-like" state observed in response to the low compliance, the keratinocytes were cultured on Soft PAH and on glass coverslip for 3 days and a phenotype-specific transcriptional profiling was undertaken by RNA-seq analysis (Fig. 2 a-c). Consistent with a specific effect of the substrate, the heat map of 200 most differentially expressed genes showed a clustering of the samples by culture conditions over interindividual variability of the three donors (Fig. 2a). A total of 1392 genes were differentially expressed (FDR  $q$ -value  $\leq 0.05$ ) between Soft PAH and glass coverslip (Fig. 2b). Among these, 808 genes were expressed at significantly higher levels in Soft PAH (gene list available in Online Resource 1), whereas 584 were expressed at significant lower levels (gene list available in Online Resource 2) compared to glass coverslip. GO pathway analysis of these differentially expressed genes in Soft PAH condition revealed an increase in the expression of genes involved in structural constituent of epidermis (23 genes belong to the epidermal differentiation complex located at 1q21 locus), metabolism and anti-oxidative machinery. In parallel, genes that decreased in expression level were preponderantly associated with extracellular matrix binding receptors and cytoskeleton (Fig. 2c). Using real time RT-PCR on keratinocytes from three other donors, the level of expression of several hits observed in the various GO categories evoked was consistent with RNA-seq data, strengthening the results (Fig 2d). The transcriptomic profile of the cells cultured on a Soft substrate was therefore similar to differentiated keratinocytes. This observation was enhanced at the protein level since the cells grown on the Soft PAH were all positive for the cytokeratin 10 marker and few cells started to express the involucrin late differentiation marker, while no staining was observed on glass coverslips (Fig. 2e). However, cell cycle-related genes expression levels (*CDKN1A* and *CDKNA2*) were also analyzed and

a slight increase of expression level was observed for both genes (Fig 2d). Hence, the lack of down-regulation of genes linked to the cell cycle tended to show that these cells had not fully entered a terminal differentiation pathway; neither could they be related to a quiescent state. Then, preconditioned cells cultured for 3 days on Soft PAH or on a glass coverslip were transplanted in 6-well plastic plates (> GPa) to observe colony-forming efficiency over three generations (Fig. 2f). The results showed that the cells previously engaged in the differentiation pathway on Soft PAH were able to proliferate again once put back on a rigid substrate. During the two first generations, cells transplanted from Soft PAH showed a slight but significant decrease of colony formation compared to cells transplanted from glass. This observation was reversed during the third generation showing that cells from the Soft PAH kept an important proliferative potential. However, in both experimental conditions, an overall decrease in proliferative capacity was observed over successive generations.

Finally, since the keratinocyte proliferates normally above 4 kPa, we investigated whether intermediate rigidities could affect the keratinocyte differentiation program. To address this, the keratinocytes were seeded on the surface of Medium, Rigid PAH and glass coverslips at high density and differentiation was induced by cell confluence and growth factor deprivation at low calcium concentration. The gene expression level for the proliferation marker *MKI67* was quickly repressed in Medium PAH condition as the cells reached confluence, while it was sustained until growth factor depletion in Rigid PAH and glass coverslip conditions (Fig. 3a). Regarding the early differentiation marker *KRT10*, its expression increased with time (post-confluence) in a substrate stiffness-dependent manner, reaching a strong expression level on glass coverslip, an intermediary expression on Rigid PAH, and no expression on the Medium PAH at day 5 (Fig. 3b). Considering now the late differentiation markers, *IVL* and *CDSN* expression levels were prematurely increased in Medium PAH condition compared the two other groups (Fig. 3c,d). At day 5, cells cultured on the two PAH displayed a similar higher expression level of the late differentiation markers (*IVL* and *CDSN*) compared to the glass coverslip condition (Fig. 3c,d). These results therefore indicate an adaptive response of the human keratinocytes with respect to rigidity through their capacity to differentiate, the rigidity favoring the expression of early markers of differentiation to the detriment of later markers in contrast to low rigidity.

## Discussion

In the present study, PAH of different rigidities were used to better understand primary human keratinocyte responses in situations where their biomechanical environment is modified. We have shown that Soft (~4 kPa) PAH induced terminal differentiation while Rigid PAH (~45 kPa) favored a proliferative state similar to what is observed on glass coverslip or classical plastic culture dishes (> GPa). In addition, we demonstrated that keratinocytes committed in terminal differentiation on the softest environment could reactivate a proliferative response under a more rigid environment suggesting a strong conditioning of the genome by mechanical cell environment. Previous studies demonstrated that the adaptation of keratinocytes to the rigidity of their substrate relies mainly on the possibility for the cells to form focal adhesion points with the underlying ECM [12]. The number and the density of the focal points of adhesion decrease on soft substrates, but the occupation of the surface integrins is essential to prevent the entry into differentiation of the keratinocytes which results from the absence of activation of the signaling cascade focal adhesion kinase (FAK) / extracellular-signal-related kinase (ERK) / mitogen-activated protein kinase (MAPK) [26,22]. Stiffness also promotes proliferation through a synergistic interaction between FAK pathway and EGF receptor signaling [13]. Our observations trend in the same way showing a decrease of focal adhesion points accompanied by a stop of proliferation on the softest substrates (~4 kPa). However, we also emphasize the existence of a stiffness value (< 14 kPa) above which cells equally proliferate, suggesting a nonlinear response of keratinocyte proliferation rate to stiffness. Our results also showed that the distribution of the focal adhesion points does not vary substantially above this proliferative stiffness value, reinforcing the interrelation between the focal adhesion point assemblies and the capacity for the cell to proliferate. Below the stiffness value allowing proliferation, the keratinocytes undergo an atypical very quick differentiation in response to the low compliance.

The impact of the substrate rigidity is much more progressive with respect to the differentiation capacity of the keratinocytes. Trappmann et al. reported a similar correlation between PAH stiffness increase and involucrin synthesis inhibition in keratinocytes at 24h post-seeding [22]. Using monolayer keratinocyte cultures, we showed that the lesser the stiffness, the more the keratinocytes are able to express markers of late differentiation such as involucrin and corneodesmosin. In contrast, the early differentiation marker, cytokeratin 10, increases with increasing rigidity. Moving toward the critical proliferative stiffness value, *KRT10* gene expression is not observed at all after 3 days. However, this does not exclude the fact that this marker can be expressed at an earlier time, as evidenced by the presence of cytokeratin 10 in the softest hydrogels 3 days. Our results support the idea that on softer substrates, keratinocytes are quickly committed to terminal differentiation. Consistent with these observations, the mechanical measurements made on the human skin at different ages showed a reduced elastic modulus of 10 kPa at 30, 7.5 kPa at 60 years and 5.3 kPa at 80 year old [30]. Hence, changes in the dermis stiffness with aging could explain the phenotypic disturbances observed in keratinocytes leading to an alteration of epidermal homeostasis, and particularly the epidermal thinning [17].

The modulation of the differentiation being gradual according to rigidity, it cannot be directly related to the density of the focal adhesion points that were constant above the proliferative stiffness value. Indeed, differentiating keratinocytes are supposed to leave the basal membrane and no longer establish focal adhesion points. Our results showed that the cytoskeleton organization changes in a more gradual way with rigidity through the clustering of actin filaments in the peri-cytoplasmic region, beneath the plasma membrane, and across the cytoplasm. Interestingly, the spectrin cytoskeleton, a cross-linker of actin filaments and mainly implicated in cell shape maintenance [16], is abundant in differentiated keratinocytes, and the disorganization of this architecture prevents the correct differentiation of the keratinocyte [31]. Moreover, recent studies have shown that the spectrin cytoskeleton plays an important role in the mechanotransduction of osteocytes [28], so it would be interesting to explore the involvement of the stiffness related to spectrin cytoskeleton changes on keratinocyte differentiation.

Thus, there would be an optimal rigidity allowing to maintain a proliferative state of keratinocytes and their complete differentiation capacity as previously demonstrated in mouse skin wound healing by using poly(amidoamine) and poly(n-isopropyl acrylamide) hydrogels of varying rigidity [4]. Indeed the authors indicated that hydrogels of medium rigidity (in the order of the kPa) improve the wound healing *in vivo* by promoting fibroblast transformation, wound closure and proliferation of keratinocytes; while very soft (< kPa) or more rigid (~50 kPa) hydrogels hinder these processes. Interestingly, our results are concordant with the delay of proliferation but also show a premature expression of late differentiation markers on soft substrates. These observations are consistent with the histological description of an aged epidermis in which the suprabasal layers decrease in number, giving rise to a thinner epidermis, although the aged cells are capable of forming a stratum corneum [17]. Together with our results, this suggests that soft substrate would confer an aged phenotype to cells obtained from young donors as it is the case in our study.

We also studied the phenotype reversibility of cultured keratinocyte differentiation on the softest substrates. In the late 80's, Adams and Watt demonstrated that keratinocytes suspended in methylcellulose leave the cell cycle and express terminal differentiation genes such as involucrin after only 24 hours [2]. The addition of fibronectin in the suspension abrogated the expression of the differentiation genes but did not allow re-inducing the cell cycle. These previous data suggest that the occupation of surface integrins by their ligand is not sufficient to promote proliferation and that it is necessary for the keratinocyte to supplement this signaling by other means of mechanical perception. In our study, we pushed keratinocyte culture up to 3 days on the softest substrates to commit them more downstream in the differentiation program despite low calcium concentration and lack of cell-cell junctions. Gene expression profile is strongly modified, probably through epigenetic reprogramming insofar as a majority of the genes contained in the epidermal differentiation complex is expressed [1]. At the protein level, all the cells grown on Soft PAH express the cytokeratin 10 marker, and several cells already produce the involucrin late differentiation marker. Our results demonstrate that the differentiated cells replated on a rigid substrate were able to readapt to this new biomechanical environment and to start proliferating again with a colony-forming efficiency slightly lower during the two first generations than cells that have not been differentiated and even higher during the third generation. This increase during the third generation could be explained by the fact that cells from Soft PAH were less divided

during the two first generations, thus preserving their proliferative potential compared to cells preconditioned on glass coverslips. It therefore appears that the keratinocytes initially grown at low density on soft substrates preserved an important proliferative potential despite the prior induction of differentiation. Previously, Poumay and Pittelkow showed that an entry into differentiation induced by a high concentration of calcium or a depletion in growth factors does not alter the clonogenic capacity of keratinocytes and that a decrease is observed only if the keratinocytes are pushed to confluence [19]. This suggests that keratinocyte clonogenicity or proliferation potential is intimately related to their level of confluence, although the very early markers of cytokeratin 1 and 10 were only studied. However, this hypothesis remains plausible in our case.

In conclusion, we confirmed here the response of primary human keratinocytes to soft substrate by the decrease of their adhesion focal points and proliferation, and we demonstrated a quick commitment of these cells in terminal differentiation. Moreover, this study turns out that the induction of terminal differentiation on a soft substrate is reversible and open the way to interesting models to study the genome plasticity of keratinocytes. Extensive future studies of the reversible aspect of these reprogramming mechanisms would be helpful to discover new targets in pathophysiological situations displaying impaired epidermal differentiation, notably when dermal mechanical properties are modified.

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**Conflict of Interest**

The authors have no interest to disclose.

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## Figure legends

### Figure 1. Substrate mechanical properties affect keratinocyte behavior.

(a) Viscoelastic properties of PAH were determined by Dynamical Mechanic Analysis, using an amplitude of 55  $\mu\text{m}$ , a frequency of 1Hz and 10% constraint. ( $E^*$ ) complex modulus. (n=5) The data are presented as mean  $\pm$  SD; \*\*\*P < 0.001 and \*\*\*\*P < 0.0001 using one-way ANOVA with a Bonferroni post-test.

(b) Human primary keratinocytes were cultured on glass and PAH with different rigidities. After 24 hours, cells were stained for F-actin content (phalloidin staining: red) and nuclei were counterstained with DAPI (blue). Immunostained for talin (green) after 24 hours in culture. Scale bar: 25  $\mu\text{m}$ .

(c) Human primary keratinocytes were cultured on glass (black dot), Soft (green square), Medium (blue diamond) and Rigid (red triangle) PAH. Nuclei were counterstained with DAPI and proliferation rate was measured by cell counting after 1, 2 and 3 days in culture. (n=3) All data are presented as mean  $\pm$  SD, \*\*P < 0.01 and \*\*\*P < 0.001, using two-way ANOVA with a Bonferroni post-test, compared to Soft PAH condition.

(d) After 3 days in culture on PAH with different rigidities or glass coverslip, living cells and dead cells were visualized and counted by LIVE/DEAD™ Cell Imaging. Histograms represent cell viability as the percentage of living cells over dead cells. All data are presented as mean  $\pm$  SD. A two-way ANOVA with a Bonferroni post-test was applied, compared to Soft PAH condition.

### Figure 2. Transcriptomic profiling and colony forming efficiency.

(a) Hierarchical clustering of 200 most differentially expressed genes in keratinocytes cultured for 72h on Soft PAH (S\_soft) or glass (S\_glass). Green color corresponds to under-expressed and red color to overexpressed genes.

(b) Smear plot of RNA-seq data showing average log signal intensity (x axis) vs. log<sub>2</sub> fold change in gene expression (Soft PAH/Glass). Differentially expressed genes (FDR  $q \leq 0.05$ ), are shown in red for up regulated genes (n=808), in green for down regulated genes (n=584), and non-significant changes are shown in black.

(c) Gene ontology enrichment analysis of the 5 top molecular functions (GORilla). Significance of term enrichment by FDR q-values is represented by log<sub>10</sub> bar values.

(d) qPCR validation of 2 unmodulated (black) and 13 modulated (green and red) genes on Soft substrate. (n=3) Data are presented as mean  $\pm$  SD.

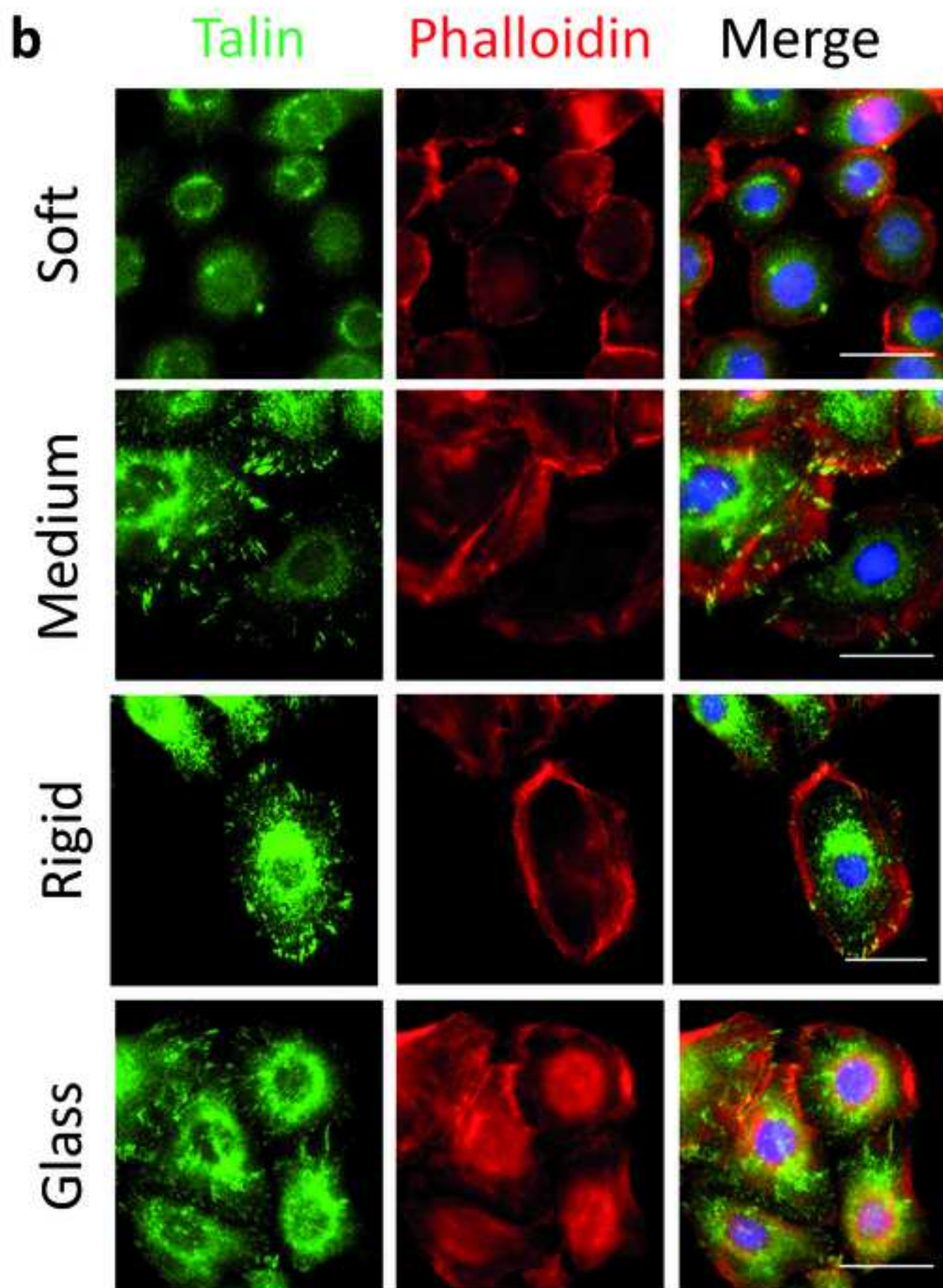
(e) Human primary keratinocytes were cultured on glass and Soft PAH. After 72 hours, cells were immunostained for cytokeratin 10 or involucrin (red) and nuclei were counterstained with DAPI (blue). . . Scale bar: 100  $\mu\text{m}$ .

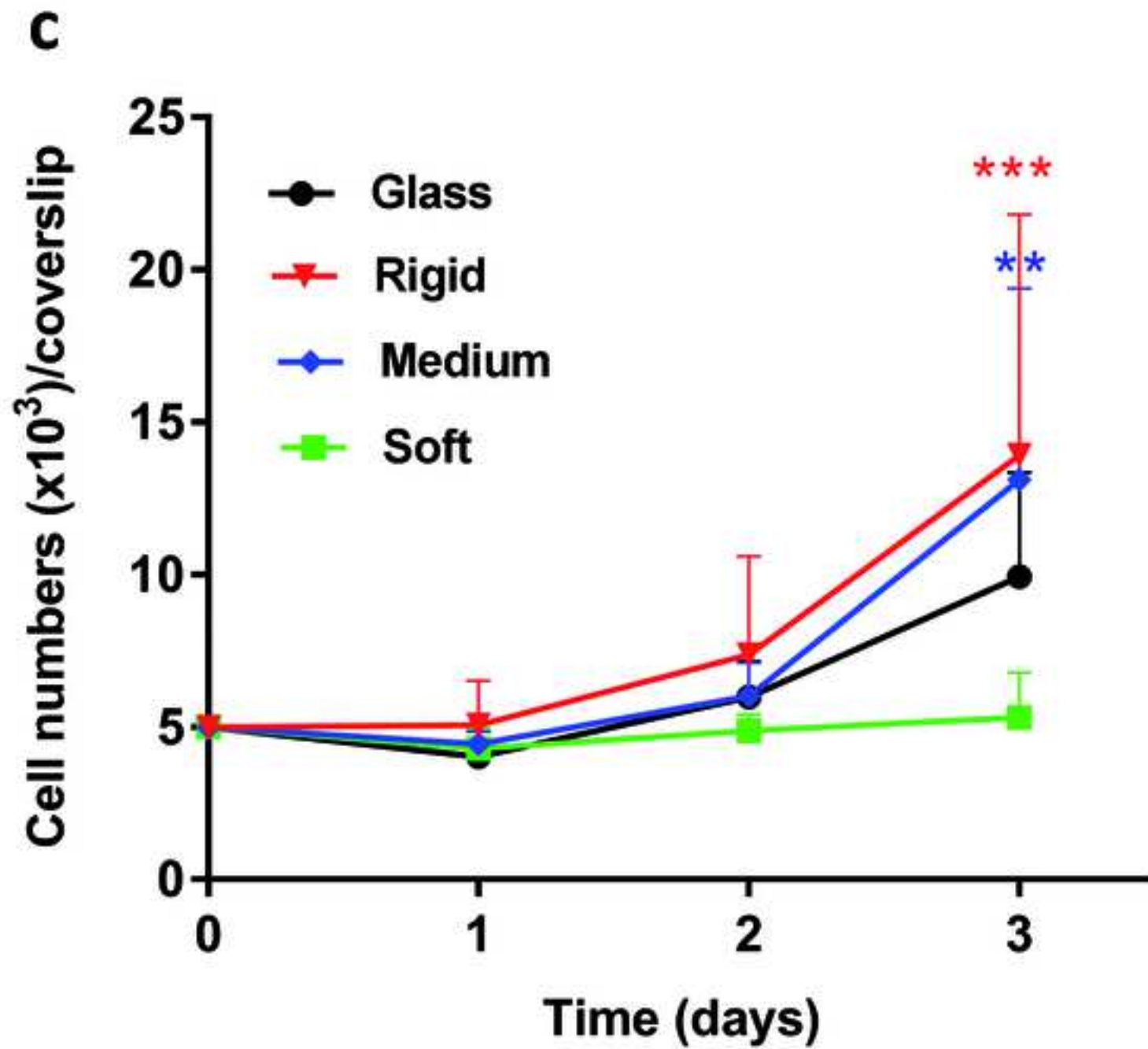
(f) Preconditioned cells grown for 72h on Soft PAH (black) or glass coverslips (grey) were replated on 6-well plates to evaluate colony forming efficiency for three generations. (n=3) Data are presented as mean  $\pm$  SD, \*P < 0.05, \*\*P < 0.01, unpaired T-test.

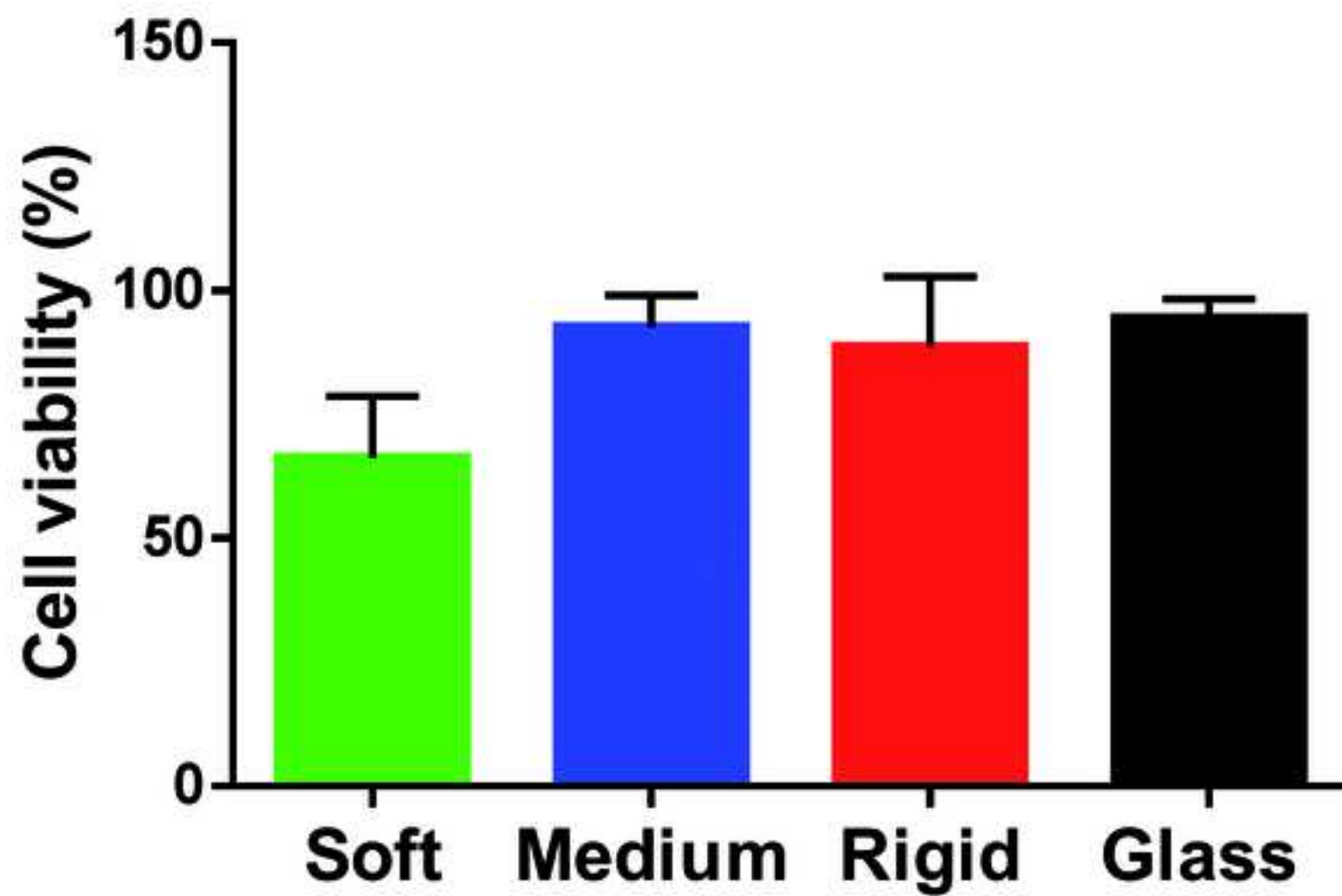
### Figure 3. Substrate stiffness impacts keratinocyte's differentiation.

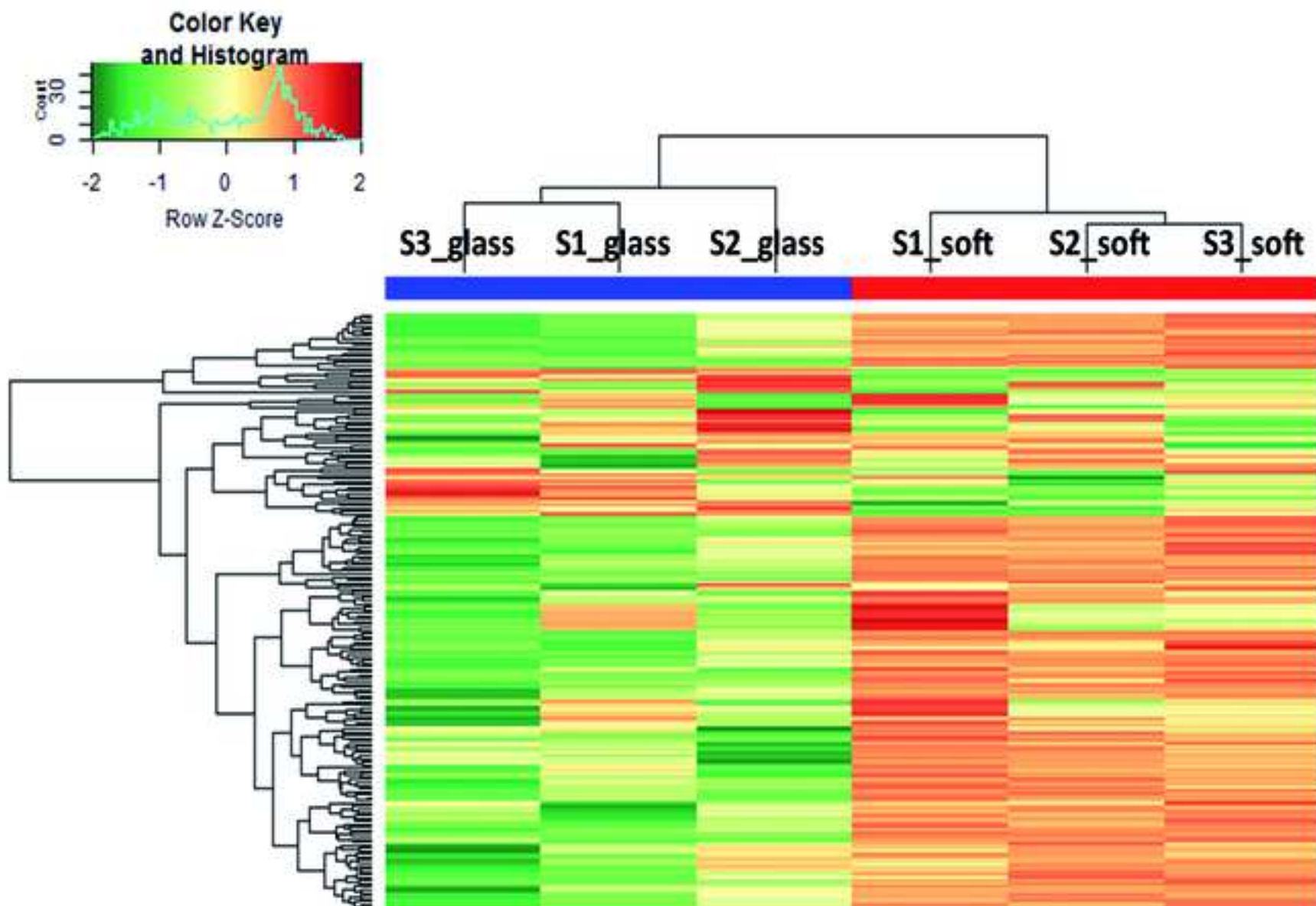
(a-d) Cells were plated on Medium (blue triangle), Rigid (red square) PAH and glass (black dot). mRNA expression was analyzed by qPCR at indicated time (day 0 corresponds to the moment cells reach confluence): proliferation marker *MKI67* (a), keratinocyte early differentiation marker *KRT10* (b) and keratinocyte late differentiation markers *IVL* (c) and *CDSN* (d) at the indicated points. (n=3) All data are presented as mean  $\pm$  SD, \*P< 0.05, \*\*P< 0.01, \*\*\*P< 0.001 and \*\*\*\* P< 0.0001, using two-way ANOVA with a Bonferroni post-test, compared to glass condition.

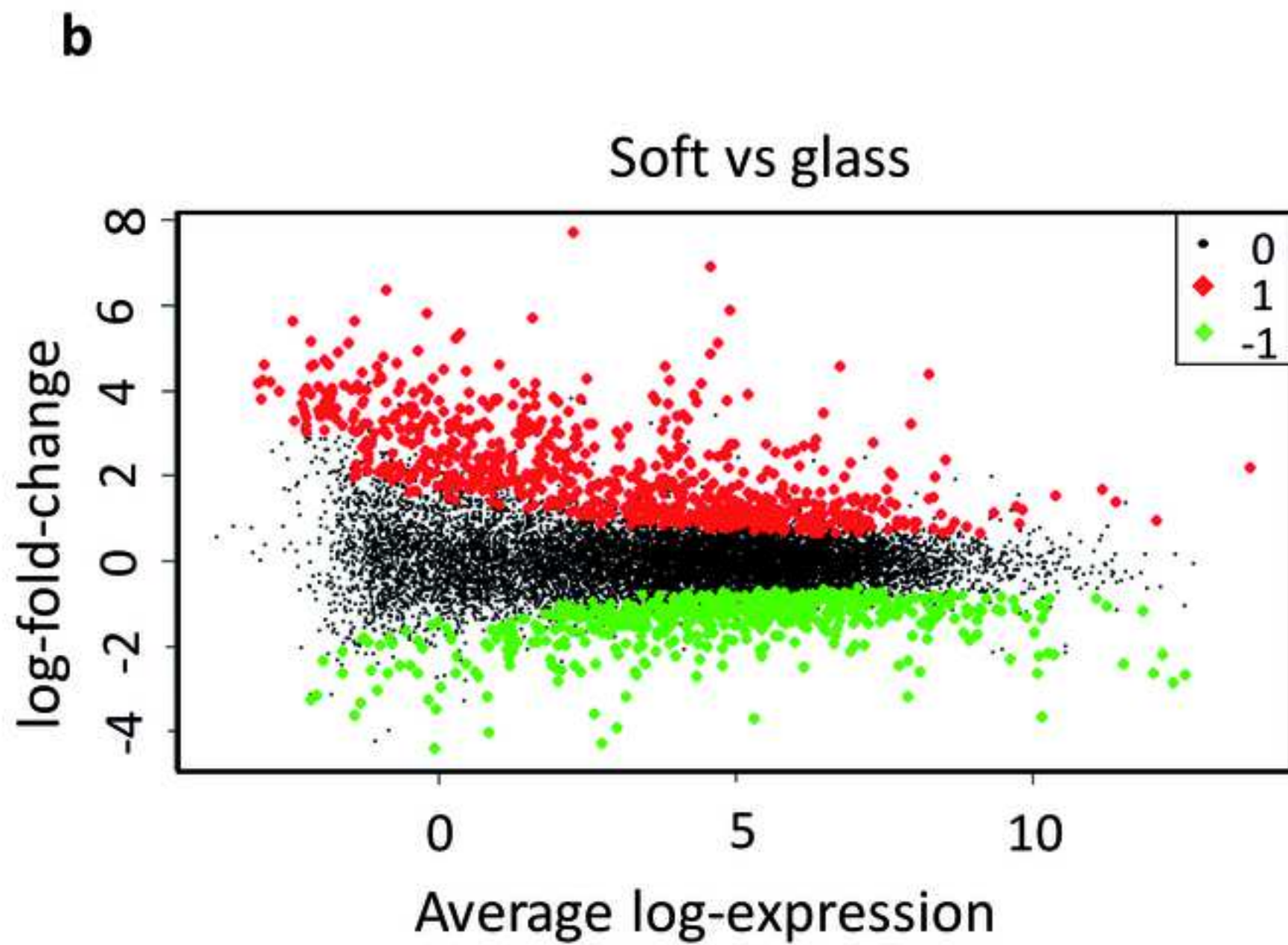


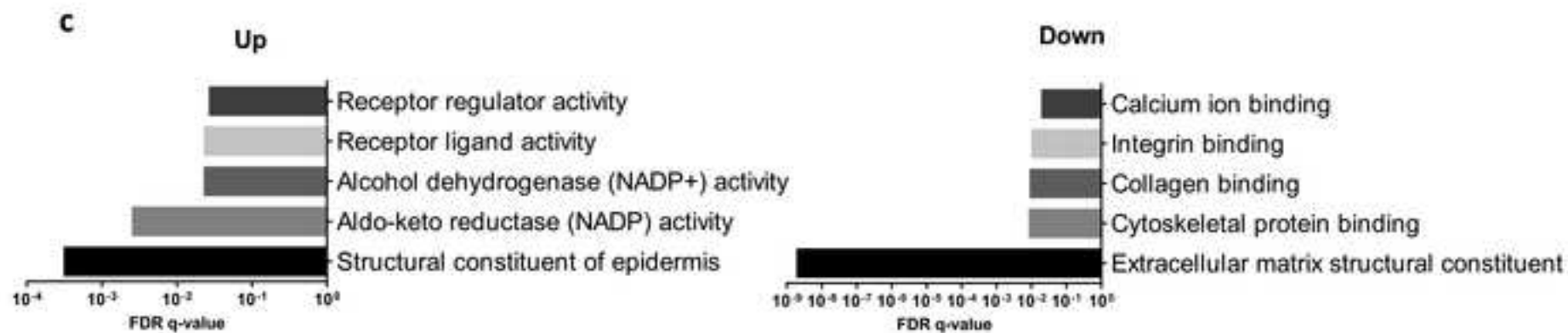


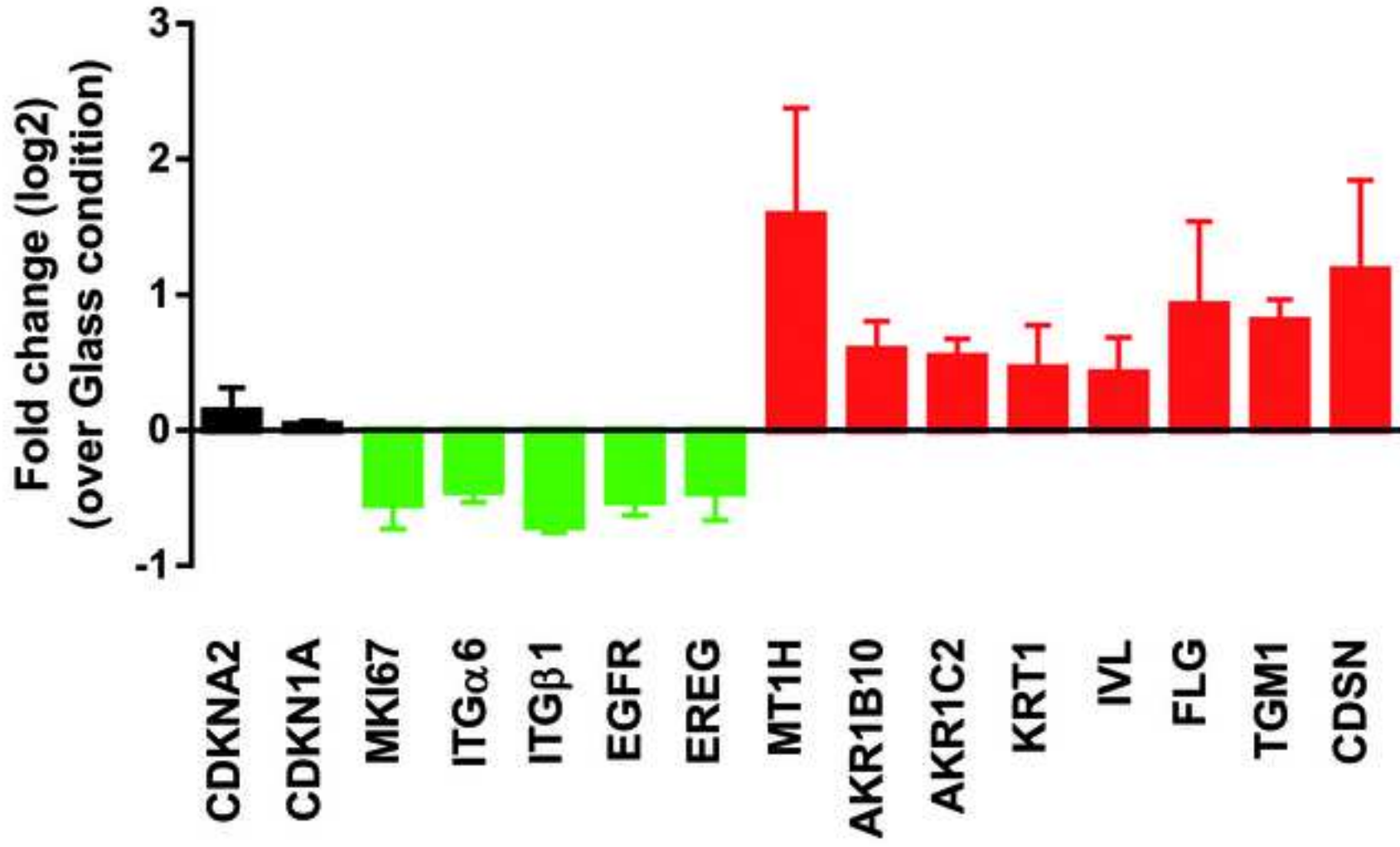


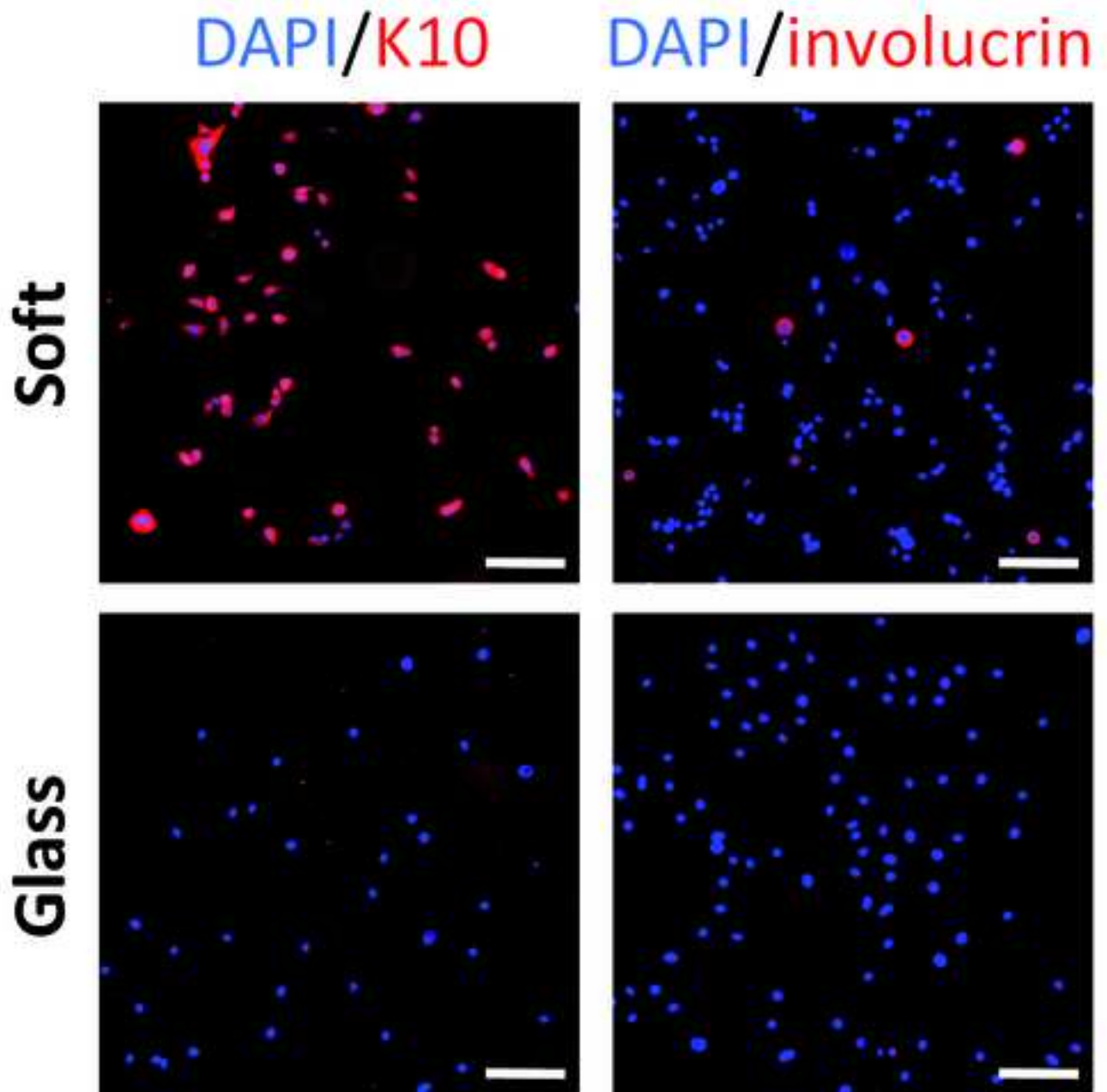
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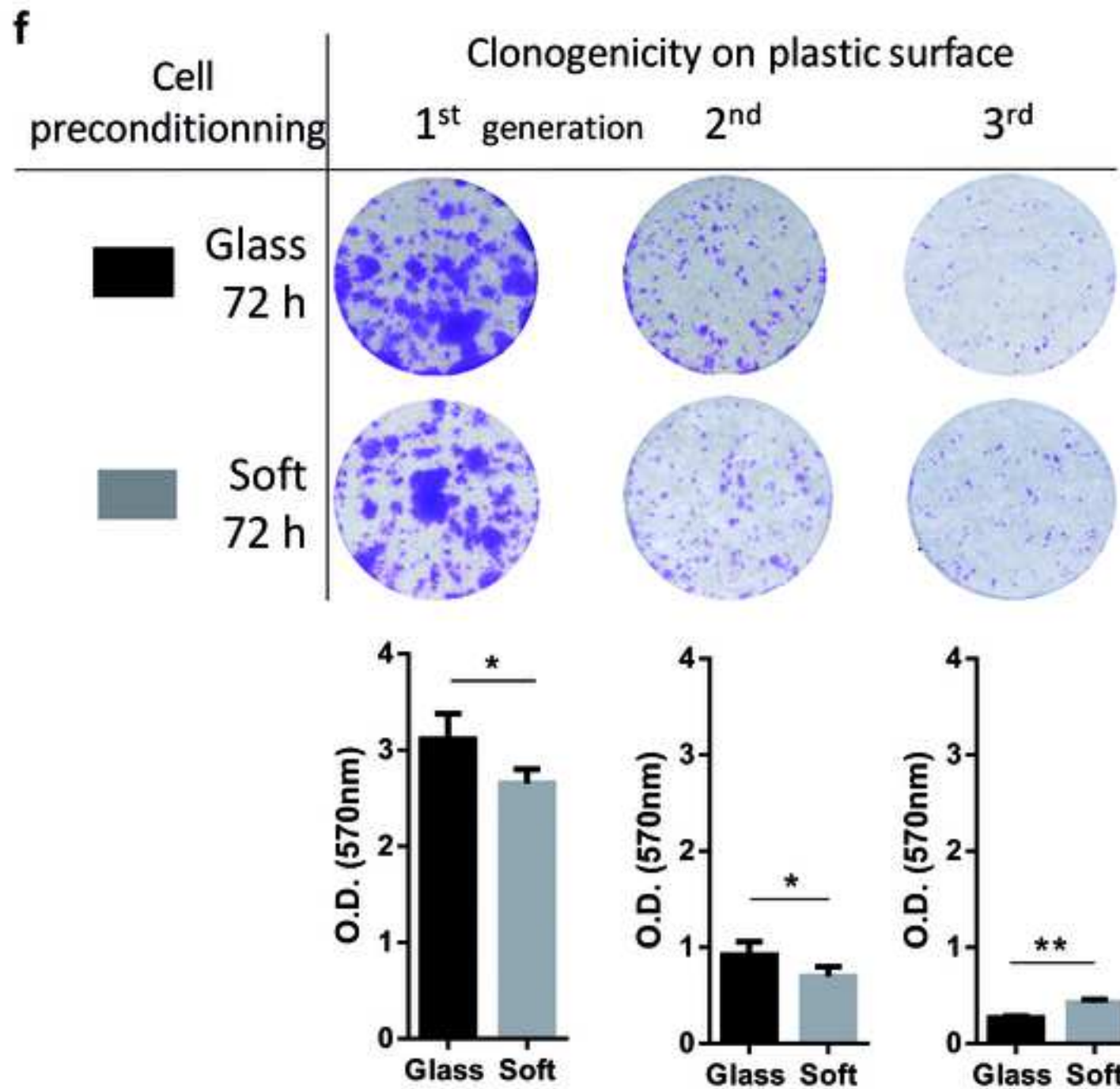
**a**

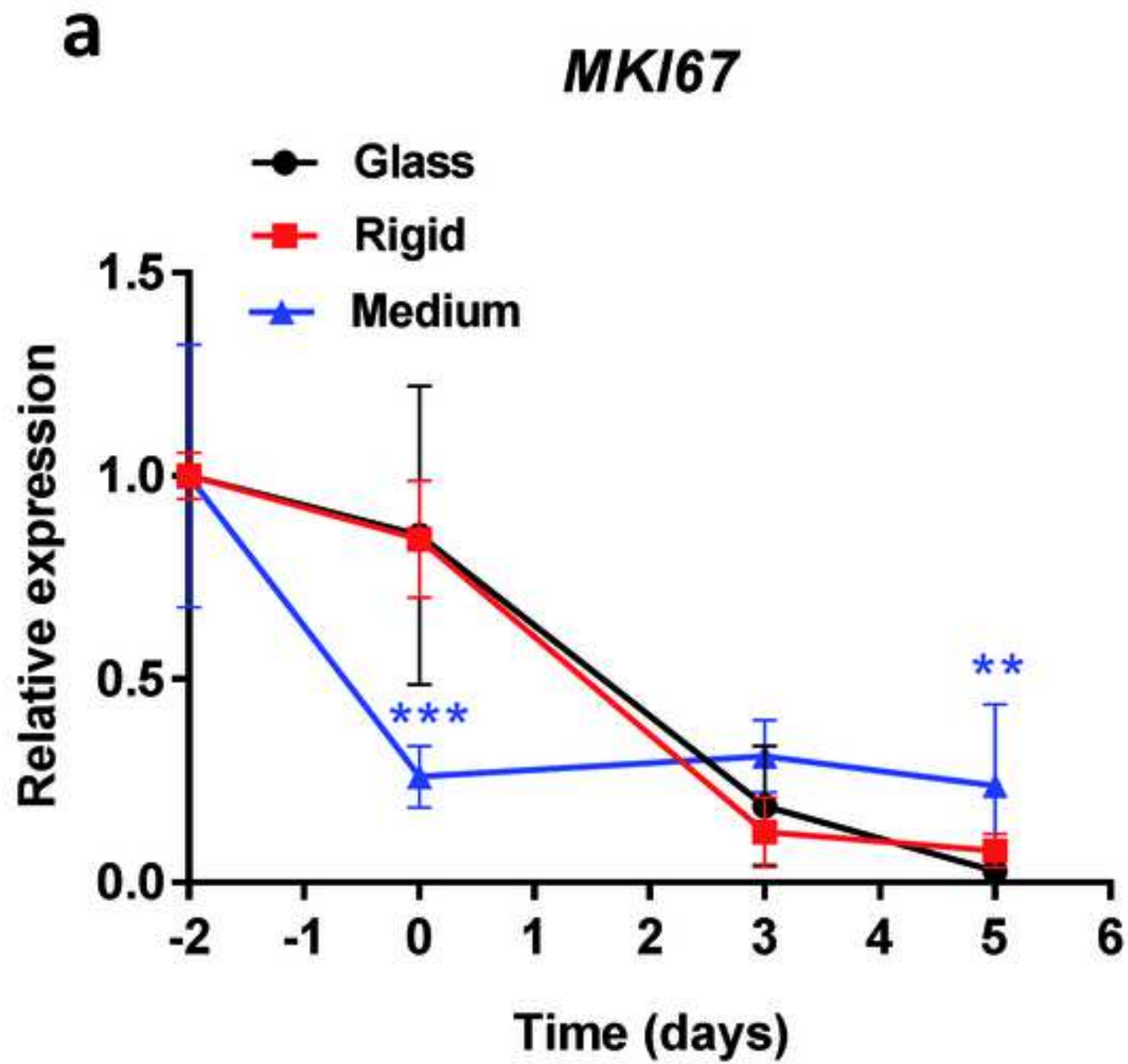


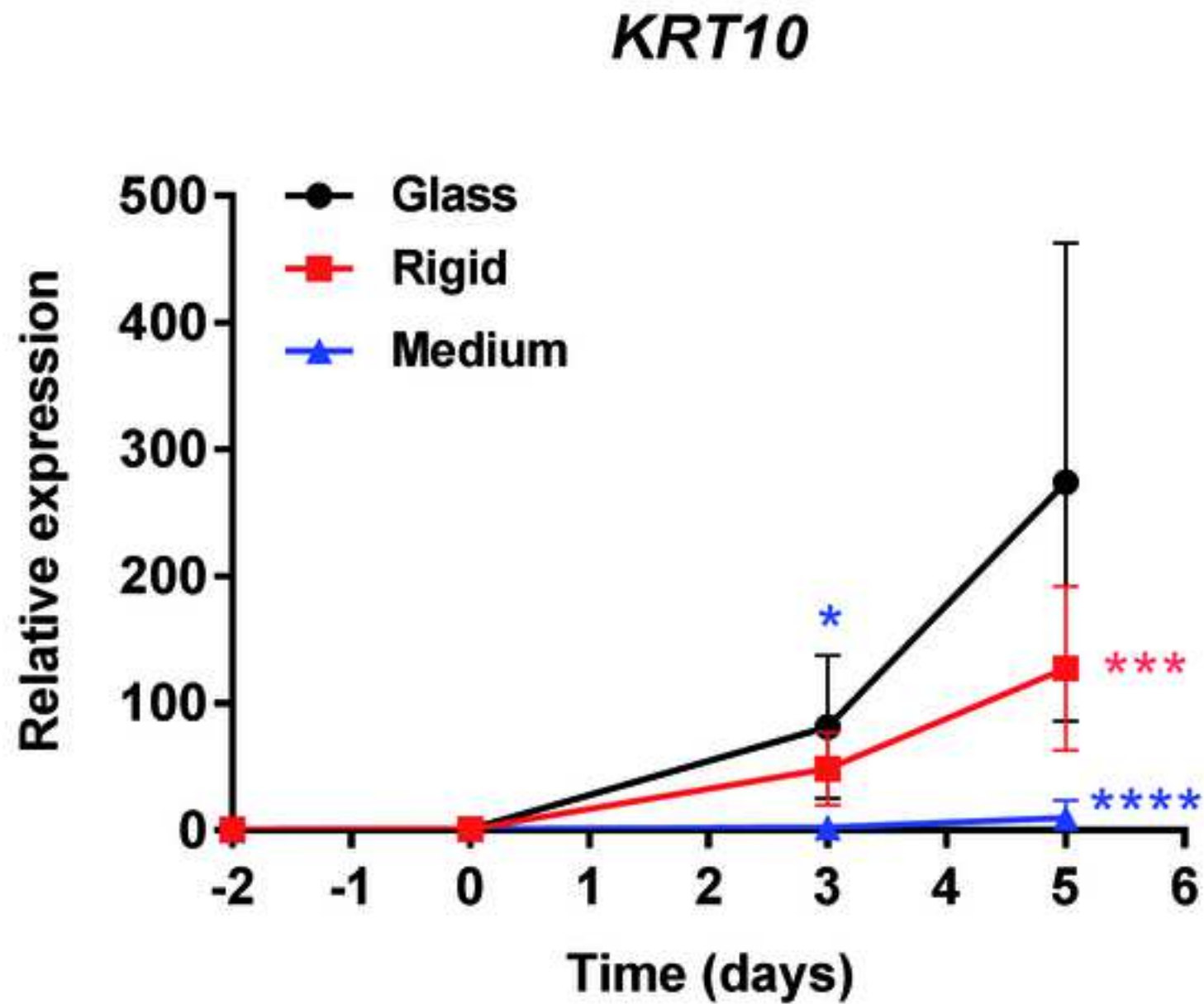


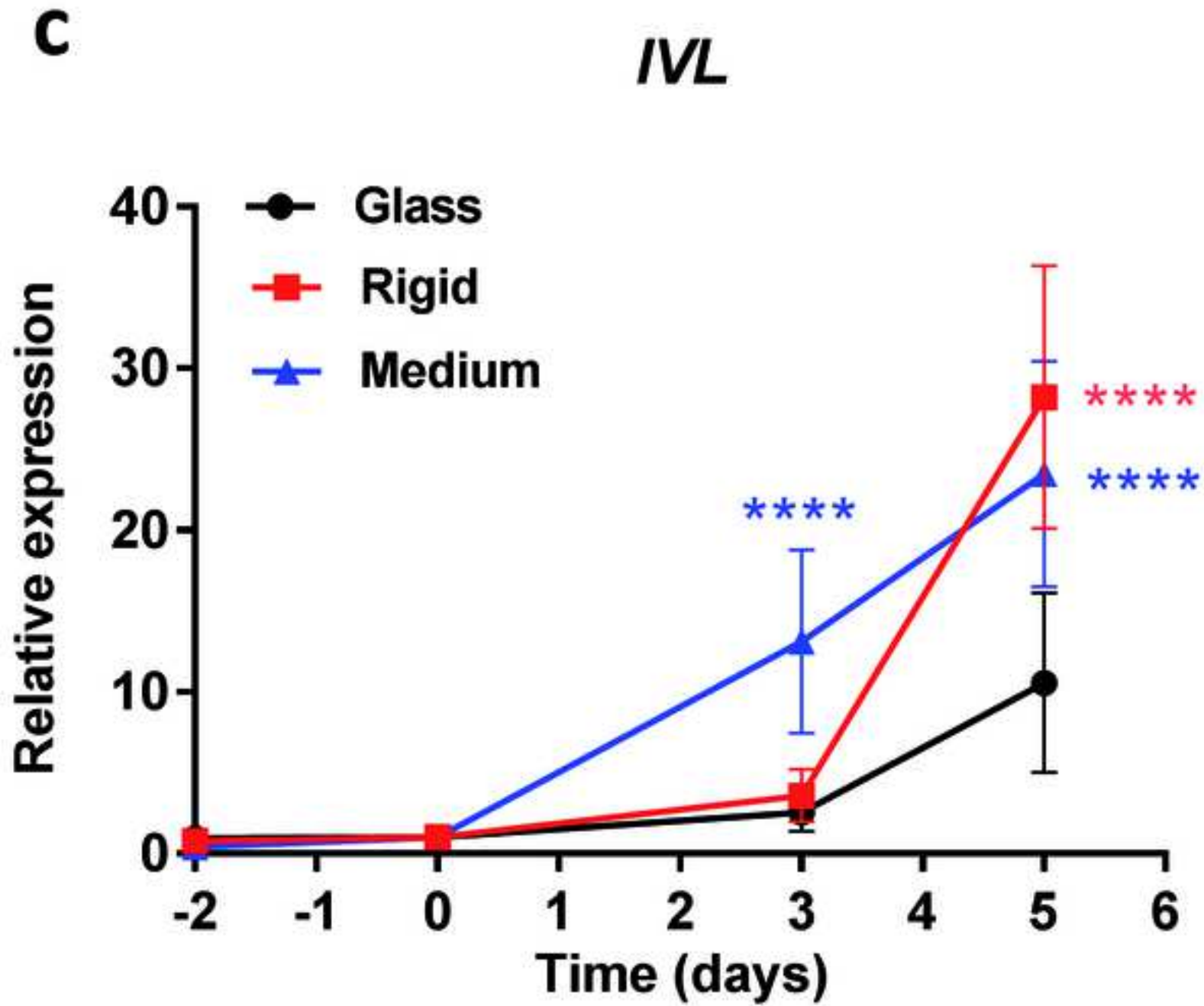
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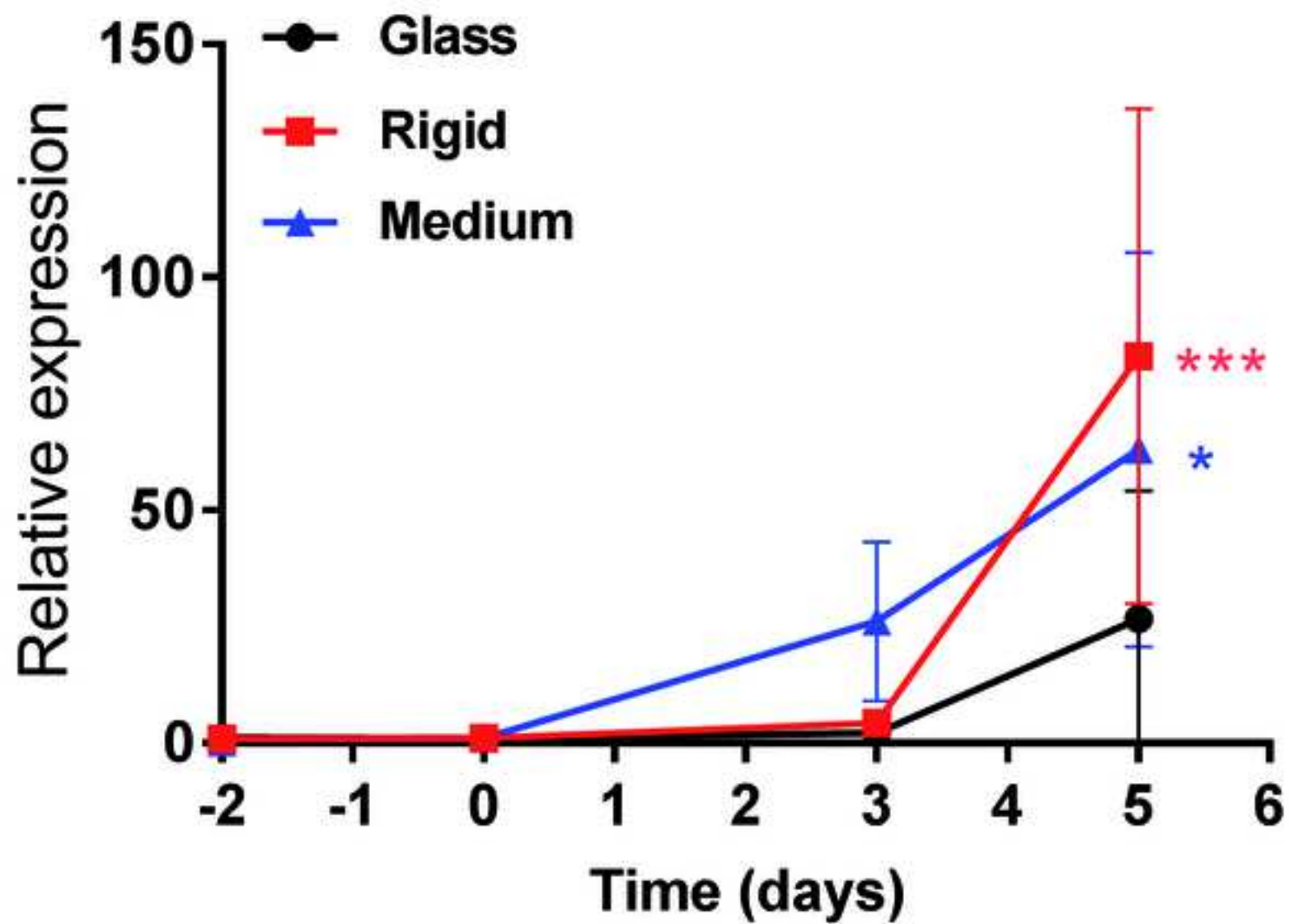
**e**





**b**



**d*****CDSN***

## Substrate softness promotes a reversible switch from proliferation to terminal differentiation in human keratinocytes

Archives of Dermatological Research

Choua Ya, Mariana Carrancá, Dominique Sigauco-Roussel, Philippe Faure, Bérengère Fromy, Romain Debret

Corresponding author: Romain Debret  
LBTI, UMR5305 CNRS/UCBL  
7, passage du Vercors  
F-69367 LYON cedex 7  
[romain.debret@ibcp.fr](mailto:romain.debret@ibcp.fr)

**ESM 1:** List of genes significantly up-regulated in Soft PAH conditions (FDR < 0.05)

ENTREZID	SYMBOL	GENENAME	logFC	P.Value	adj.P.Val
4496	MT1H	metallothionein 1H	7.704744986	0.00000025	0.000445626
4495	MT1G	metallothionein 1G	6.9150163	0.0000000891	0.000318165
190	NR0B1	nuclear receptor subfamily 0 group B member 1	6.356528973	0.00000043	0.000613997
3162	HMOX1	heme oxygenase 1	5.879224458	0.0000162	0.003122189
51655	RASD1	ras related dexamethasone induced 1	5.81352463	0.000036	0.004829526
151516	ASPRV1	aspartic peptidase retroviral like 1	5.69636296	0.0000599	0.006200796
2020	EN2	engrailed homeobox 2	5.650989002	0.0000093	0.002457072
79836	LONRF3	LON peptidase N-terminal domain and ring finger 3	5.621512989	0.0000175	0.003297014
4499	MT1M	metallothionein 1M	5.339928479	0.0000158	0.003088477
57495	NWD2	NACHT and WD repeat domain containing 2	5.227212738	0.0000477	0.005537686
4023	LPL	lipoprotein lipase	5.148438939	0.000130785	0.008545701
53405	CLIC5	chloride intracellular channel 5	5.141434644	0.0000403	0.004965955
6704	SPRR2E	small proline rich protein 2E	5.130676087	0.0000296	0.004227181

9687	GREB1	growth regulation by estrogen in breast cancer 1	4.935199125	0.001827889	0.0298467
29113	C6orf15	chromosome 6 open reading frame 15	4.903411379	0.0000599	0.006200796
26353	HSPB8	heat shock protein family B (small) member 8	4.878194603	0.000000123	0.000331905
10891	PPARGC1A	PPARG coactivator 1 alpha	4.805906724	0.0000607	0.006236022
353144	LCE3C	late cornified envelope 3C	4.704537239	0.0000687	0.006576086
9945	GFPT2	glutamine-fructose-6-phosphate transaminase 2	4.638976365	0.001829906	0.0298467
55894	DEFB103B	defensin beta 103B	4.629153041	0.0000947	0.0074074
3800	KIF5C	kinesin family member 5C	4.627380167	0.0000281	0.004193336
117248	GALNT15	polypeptide N-acetylgalactosaminyltransferase 15	4.627047841	0.00080042	0.020025925
448835	LCE6A	late cornified envelope 6A	4.599498938	0.0000967	0.0074319
84457	PHYHIPL	phytanoyl-CoA 2-hydroxylase interacting protein like	4.586148698	0.000330826	0.013091918
970	CD70	CD70 molecule	4.579584802	0.002773543	0.036894776
84648	LCE3D	late cornified envelope 3D	4.568382086	0.00042281	0.014625328
1646	AKR1C2	aldo-keto reductase family 1 member C2	4.557519331	0.000000000417	0.00000595
3310	HSPA6	heat shock protein family A (Hsp70) member 6	4.500275787	0.00000514	0.001910982
353132	LCE1B	late cornified envelope 1B	4.469123128	0.0000135	0.002803363
285629	LINC02159	long intergenic non-protein coding RNA 2159	4.431235781	0.000165437	0.009607466
3303	HSPA1A	heat shock protein family A (Hsp70) member 1A	4.393462604	0.000000194	0.000396648
79919	C2orf54	chromosome 2 open reading frame 54	4.372198571	0.000334864	0.013199701
563	AZGP1	alpha-2-glycoprotein 1, zinc-binding	4.285934108	0.00229109	0.033061129
4494	MT1F	metallothionein 1F	4.274857819	0.00000522	0.001910982
124976	SPNS2	sphingolipid transporter 2	4.269422281	0.000527127	0.016478185
139411	PTCHD1	patched domain containing 1	4.239007327	0.001800097	0.029828366
6707	SPRR3	small proline rich protein 3	4.236004634	0.00000212	0.001453041
145226	RDH12	retinol dehydrogenase 12 (all-trans/9-cis/11-cis)	4.223020006	0.000221507	0.010949647
3400	ID4	inhibitor of DNA binding 4, HLH protein	4.201490642	0.0000445	0.005210942
201780	SLC10A4	solute carrier family 10 member 4	4.177777788	0.003916534	0.044202495
153020	RASGEF1B	RasGEF domain family member 1B	4.171423638	0.000175665	0.009769532
353145	LCE3E	late cornified envelope 3E	4.168023556	0.000432183	0.014806154
6706	SPRR2G	small proline rich protein 2G	4.166890684	0.002237227	0.032646609
25984	KRT23	keratin 23	4.160071428	0.000282199	0.01201676

30061	SLC40A1	solute carrier family 40 member 1	4.152091104	0.00452598	0.048001592
353140	LCE2C	late cornified envelope 2C	4.129810536	0.001358917	0.025577715
149773	APCDD1L-AS1	APCDD1L antisense RNA 1 (head to head)	4.084399725	0.001671997	0.028640461
1474	CST6	cystatin E/M	4.079632448	0.0011824	0.024210904
63895	PIEZO2	piezo type mechanosensitive ion channel component 2	4.070869099	0.000151297	0.009055347
29986	SLC39A2	solute carrier family 39 member 2	4.060824468	0.001565883	0.027481821
57091	CASS4	Cas scaffolding protein family member 4	4.029648357	0.000476941	0.015399024
100505817	LOC100505817	uncharacterized LOC100505817	4.012869178	0.000350213	0.013454179
100506867	NA	NA	4.010955866	0.000446051	0.014902292
85004	REGG	RAS like estrogen regulated growth inhibitor	3.995337586	0.000932116	0.021443175
29935	RPA4	replication protein A4	3.991131575	0.001533352	0.027245611
1776	DNASE1L3	deoxyribonuclease 1 like 3	3.960409514	0.000400426	0.014395639
6523	SLC5A1	solute carrier family 5 member 1	3.957226394	0.000260388	0.011607762
27063	ANKRD1	ankyrin repeat domain 1	3.945726943	0.000614718	0.01751319
338322	NLRP10	NLR family pyrin domain containing 10	3.944247638	0.003986743	0.044711127
5733	PTGER3	prostaglandin E receptor 3	3.93860322	0.000709023	0.018792406
340654	LIPM	lipase family member M	3.937863786	0.001441892	0.026307631
10461	MERTK	MER proto-oncogene, tyrosine kinase	3.933901517	0.000274157	0.011868506
645687	LINC00520	long intergenic non-protein coding RNA 520	3.917278157	0.000254829	0.0115571
1999	ELF3	E74 like ETS transcription factor 3	3.914653374	0.0000204	0.003489411
388533	KRTDAP	keratinocyte differentiation associated protein	3.907230736	0.000114137	0.008094508
401934	RNF223	ring finger protein 223	3.899423855	0.001445087	0.026332283
448834	KPRP	keratinocyte proline rich protein	3.885229529	0.000439191	0.014857064
6004	RGS16	regulator of G protein signaling 16	3.84346384	0.00000135	0.001072505
100507025	NA	NA	3.821399503	0.00000835	0.002434283
100289255	TMEM238L	transmembrane protein 238 like	3.819465355	0.001995685	0.031192953
163778	SPRR4	small proline rich protein 4	3.816562223	0.00057416	0.016938968
51806	CALML5	calmodulin like 5	3.814418295	0.000000705	0.000775281
139221	MUM1L1	MUM1 like 1	3.805248555	0.004833381	0.04981655
383	ARG1	arginase 1	3.776923493	0.001767457	0.029629817
27289	RND1	Rho family GTPase 1	3.776497092	0.000576252	0.016938968

793	CALB1	calbindin 1	3.773418073	0.0000884	0.007372188
3569	IL6	interleukin 6	3.77092414	0.002737703	0.036672339
467	ATF3	activating transcription factor 3	3.76392836	0.0000000711	0.000318165
57161	PELI2	pellino E3 ubiquitin protein ligase family member 2	3.761801072	0.00088565	0.020771655
2520	GAST	gastrin	3.759517284	0.000173944	0.009744936
79689	STEAP4	STEAP4 metalloreductase	3.7566179	0.000000301	0.000478184
54544	CRCT1	cysteine rich C-terminal 1	3.750032598	0.000353103	0.013454179
57569	ARHGAP20	Rho GTPase activating protein 20	3.737643519	0.000997852	0.022503611
6615	SNAI1	snail family transcriptional repressor 1	3.73335791	0.0000303	0.004282304
345079	SOWAHB	sosondowah ankyrin repeat domain family member B	3.733262288	0.002237081	0.032646609
27165	GLS2	glutaminase 2	3.723297139	0.00000249	0.001453041
5669	PSG1	pregnancy specific beta-1-glycoprotein 1	3.709034552	0.000178242	0.009769532
374897	SBSN	suprabasin	3.699110393	0.0000651	0.006549405
57828	CATSPERG	cation channel sperm associated auxiliary subunit gamma	3.696106534	0.000172021	0.009744936
5166	PDK4	pyruvate dehydrogenase kinase 4	3.682319106	0.0000887	0.007372188
114907	FBXO32	F-box protein 32	3.674839671	0.0000206	0.003489411
121214	SDR9C7	short chain dehydrogenase/reductase family 9C member 7	3.669814202	0.000540253	0.01663374
339983	NAT8L	N-acetyltransferase 8 like	3.648591	0.000969505	0.022019625
23120	ATP10B	ATPase phospholipid transporting 10B (putative)	3.632090996	0.000910151	0.02120724
23237	ARC	activity regulated cytoskeleton associated protein	3.630229079	0.000185739	0.00991605
1380	CR2	complement C3d receptor 2	3.620570597	0.002676852	0.036316716
5801	PTPRR	protein tyrosine phosphatase, receptor type R	3.61568239	0.000737733	0.019267384
79852	EPHX3	epoxide hydrolase 3	3.604632833	0.0000847	0.007242077
118788	PIK3AP1	phosphoinositide-3-kinase adaptor protein 1	3.582866662	0.001245994	0.024688313
1562	CYP2C18	cytochrome P450 family 2 subfamily C member 18	3.57481204	0.00108615	0.023056065
337882	KRTAP19-1	keratin associated protein 19-1	3.564723795	0.003774028	0.04327528
196374	KRT78	keratin 78	3.54443253	0.0000558	0.006041402
55531	ELMOD1	ELMO domain containing 1	3.542426462	0.000336113	0.013199701
3169	FOXA1	forkhead box A1	3.525614702	0.001492922	0.026760208
401546	C9orf152	chromosome 9 open reading frame 152	3.507848502	0.003317353	0.040196532
54836	BSPRY	B-box and SPRY domain containing	3.50605376	0.000231942	0.011035795

57016	AKR1B10	aldo-keto reductase family 1 member B10	3.50462307	0.00000127	0.001072505
8000	PSCA	prostate stem cell antigen	3.493374394	0.000341911	0.013363601
1193	CLIC2	chloride intracellular channel 2	3.469854906	0.0000553	0.006041402
1645	AKR1C1	aldo-keto reductase family 1 member C1	3.459400279	0.00000132	0.001072505
163933	FAM43B	family with sequence similarity 43 member B	3.45913028	0.003145969	0.039081145
5017	OVOL1	ovo like transcriptional repressor 1	3.458270866	0.00000277	0.001520095
100507177	NA	NA	3.439363182	0.004579482	0.048246669
8365	HIST1H4H	histone cluster 1 H4 family member h	3.43748974	0.000622228	0.01760244
2627	GATA6	GATA binding protein 6	3.434982131	0.001849229	0.029952483
925	CD8A	CD8a molecule	3.419414552	0.001151579	0.023842694
655	BMP7	bone morphogenetic protein 7	3.411922141	0.000226492	0.011035795
8644	AKR1C3	aldo-keto reductase family 1 member C3	3.403542801	0.00000619	0.002103942
112399	EGLN3	egl-9 family hypoxia inducible factor 3	3.388348037	0.00005	0.005667281
4314	MMP3	matrix metalloproteinase 3	3.37578398	0.000319994	0.01287727
83698	CALN1	calneuron 1	3.369234529	0.000579397	0.016961605
389336	C5orf46	chromosome 5 open reading frame 46	3.343006271	0.001070276	0.022891564
3486	IGFBP3	insulin like growth factor binding protein 3	3.34139111	0.002477279	0.034560938
1775	DNASE1L2	deoxyribonuclease 1 like 2	3.339480546	0.004052842	0.045092597
254240	BPIFC	BPI fold containing family C	3.32193632	0.002739002	0.036672339
10788	IQGAP2	IQ motif containing GTPase activating protein 2	3.316220471	0.000868631	0.02071664
84518	CNFN	cornifelin	3.316057826	0.001192661	0.024271159
3352	HTR1D	5-hydroxytryptamine receptor 1D	3.313686148	0.000256139	0.011579761
10125	RASGRP1	RAS guanyl releasing protein 1	3.310248394	0.0000213	0.003489411
342897	NCCRP1	non-specific cytotoxic cell receptor protein 1 homolog (zebrafish)	3.30914067	0.000243326	0.011268069
8424	BBOX1	gamma-butyrobetaine hydroxylase 1	3.303236434	0.000260148	0.011607762
143630	UBQLNL	ubiquilin like	3.301653647	0.001813605	0.029828366
6236	RRAD	RRAD, Ras related glycolysis inhibitor and calcium channel regulator	3.301347349	0.000118011	0.008264262
58528	RRAGD	Ras related GTP binding D	3.284884799	0.000148117	0.00904275
158158	RASEF	RAS and EF-hand domain containing	3.280516233	0.000201915	0.010414046

171177	RHOV	ras homolog family member V	3.270088724	0.000477665	0.015399024
26525	IL36RN	interleukin 36 receptor antagonist	3.254819436	0.00034643	0.013448625
29948	OSGIN1	oxidative stress induced growth inhibitor 1	3.216269282	0.0000125	0.002709607
81607	NECTIN4	nectin cell adhesion molecule 4	3.214337924	0.0000123	0.002709607
353133	LCE1C	late cornified envelope 1C	3.21269423	0.0000713	0.006613006
283422	LINC01559	long intergenic non-protein coding RNA 1559	3.211828308	0.004690509	0.049018734
286676	ILDR1	immunoglobulin like domain containing receptor 1	3.205077983	0.003341938	0.040391647
284207	METRNL	meteorin like, glial cell differentiation regulator	3.204881929	0.0000407	0.004965955
3304	HSPA1B	heat shock protein family A (Hsp70) member 1B	3.204134546	0.000000627	0.000746709
8900	CCNA1	cyclin A1	3.203327208	0.000231106	0.011035795
7704	ZBTB16	zinc finger and BTB domain containing 16	3.197300796	0.001132478	0.023618367
285973	ATG9B	autophagy related 9B	3.189339355	0.001625184	0.02817643
126410	CYP4F22	cytochrome P450 family 4 subfamily F member 22	3.18691503	0.003455127	0.041133289
218	ALDH3A1	aldehyde dehydrogenase 3 family member A1	3.182022559	0.000122339	0.008371516
152206	CCDC13	coiled-coil domain containing 13	3.176147703	0.004349966	0.04697174
353135	LCE1E	late cornified envelope 1E	3.175985325	0.0000921	0.0074074
1543	CYP1A1	cytochrome P450 family 1 subfamily A member 1	3.151164516	0.0000989	0.007507048
6286	S100P	S100 calcium binding protein P	3.145815641	0.00053939	0.01663374
196446	MYRFL	myelin regulatory factor-like	3.139076541	0.0000142	0.002852226
54855	FAM46C	family with sequence similarity 46 member C	3.137506303	0.00000756	0.002296975
2318	FLNC	filamin C	3.131429913	0.000243723	0.011268069
6318	SERPINB4	serpin family B member 4	3.122770174	0.000326806	0.013041198
402415	XKRX	XK related, X-linked	3.121631686	0.004861055	0.049888676
1152	CKB	creatine kinase B	3.120194046	0.000036	0.004829526
645638	WFDC21P	WAP four-disulfide core domain 21, pseudogene	3.119588179	0.000153258	0.009122657
8645	KCNK5	potassium two pore domain channel subfamily K member 5	3.09488941	0.00065176	0.018044661
29091	STXBP6	syntaxin binding protein 6	3.093549397	0.0000256	0.003974103
9935	MAFB	MAF bZIP transcription factor B	3.088391454	0.00000228	0.001453041
245711	SPDYA	speedy/RINGO cell cycle regulator family member A	3.086847891	0.000162331	0.009543447
1364	CLDN4	claudin 4	3.08655607	0.000865322	0.02071664
93145	OLFM2	olfactomedin 2	3.081412011	0.000654251	0.018055543

126638	RPTN	repetin	3.075197849	0.000881698	0.020771655
100505994	LUCAT1	lung cancer associated transcript 1 (non-protein coding)	3.069048081	0.002229178	0.032646609
9333	TGM5	transglutaminase 5	3.0623187	0.002873829	0.0376018
206338	LVRN	laeverin	3.06040353	0.001781605	0.029629817
3034	HAL	histidine ammonia-lyase	3.055803198	0.001439666	0.026300607
440854	CAPN14	calpain 14	3.055629222	0.003141938	0.039081145
143662	MUC15	mucin 15, cell surface associated	3.055027376	0.00000254	0.001453041
165679	SPTSSB	serine palmitoyltransferase small subunit B	3.0533622	0.0000775	0.006817464
201516	ZSCAN4	zinc finger and SCAN domain containing 4	3.047335113	0.000632783	0.017767036
441478	NRARP	NOTCH regulated ankyrin repeat protein	3.038728146	0.00000754	0.002296975
100506140	NA	NA	3.038472543	0.00011309	0.008078013
1960	EGR3	early growth response 3	3.034664957	0.000650348	0.018044661
84000	TMPRSS13	transmembrane protease, serine 13	3.028217745	0.000217406	0.010859641
162333	MARCH10	membrane associated ring-CH-type finger 10	3.024453753	0.001237139	0.024615274
9173	IL1RL1	interleukin 1 receptor like 1	3.019449949	0.000597506	0.017244398
2669	GEM	GTP binding protein overexpressed in skeletal muscle	3.00126695	0.00000864	0.002457072
7006	TEC	tec protein tyrosine kinase	3.000732123	0.0000381	0.004953305
6947	TCN1	transcobalamin 1	2.997317867	0.00196567	0.030892812
57801	HES4	hes family bHLH transcription factor 4	2.993036759	0.000110811	0.007955022
57526	PCDH19	protocadherin 19	2.990897067	0.000758747	0.019429455
285848	PNPLA1	patatin like phospholipase domain containing 1	2.976908942	0.000702743	0.018695317
4886	NPY1R	neuropeptide Y receptor Y1	2.976172469	0.000126483	0.008444765
57221	ARFGEF3	ARFGEF family member 3	2.969541488	0.0000436	0.005143579
1050	CEBPA	CCAAT/enhancer binding protein alpha	2.952483024	0.00000946	0.002457072
144501	KRT80	keratin 80	2.942474201	0.000296252	0.012285888
11001	SLC27A2	solute carrier family 27 member 2	2.926901403	0.000021	0.003489411
242	ALOX12B	arachidonate 12-lipoxygenase, 12R type	2.891482398	0.000715378	0.01891603
100506657	NA	NA	2.872264458	0.002034256	0.031335479
627	BDNF	brain derived neurotrophic factor	2.850062716	0.000238166	0.011119076
5266	PI3	peptidase inhibitor 3	2.843279033	0.00101171	0.022599838
5396	PRRX1	paired related homeobox 1	2.830006196	0.002771622	0.036894776

6564	SLC15A1	solute carrier family 15 member 1	2.819424852	0.001056139	0.022821411
7425	VGf	VGf nerve growth factor inducible	2.805703055	0.001644242	0.028403434
64063	PRSS22	protease, serine 22	2.804691335	0.003144288	0.039081145
57482	KIAA1211	KIAA1211	2.798748664	0.001764987	0.029629817
4051	CYP4F3	cytochrome P450 family 4 subfamily F member 3	2.796490953	0.000600246	0.017256508
79153	GDPD3	glycerophosphodiester phosphodiesterase domain containing 3	2.776824976	0.001271532	0.024951404
10457	GPNMB	glycoprotein nmb	2.776548146	0.0000000592	0.000318165
388698	FLG2	filaggrin family member 2	2.773940684	0.001214477	0.024426494
11254	SLC6A14	solute carrier family 6 member 14	2.758044958	0.00098151	0.022256913
1191	CLU	clusterin	2.746137089	0.00000573	0.00199616
1041	CDSN	corneodesmosin	2.74342016	0.002837471	0.03740952
29760	BLNK	B-cell linker	2.740009336	0.00000888	0.002457072
23225	NUP210	nucleoporin 210	2.73825198	0.00083442	0.020411863
3398	ID2	inhibitor of DNA binding 2	2.735388712	0.000422225	0.014625328
114771	PGLYRP3	peptidoglycan recognition protein 3	2.733819995	0.003341147	0.040391647
79755	ZNF750	zinc finger protein 750	2.731716572	0.000128429	0.008533639
140290	TCP10L	t-complex 10 like	2.731651306	0.003864432	0.043954842
5650	KLK7	kallikrein related peptidase 7	2.720017487	0.000109753	0.007918819
130367	SGPP2	sphingosine-1-phosphate phosphatase 2	2.719167752	0.000211034	0.010615622
6590	SLPI	secretory leukocyte peptidase inhibitor	2.70790201	0.00445918	0.047681566
283120	H19	H19, imprinted maternally expressed transcript (non-protein coding)	2.704235862	0.002890343	0.037607316
2312	FLG	filaggrin	2.688784706	0.0000182	0.003318628
23645	PPP1R15A	protein phosphatase 1 regulatory subunit 15A	2.68852181	0.00000933	0.002457072
9518	GDF15	growth differentiation factor 15	2.686775989	0.0000224	0.003587675
22996	TTC39A	tetratricopeptide repeat domain 39A	2.674410485	0.001411312	0.026171944
643008	SMIM5	small integral membrane protein 5	2.669656686	0.000736988	0.019267384
124975	GGT6	gamma-glutamyltransferase 6	2.663814017	0.001617689	0.028080569
83715	ESPN	espin	2.661303501	0.0000726	0.006670581
8349	HIST2H2BE	histone cluster 2 H2B family member e	2.648324407	0.00000455	0.00185843

4884	NPTX1	neuronal pentraxin 1	2.641545222	0.000573847	0.016938968
10686	CLDN16	claudin 16	2.63643134	0.001156248	0.023894394
3713	IVL	involucrin	2.625687875	0.000857104	0.020615005
57822	GRHL3	grainyhead like transcription factor 3	2.60472092	0.00000515	0.001910982
344887	NMRAL2P	NmrA like redox sensor 2, pseudogene	2.601951291	0.0000254	0.003974103
1608	DGKG	diacylglycerol kinase gamma	2.60146104	0.0000993	0.007507048
57530	CGN	cingulin	2.590823909	0.001500544	0.026829498
55879	GABRQ	gamma-aminobutyric acid type A receptor theta subunit	2.590446892	0.000934543	0.021464449
286006	LSMEM1	leucine rich single-pass membrane protein 1	2.563259321	0.000868364	0.02071664
6280	S100A9	S100 calcium binding protein A9	2.557828096	0.000011	0.002629143
56649	TMPRSS4	transmembrane protease, serine 4	2.546311462	0.0000665	0.006558963
91608	RASL10B	RAS like family 10 member B	2.540632419	0.00021655	0.01085485
84659	RNASE7	ribonuclease A family member 7	2.538027306	0.0000208	0.003489411
390928	ACP7	acid phosphatase 7, tartrate resistant (putative)	2.534628008	0.001427601	0.026228184
27111	SDCBP2	syndecan binding protein 2	2.52104674	0.000347461	0.013452117
3576	CXCL8	C-X-C motif chemokine ligand 8	2.520507947	0.000309709	0.012744968
23026	MYO16	myosin XVI	2.519795739	0.000384919	0.014136139
440028	LOC440028	uncharacterized LOC440028	2.514825885	0.002211103	0.03249797
283404	LINC00592	long intergenic non-protein coding RNA 592	2.513750103	0.000873699	0.020771655
340526	RTL5	retrotransposon Gag like 5	2.508970359	0.002916457	0.037742954
151534	LBX2-AS1	LBX2 antisense RNA 1	2.502379053	0.0000557	0.006041402
643161	FAM25A	family with sequence similarity 25 member A	2.499935989	0.004610499	0.048447975
3305	HSPA1L	heat shock protein family A (Hsp70) member 1 like	2.489970673	0.000551702	0.016657922
1410	CRYAB	crystallin alpha B	2.488759583	0.000629774	0.017745466
286	ANK1	ankyrin 1	2.486107519	0.00090343	0.021088892
1363	CPE	carboxypeptidase E	2.484912494	0.000269922	0.011756407
6317	SERPINB3	serpin family B member 3	2.48227558	0.00000515	0.001910982
133	ADM	adrenomedullin	2.477978653	0.0000495	0.005656888
414149	ACBD7	acyl-CoA binding domain containing 7	2.47028854	0.000843355	0.020524998
652995	UCA1	urothelial cancer associated 1 (non-protein coding)	2.464463403	0.000122262	0.008371516
26999	CYFIP2	cytoplasmic FMR1 interacting protein 2	2.461310916	0.00000346	0.001703145

131583	FAM43A	family with sequence similarity 43 member A	2.460598785	0.003056064	0.038602062
79784	MYH14	myosin heavy chain 14	2.450203715	0.002550893	0.035175736
3383	ICAM1	intercellular adhesion molecule 1	2.443935219	0.004776824	0.04948637
154064	RAET1L	retinoic acid early transcript 1L	2.44265215	0.000913901	0.02120724
29841	GRHL1	grainyhead like transcription factor 1	2.442449962	0.00014349	0.008909595
255189	PLA2G4F	phospholipase A2 group IVF	2.440971304	0.003346005	0.04039799
4854	NOTCH3	notch 3	2.438977436	0.000437235	0.014857064
25833	POU2F3	POU class 2 homeobox 3	2.431296601	0.000209842	0.01059292
149175	MANEAL	mannosidase endo-alpha like	2.421164177	0.002265583	0.032892392
100506737	LINC01589	long intergenic non-protein coding RNA 1589	2.416311169	0.000273009	0.011854751
56300	IL36G	interleukin 36 gamma	2.414542194	0.0000929	0.0074074
745	MYRF	myelin regulatory factor	2.409557341	0.004465768	0.04768159
66004	LYNX1	Ly6/neurotoxin 1	2.405896339	0.000349789	0.013454179
10417	SPON2	spondin 2	2.399429746	0.001450624	0.0263856
8676	STX11	syntaxin 11	2.386439775	0.00055255	0.016657922
284391	ZNF844	zinc finger protein 844	2.385102817	0.000402898	0.014395639
1628	DBP	D-box binding PAR bZIP transcription factor	2.38165621	0.000247409	0.011342969
8878	SQSTM1	sequestosome 1	2.365824293	0.0000124	0.002709607
147166	TRIM16L	tripartite motif containing 16 like	2.35593176	0.000667004	0.018219529
25841	ABTB2	ankyrin repeat and BTB domain containing 2	2.35486025	0.0000778	0.006817464
200879	LIPH	lipase H	2.345547074	0.001670694	0.028640461
3857	KRT9	keratin 9	2.339351	0.003277032	0.040013401
23109	DDN	dendrin	2.320037636	0.000367723	0.013680451
1850	DUSP8	dual specificity phosphatase 8	2.318752922	0.001492676	0.026760208
8997	KALRN	kalirin RhoGEF kinase	2.311678716	0.003098299	0.03882044
3848	KRT1	keratin 1	2.309002949	0.001422001	0.026191703
3017	HIST1H2BD	histone cluster 1 H2B family member d	2.295125875	0.0000292	0.004210357
2628	GATM	glycine amidinotransferase	2.289674969	0.000236028	0.011091773
3868	KRT16	keratin 16	2.289278901	0.000850587	0.020615005
3570	IL6R	interleukin 6 receptor	2.273238813	0.00000634	0.002105421
79365	BHLHE41	basic helix-loop-helix family member e41	2.268951385	0.0000319	0.004428768

4688	NCF2	neutrophil cytosolic factor 2	2.260923926	0.0000315	0.004412237
100507004	NA	NA	2.259533853	0.003237411	0.039767541
1143	CHRNB4	cholinergic receptor nicotinic beta 4 subunit	2.254240204	0.002183493	0.03248105
6279	S100A8	S100 calcium binding protein A8	2.240775587	0.0000506	0.005690047
1326	MAP3K8	mitogen-activated protein kinase kinase kinase 8	2.232754926	0.0000188	0.003318628
2498	FTH1P3	ferritin heavy chain 1 pseudogene 3	2.231145088	0.000403422	0.014395639
55466	DNAJA4	DnaJ heat shock protein family (Hsp40) member A4	2.228589002	0.00000056	0.000727929
56920	SEMA3G	semaphorin 3G	2.22830579	0.000813906	0.020115597
389208	TMPRSS11F	transmembrane protease, serine 11F	2.226046227	0.002752228	0.036746098
2049	EPHB3	EPH receptor B3	2.22522904	0.000182638	0.00988323
647859	LOC647859	occludin pseudogene	2.222428396	0.004268349	0.046451934
65009	NDRG4	NDRG family member 4	2.221412184	0.000139879	0.00884638
118932	ANKRD22	ankyrin repeat domain 22	2.218065326	0.0000801	0.006958628
100129781	MIR193BHG	MIR193B host gene	2.213100386	0.000647383	0.018044661
55803	ADAP2	ArfGAP with dual PH domains 2	2.211363608	0.001005478	0.022599138
92815	HIST3H2A	histone cluster 3 H2A	2.203035904	0.000191403	0.010148185
11012	KLK11	kallikrein related peptidase 11	2.202120605	0.004356547	0.047003843
2495	FTH1	ferritin heavy chain 1	2.200523825	0.000176664	0.009769532
11221	DUSP10	dual specificity phosphatase 10	2.193660413	0.00001	0.002556081
643338	C15orf62	chromosome 15 open reading frame 62	2.192114289	0.000204237	0.01045454
161145	TMEM229B	transmembrane protein 229B	2.190518333	0.000957951	0.02193156
23024	PDZRN3	PDZ domain containing ring finger 3	2.18888367	0.002635791	0.03586182
171024	SYNPO2	synaptopodin 2	2.175734192	0.000265209	0.011657786
80352	RNF39	ring finger protein 39	2.173275112	0.0000108	0.002611285
785	CACNB4	calcium voltage-gated channel auxiliary subunit beta 4	2.168294635	0.001541574	0.02735535
22843	PPM1E	protein phosphatase, Mg <sup>2+</sup> /Mn <sup>2+</sup> dependent 1E	2.16046619	0.001386612	0.025894296
148523	CIART	circadian associated repressor of transcription	2.154780935	0.000510063	0.016156899
2861	GPR37	G protein-coupled receptor 37	2.151862967	0.000199096	0.010380622
84856	LINC00839	long intergenic non-protein coding RNA 839	2.138949901	0.001699157	0.029001382
83478	ARHGAP24	Rho GTPase activating protein 24	2.137041084	0.000043	0.005135249
8339	HIST1H2BG	histone cluster 1 H2B family member g	2.135672987	0.001851938	0.029954899

8334	HIST1H2AC	histone cluster 1 H2A family member c	2.135370705	0.001043838	0.022794514
64288	ZSCAN31	zinc finger and SCAN domain containing 31	2.134728856	0.001276749	0.024951404
91768	CABLES1	Cdk5 and Abl enzyme substrate 1	2.131438653	0.000635736	0.017808088
202915	TMEM184A	transmembrane protein 184A	2.128519897	0.001095737	0.02320743
4915	NTRK2	neurotrophic receptor tyrosine kinase 2	2.126831729	0.003437138	0.041055976
148534	TMEM56	transmembrane protein 56	2.123436106	0.000492489	0.015775093
11009	IL24	interleukin 24	2.121629257	0.002068359	0.031468129
100505730	NA	NA	2.120034148	0.00344754	0.041077199
100302742	RNU6-42P	RNA, U6 small nuclear 42, pseudogene	2.119113573	0.002884798	0.037607316
23242	COBL	cordon-bleu WH2 repeat protein	2.118128909	0.000150767	0.009055347
3207	HOXA11	homeobox A11	2.118091065	0.003819732	0.043550433
4501	MT1X	metallothionein 1X	2.116503634	0.000204083	0.01045454
55640	FLVCR2	feline leukemia virus subgroup C cellular receptor family member 2	2.113613276	0.000761841	0.019463922
1591	CYP24A1	cytochrome P450 family 24 subfamily A member 1	2.110937781	0.002711236	0.03643717
283553	LINC00640	long intergenic non-protein coding RNA 640	2.107591701	0.003797323	0.043337779
1843	DUSP1	dual specificity phosphatase 1	2.103514846	0.00012366	0.008405145
284029	LINC00324	long intergenic non-protein coding RNA 324	2.09539949	0.00184446	0.029952483
55800	SCN3B	sodium voltage-gated channel beta subunit 3	2.095339922	0.003536512	0.041858009
7037	TFRC	transferrin receptor	2.094280837	0.000029	0.004210357
8013	NR4A3	nuclear receptor subfamily 4 group A member 3	2.091991394	0.002818415	0.037302225
23409	SIRT4	sirtuin 4	2.085638074	0.000792282	0.019891991
57118	CAMK1D	calcium/calmodulin dependent protein kinase ID	2.077963694	0.003181641	0.039329306
314	AOC2	amine oxidase, copper containing 2	2.065906314	0.0000888	0.007372188
8581	LY6D	lymphocyte antigen 6 family member D	2.063150404	0.002570384	0.035274257
55057	CRYBG2	crystallin beta-gamma domain containing 2	2.056683985	0.002189751	0.03248105
2877	GPX2	glutathione peroxidase 2	2.04848647	0.002969897	0.038086132
57447	NDRG2	NDRG family member 2	2.048371991	0.00000132	0.001072505
339488	TFAP2E	transcription factor AP-2 epsilon	2.047358846	0.002689739	0.036353465
57110	HRASLS	HRAS like suppressor	2.046111569	0.003903502	0.044153154
80345	ZSCAN16	zinc finger and SCAN domain containing 16	2.042495025	0.000121385	0.008371516

54209	TREM2	triggering receptor expressed on myeloid cells 2	2.035331798	0.001062091	0.022821411
388697	HRNR	hornerin	2.034330669	0.004190927	0.046161594
1545	CYP1B1	cytochrome P450 family 1 subfamily B member 1	2.027060322	0.000227308	0.011035795
89874	SLC25A21	solute carrier family 25 member 21	2.026091637	0.004134853	0.045774261
4256	MGP	matrix Gla protein	2.02419542	0.002003289	0.031261963
10017	BCL2L10	BCL2 like 10	2.020925501	0.000139947	0.00884638
5016	OVGP1	oviductal glycoprotein 1	2.020858092	0.001011624	0.022599838
57633	LRRN1	leucine rich repeat neuronal 1	2.016017773	0.00055886	0.016737676
55853	IDI2-AS1	IDI2 antisense RNA 1	2.009422615	0.001186311	0.024210904
2786	GNG4	G protein subunit gamma 4	2.001619795	0.004702594	0.049037411
9076	CLDN1	claudin 1	1.997662732	0.0000406	0.004965955
246181	AKR7L	aldo-keto reductase family 7 like (gene/pseudogene)	1.993792184	0.002935283	0.037811947
51560	RAB6B	RAB6B, member RAS oncogene family	1.989311643	0.000531549	0.016528079
123745	PLA2G4E	phospholipase A2 group IVE	1.988129367	0.004826532	0.04981655
8710	SERPINB7	serpin family B member 7	1.985268744	0.00243014	0.034277902
3976	LIF	LIF, interleukin 6 family cytokine	1.983329014	0.000660852	0.018146906
7296	TXNRD1	thioredoxin reductase 1	1.970535237	0.000208921	0.010583825
170685	NUDT10	nudix hydrolase 10	1.966242321	0.002236333	0.032646609
144100	PLEKHA7	pleckstrin homology domain containing A7	1.961485117	0.00075806	0.019429455
9118	INA	internexin neuronal intermediate filament protein alpha	1.960346582	0.000376728	0.013906821
80852	GRIP2	glutamate receptor interacting protein 2	1.959720401	0.004855019	0.049862549
23329	TBC1D30	TBC1 domain family member 30	1.955913994	0.001510376	0.026937861
1828	DSG1	desmoglein 1	1.953340126	0.001716404	0.029260804
388403	YPEL2	yippee like 2	1.949765534	0.000064	0.00648345
6272	SORT1	sortilin 1	1.944886762	0.002453482	0.034440116
7062	TCHH	trichohyalin	1.936204152	0.000430297	0.014776981
639	PRDM1	PR/SET domain 1	1.92906911	0.0000942	0.0074074
23401	FRAT2	FRAT2, WNT signaling pathway regulator	1.926240112	0.000243024	0.011268069
84667	HES7	hes family bHLH transcription factor 7	1.924429535	0.000513546	0.016227506
127845	GOLT1A	golgi transport 1A	1.924207111	0.00436164	0.047003843
27293	SMPDL3B	sphingomyelin phosphodiesterase acid like 3B	1.921784099	0.001551789	0.027368962

84915	FAM222A	family with sequence similarity 222 member A	1.919948807	0.003027191	0.038488695
100289098	GS1-124K5.4	uncharacterized LOC100289098	1.919753229	0.004560064	0.048208126
3695	ITGB7	integrin subunit beta 7	1.916519573	0.003700811	0.042863912
221468	TMEM217	transmembrane protein 217	1.915980128	0.002454189	0.034440116
53342	IL17D	interleukin 17D	1.913622003	0.000138212	0.00884638
7127	TNFAIP2	TNF alpha induced protein 2	1.895385643	0.002258408	0.032855001
442213	PTCHD4	patched domain containing 4	1.888939648	0.000651749	0.018044661
2745	GLRX	glutaredoxin	1.885990332	0.001499442	0.026829498
2651	GCNT2	glucosaminyl (N-acetyl) transferase 2, I-branching enzyme (I blood group)	1.880715244	0.000208861	0.010583825
201501	ZBTB7C	zinc finger and BTB domain containing 7C	1.876221253	0.000770906	0.019596383
5292	PIM1	Pim-1 proto-oncogene, serine/threonine kinase	1.876179576	0.0000682	0.006576086
57134	MAN1C1	mannosidase alpha class 1C member 1	1.871452934	0.002414026	0.03421307
153222	CREBRF	CREB3 regulatory factor	1.869343668	0.000469766	0.015287201
149428	BNIP1	BCL2 interacting protein like	1.864643537	0.000446464	0.014902292
147645	VSIG10L	V-set and immunoglobulin domain containing 10 like	1.864284394	0.00175689	0.029612453
51083	GAL	galanin and GMAP prepropeptide	1.8634887	0.00335643	0.040454568
64127	NOD2	nucleotide binding oligomerization domain containing 2	1.851786657	0.004547216	0.048191049
115123	MARCH3	membrane associated ring-CH-type finger 3	1.851230355	0.004362809	0.047003843
9119	KRT75	keratin 75	1.850291728	0.0000974	0.007442816
25805	BAMBI	BMP and activin membrane bound inhibitor	1.850282742	0.000391896	0.014209703
57823	SLAMF7	SLAM family member 7	1.847571122	0.0000765	0.006811171
4929	NR4A2	nuclear receptor subfamily 4 group A member 2	1.844899548	0.000412293	0.01450743
4824	NKX3-1	NK3 homeobox 1	1.843367975	0.000791972	0.019891991
3708	ITPR1	inositol 1,4,5-trisphosphate receptor type 1	1.841257699	0.000679758	0.018347544
84708	LN3	ligand of numb-protein X 1	1.836466236	0.001308898	0.025200694
84803	GPAT3	glycerol-3-phosphate acyltransferase 3	1.83442306	0.000103737	0.00767872
9099	USP2	ubiquitin specific peptidase 2	1.830954623	0.004694181	0.04902125
143903	LAYN	layilin	1.829491427	0.003093032	0.03882044
5275	SERPINB13	serpin family B member 13	1.816224552	0.0000185	0.003318628
8493	PPM1D	protein phosphatase, Mg <sup>2+</sup> /Mn <sup>2+</sup> dependent 1D	1.805976373	0.0000377	0.004953305

6261	RYR1	ryanodine receptor 1	1.804846888	0.000961327	0.021973639
220001	VWCE	von Willebrand factor C and EGF domains	1.804087499	0.001555722	0.027392245
8793	TNFRSF10D	TNF receptor superfamily member 10d	1.801903588	0.00000418	0.00185843
54681	P4HTM	prolyl 4-hydroxylase, transmembrane	1.800408998	0.003600244	0.042227488
200942	KLHDC8B	kelch domain containing 8B	1.791154519	0.000478592	0.015399024
10626	TRIM16	tripartite motif containing 16	1.780711687	0.0000114	0.002680286
154664	ABCA13	ATP binding cassette subfamily A member 13	1.780431805	0.003114731	0.038896026
150946	GAREM2	GRB2 associated regulator of MAPK1 subtype 2	1.780369842	0.002029201	0.031335479
8942	KYNU	kynureninase	1.776826192	0.001873205	0.0300681
22997	IGSF9B	immunoglobulin superfamily member 9B	1.771057321	0.003348118	0.04039799
54898	ELOVL2	ELOVL fatty acid elongase 2	1.763854055	0.00175621	0.029612453
128876	FAM83C	family with sequence similarity 83 member C	1.762068985	0.004204428	0.046203426
8637	EIF4EBP3	eukaryotic translation initiation factor 4E binding protein 3	1.756670151	0.00351432	0.04162983
56997	COQ8A	coenzyme Q8A	1.752309188	0.0000381	0.004953305
9846	GAB2	GRB2 associated binding protein 2	1.743758175	0.002916717	0.037742954
3006	HIST1H1C	histone cluster 1 H1 family member c	1.739683865	0.000173457	0.009744936
55603	FAM46A	family with sequence similarity 46 member A long intergenic non-protein coding RNA, p53 induced	1.739128293	0.0000673	0.006558963
378805	LINC-PINT	transcript	1.737127171	0.000572975	0.016938968
57535	KIAA1324	KIAA1324	1.734834163	0.004519659	0.048001592
23526	ARHGAP45	Rho GTPase activating protein 45	1.733188768	0.001292369	0.025026186
668	FOXL2	forkhead box L2	1.731728477	0.00434489	0.046952418
100506658	OCLN	occludin	1.730929806	0.000193218	0.010148185
604	BCL6	B-cell CLL/lymphoma 6	1.730471193	0.0000172	0.003281203
80318	GKAP1	G kinase anchoring protein 1	1.728819668	0.000920746	0.021250033
2043	EPHA4	EPH receptor A4	1.722096468	0.000857155	0.020615005
7633	ZNF79	zinc finger protein 79	1.720220268	0.000105986	0.007764722
201161	CENPV	centromere protein V	1.705004318	0.001917819	0.030599186
10437	IFI30	IFI30, lysosomal thiol reductase	1.702798572	0.000407466	0.014395639
1119	CHKA	choline kinase alpha	1.699827928	0.0000732	0.006670581
2512	FTL	ferritin light chain	1.697201162	0.001968571	0.030904406

231	AKR1B1	aldo-keto reductase family 1 member B	1.696165081	0.0000194	0.003375142
9314	KLF4	Kruppel like factor 4	1.695813507	0.00088292	0.020771655
415116	PIM3	Pim-3 proto-oncogene, serine/threonine kinase	1.685729033	0.000131003	0.008545701
4741	NEFM	neurofilament medium	1.684998152	0.001277829	0.024951404
284408	ZNF790-AS1	ZNF790 antisense RNA 1	1.681819677	0.004822095	0.04981655
1612	DAPK1	death associated protein kinase 1	1.672778361	0.000232418	0.011035795
266812	NAP1L5	nucleosome assembly protein 1 like 5	1.671845308	0.001274617	0.024951404
140775	SMCR8	Smith-Magenis syndrome chromosome region, candidate 8	1.670901424	0.0000538	0.006001285
658	BMPR1B	bone morphogenetic protein receptor type 1B	1.67088091	0.000518571	0.016246284
8844	KSR1	kinase suppressor of ras 1	1.665057534	0.001084876	0.023056065
284071	MEIOC	meiosis specific with coiled-coil domain	1.663666594	0.003316295	0.040196532
56963	RGMA	repulsive guidance molecule family member a	1.66306073	0.002220002	0.032566553
1634	DCN	decorin	1.646928133	0.001547188	0.02735535
26996	GPR160	G protein-coupled receptor 160	1.641236883	0.004831909	0.04981655
54800	KLHL24	kelch like family member 24	1.637874968	0.000317813	0.012861957
4808	NHLH2	nescient helix-loop-helix 2	1.637453612	0.003128153	0.039029511
11005	SPINK5	serine peptidase inhibitor, Kazal type 5	1.635552957	0.003055022	0.038602062
55290	BRF2	BRF2, RNA polymerase III transcription initiation factor subunit	1.633899183	0.003059189	0.0386074
390	RND3	Rho family GTPase 3	1.627528431	0.0000217	0.003521996
58476	TP53INP2	tumor protein p53 inducible nuclear protein 2	1.623652148	0.001046518	0.022794514
8987	STBD1	starch binding domain 1	1.613814171	0.001050158	0.022821411
7345	UCHL1	ubiquitin C-terminal hydrolase L1	1.607977817	0.000062	0.006329383
26154	ABCA12	ATP binding cassette subfamily A member 12	1.606401602	0.000026	0.003998079
25819	NOCT	nocturnin	1.606333538	0.00023252	0.011035795
1466	CSRP2	cysteine and glycine rich protein 2	1.601763606	0.0000599	0.006200796
1139	CHRNA7	cholinergic receptor nicotinic alpha 7 subunit	1.597818356	0.004257521	0.046429726
83481	EPPK1	epiplakin 1	1.59740142	0.002466819	0.034516132
26507	CNNM1	cyclin and CBS domain divalent metal cation transport mediator 1	1.590579848	0.000168648	0.009697752
10297	APC2	APC2, WNT signaling pathway regulator	1.583660499	0.001486255	0.026707724
201163	FLCN	folliculin	1.567564068	0.0000423	0.00512584

132946	ARL9	ADP ribosylation factor like GTPase 9	1.566519558	0.001460504	0.02648387
81572	PDRG1	p53 and DNA damage regulated 1	1.556348452	0.000534383	0.016528079
124935	SLC43A2	solute carrier family 43 member 2	1.551670019	0.002959407	0.03801986
4008	LMO7	LIM domain 7	1.546980118	0.001308782	0.025200694
27314	RAB30	RAB30, member RAS oncogene family	1.546750979	0.000743979	0.019289439
196264	MPZL3	myelin protein zero like 3	1.545194554	0.000144689	0.008909595
6303	SAT1	spermidine/spermine N1-acetyltransferase 1	1.544514915	0.000434657	0.014819822
4758	NEU1	neuraminidase 1	1.539861454	0.000297244	0.012285888
3858	KRT10	keratin 10	1.530730455	0.000509682	0.016156899
1749	DLX5	distal-less homeobox 5	1.521349057	0.002054749	0.031394807
4638	MYLK	myosin light chain kinase	1.512933219	0.000815269	0.020115597
7832	BTG2	BTG anti-proliferation factor 2	1.510736567	0.002474615	0.034557523
7779	SLC30A1	solute carrier family 30 member 1	1.507493727	0.000690633	0.018441848
54897	CASZ1	castor zinc finger 1	1.507241982	0.0000565	0.006064759
25888	ZNF473	zinc finger protein 473	1.506727902	0.000151493	0.009055347
120224	TMEM45B	transmembrane protein 45B	1.505732797	0.000445155	0.014902292
30811	HUNK	hormonally up-regulated Neu-associated kinase	1.505300289	0.004612869	0.048447975
25797	QPCT	glutaminyl-peptide cyclotransferase	1.499230296	0.0001265	0.008444765
57568	SIPA1L2	signal induced proliferation associated 1 like 2	1.498904239	0.000516836	0.016227506
10808	HSPH1	heat shock protein family H (Hsp110) member 1	1.495435896	0.001776007	0.029629817
79797	ZNF408	zinc finger protein 408	1.493802138	0.001021101	0.022651327
79029	SPATA5L1	spermatogenesis associated 5 like 1	1.485991758	0.0000675	0.006558963
10950	BTG3	BTG anti-proliferation factor 3	1.476489847	0.00000434	0.00185843
286887	KRT6C	keratin 6C	1.472008101	0.002425293	0.034277902
4616	GADD45B	growth arrest and DNA damage inducible beta	1.467186823	0.000964794	0.021982532
3301	DNAJA1	DnaJ heat shock protein family (Hsp40) member A1	1.463148982	0.000290586	0.012285888
23119	HIC2	HIC ZBTB transcriptional repressor 2	1.457024112	0.002205419	0.03248105
3005	H1FO	H1 histone family member 0	1.450324881	0.0000155	0.003085317
3635	INPP5D	inositol polyphosphate-5-phosphatase D	1.448966222	0.003168648	0.039253342
631	BFSP1	beaded filament structural protein 1	1.448674049	0.002335231	0.033596287
22949	PTGR1	prostaglandin reductase 1	1.447616003	0.000441989	0.014857064

64651	CSRNP1	cysteine and serine rich nuclear protein 1	1.444774576	0.00007	0.006576086
89848	FCHSD1	FCH and double SH3 domains 1	1.444014617	0.004743377	0.049223256
85453	TSPYL5	TSPY like 5	1.440956042	0.001824581	0.0298467
91947	ARRDC4	arrestin domain containing 4	1.440116172	0.000055	0.006041402
9734	HDAC9	histone deacetylase 9	1.439769786	0.001948335	0.030742438
64110	MAGEF1	MAGE family member F1	1.436933145	0.000799032	0.020025925
10127	ZNF263	zinc finger protein 263	1.435665143	0.000456476	0.015080192
84898	PLXDC2	plexin domain containing 2	1.435565094	0.000102497	0.00762642
10370	CITED2	Cbp/p300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 2	1.431396025	0.000854945	0.020615005
5097	PCDH1	protocadherin 1	1.430233942	0.000438813	0.014857064
1604	CD55	CD55 molecule (Cromer blood group)	1.422160581	0.00324603	0.039804464
1244	ABCC2	ATP binding cassette subfamily C member 2	1.421726976	0.00126543	0.024951404
220136	CFAP53	cilia and flagella associated protein 53	1.420643507	0.004730119	0.049145072
5228	PGF	placental growth factor	1.417488181	0.002211118	0.03249797
1942	EFNA1	ephrin A1	1.404181372	0.000149055	0.009055347
2052	EPHX1	epoxide hydrolase 1	1.403468099	0.000275158	0.011875856
58191	CXCL16	C-X-C motif chemokine ligand 16	1.403451557	0.004850134	0.049848208
140809	SRXN1	sulfiredoxin 1	1.398813242	0.0000282	0.004193336
6809	STX3	syntaxin 3	1.396533345	0.0000127	0.002709607
284023	LINC02581	long intergenic non-protein coding RNA 2581	1.3953047	0.000622234	0.01760244
27	ABL2	ABL proto-oncogene 2, non-receptor tyrosine kinase	1.390107843	0.000139751	0.00884638
4783	NFIL3	nuclear factor, interleukin 3 regulated	1.38964991	0.000262048	0.011607762
8804	CREG1	cellular repressor of E1A stimulated genes 1	1.383281719	0.002148349	0.032238774
54852	PAQR5	progesterone and adipoQ receptor family member 5	1.381513423	0.002200483	0.03248105
3320	HSP90AA1	heat shock protein 90 alpha family class A member 1	1.379772868	0.000543212	0.016657922
100506761	NA	NA	1.379537693	0.004708697	0.049065241
80329	ULBP1	UL16 binding protein 1	1.3740737	0.000605753	0.017342257
6879	TAF7	TATA-box binding protein associated factor 7	1.370481833	0.000105476	0.007764722
147837	ZNF563	zinc finger protein 563	1.369691326	0.003111201	0.038885935
115560	ZNF501	zinc finger protein 501	1.363557397	0.002404971	0.034164663

760	CA2	carbonic anhydrase 2	1.363533215	0.001205886	0.024374625
202781	PAXIP1-AS1	PAXIP1 antisense RNA 1 (head to head)	1.358409197	0.002037073	0.031335479
64968	MRPS6	mitochondrial ribosomal protein S6	1.355925659	0.000169707	0.009697752
144568	A2ML1	alpha-2-macroglobulin like 1	1.346686992	0.004202992	0.046203426
221178	SPATA13	spermatogenesis associated 13	1.343198496	0.000882378	0.020771655
3725	JUN	Jun proto-oncogene, AP-1 transcription factor subunit	1.339599709	0.0000127	0.002709607
9762	LZTS3	leucine zipper tumor suppressor family member 3	1.335402319	0.004832164	0.04981655
79088	ZNF426	zinc finger protein 426	1.332459755	0.002033007	0.031335479
10007	GNPDA1	glucosamine-6-phosphate deaminase 1	1.3265318	0.000164258	0.009577892
23199	GSE1	Gse1 coiled-coil protein	1.321255965	0.00042501	0.014665908
526	ATP6V1B2	ATPase H <sup>+</sup> transporting V1 subunit B2	1.31030788	0.000315289	0.012796079
6785	ELOVL4	ELOVL fatty acid elongase 4	1.306068772	0.000117558	0.008264262
28970	C11orf54	chromosome 11 open reading frame 54	1.305005708	0.002890832	0.037607316
8613	PLPP3	phospholipid phosphatase 3	1.302758572	0.000417918	0.014625328
64762	GAREM1	GRB2 associated regulator of MAPK1 subtype 1	1.301819121	0.002131319	0.032050557
3983	ABLIM1	actin binding LIM protein 1	1.30032916	0.0000285	0.004203696
10172	ZNF256	zinc finger protein 256	1.300210538	0.003170822	0.039253342
573	BAG1	BCL2 associated athanogene 1	1.296800555	0.000119377	0.008319121
79693	YRDC	yrdC N6-threonylcarbamoyltransferase domain containing	1.296427943	0.000553865	0.016657922
83593	RASSF5	Ras association domain family member 5	1.295485803	0.001103039	0.023207686
79663	HSPBAP1	HSPB1 associated protein 1	1.29461513	0.000186021	0.00991605
57480	PLEKHG1	pleckstrin homology and RhoGEF domain containing G1	1.292655918	0.001037015	0.022786467
51531	TRMO	tRNA methyltransferase O	1.290903753	0.000237511	0.011119076
1026	CDKN1A	cyclin dependent kinase inhibitor 1A	1.288305354	0.002041873	0.031335479
51234	EMC4	ER membrane protein complex subunit 4	1.281954679	0.000141873	0.008889455
63906	GPATCH3	G-patch domain containing 3	1.281614523	0.001018512	0.022629028
54762	GRAMD1C	GRAM domain containing 1C	1.269746987	0.002747466	0.036746098
100132909	NA	NA	1.266873351	0.002680887	0.036336959
147727	ILF3-AS1	ILF3 antisense RNA 1 (head to head)	1.2656467	0.000588847	0.017065433
23710	GABARAPL1	GABA type A receptor associated protein like 1	1.261144844	0.003324319	0.040246797
51499	TRIAP1	TP53 regulated inhibitor of apoptosis 1	1.258082446	0.001731263	0.029387352

5997	RGS2	regulator of G protein signaling 2	1.257770881	0.001052929	0.022821411
11080	DNAJB4	DnaJ heat shock protein family (Hsp40) member B4	1.256954632	0.002751435	0.036746098
91373	UAP1L1	UDP-N-acetylglucosamine pyrophosphorylase 1 like 1	1.255869377	0.001891299	0.030290461
51228	GLTP	glycolipid transfer protein	1.255592966	0.001840431	0.029945785
55544	RBM38	RNA binding motif protein 38	1.250648942	0.002197818	0.03248105
152217	NCBP2-AS2	NCBP2 antisense RNA 2 (head to head)	1.249509494	0.000168215	0.009697752
55665	URGCP	upregulator of cell proliferation	1.24733681	0.000342369	0.013363601
64795	RMND5A	required for meiotic nuclear division 5 homolog A	1.245951971	0.000967336	0.022005364
79603	CERS4	ceramide synthase 4	1.245830358	0.001196149	0.024288422
284371	ZNF841	zinc finger protein 841	1.245074587	0.00102375	0.022674871
90987	ZNF251	zinc finger protein 251	1.231429225	0.002565225	0.035271231
150726	FBXO41	F-box protein 41	1.230509705	0.004167264	0.046042948
4133	MAP2	microtubule associated protein 2	1.228743941	0.000228685	0.011035795
8846	ALKBH1	alkB homolog 1, histone H2A dioxygenase	1.223780506	0.000262038	0.011607762
1030	CDKN2B	cyclin dependent kinase inhibitor 2B	1.222522605	0.000261151	0.011607762
9923	ZBTB40	zinc finger and BTB domain containing 40	1.21892856	0.000361515	0.01351989
64782	AEN	apoptosis enhancing nuclease	1.213103852	0.000328026	0.013053422
8495	PPFIBP2	PPFIA binding protein 2	1.21244818	0.003774394	0.04327528
55076	TMEM45A	transmembrane protein 45A	1.212216472	0.000122473	0.008371516
10580	SORBS1	sorbin and SH3 domain containing 1	1.211715886	0.001930712	0.030613813
788	SLC25A20	solute carrier family 25 member 20	1.206713354	0.003880563	0.044068143
4739	NEDD9	neural precursor cell expressed, developmentally down-regulated 9	1.205885246	0.002043605	0.031335479
10105	PPIF	peptidylprolyl isomerase F	1.205437843	0.000233327	0.011037472
57035	RSRP1	arginine and serine rich protein 1	1.201628704	0.0045657	0.048208126
123	PLIN2	perilipin 2	1.200019151	0.001386326	0.025894296
85415	RHPN2	rhopilin Rho GTPase binding protein 2	1.194684096	0.000515425	0.016227506
57685	CACHD1	cache domain containing 1	1.193702106	0.000371303	0.013777754
25764	HYPK	huntingtin interacting protein K	1.193244736	0.000267446	0.011720027
5052	PRDX1	peroxiredoxin 1	1.19275286	0.000359479	0.013479032
3280	HES1	hes family bHLH transcription factor 1	1.192392345	0.000654681	0.018055543

79673	ZNF329	zinc finger protein 329	1.183323488	0.00041997	0.014625328
10929	SRSF8	serine and arginine rich splicing factor 8	1.181604507	0.0000398	0.004965955
51526	OSER1	oxidative stress responsive serine rich 1	1.171480797	0.000179152	0.009769532
6018	RLF	rearranged L-myc fusion	1.171472343	0.00175776	0.029612453
3399	ID3	inhibitor of DNA binding 3, HLH protein	1.171394715	0.003893527	0.044153154
11056	DDX52	DExD-box helicase 52	1.168487721	0.001730085	0.029387352
11116	FGFR1OP	FGFR1 oncogene partner	1.168121176	0.000381644	0.014051957
80315	CPEB4	cytoplasmic polyadenylation element binding protein 4	1.168001513	0.000310461	0.012744968
6829	SUPT5H	SPT5 homolog, DSIF elongation factor subunit	1.165815074	0.000814834	0.020115597
7074	TIAM1	T-cell lymphoma invasion and metastasis 1	1.164218181	0.0000938	0.0074074
7286	TUFT1	tuftelin 1	1.16270057	0.000114454	0.008094508
53349	ZFYVE1	zinc finger FYVE-type containing 1	1.158181641	0.0005874	0.017065433
5193	PEX12	peroxisomal biogenesis factor 12	1.150619228	0.001853572	0.029954899
643085	NA	NA	1.148505157	0.001033783	0.022786467
2355	FOSL2	FOS like 2, AP-1 transcription factor subunit	1.147920747	0.000737008	0.019267384
153527	ZMAT2	zinc finger matrin-type 2	1.145537375	0.00104151	0.022786467
65982	ZSCAN18	zinc finger and SCAN domain containing 18	1.144888292	0.001863418	0.030012167
51167	CYB5R4	cytochrome b5 reductase 4	1.143585211	0.000454488	0.01506455
10560	SLC19A2	solute carrier family 19 member 2	1.142384426	0.000297558	0.012285888
79772	MCTP1	multiple C2 and transmembrane domain containing 1	1.13874565	0.002789526	0.037070853
5538	PPT1	palmitoyl-protein thioesterase 1	1.135441583	0.000836263	0.020421981
644096	SDHAF1	succinate dehydrogenase complex assembly factor 1	1.126459729	0.00320948	0.039526408
23210	JMJD6	arginine demethylase and lysine hydroxylase	1.126372225	0.000588916	0.017065433
25988	HINFP	histone H4 transcription factor	1.121258522	0.002175302	0.03248105
6046	BRD2	bromodomain containing 2	1.120261618	0.000219089	0.010905598
3300	DNAJB2	DnaJ heat shock protein family (Hsp40) member B2	1.117052943	0.002346004	0.033649609
27153	ZNF777	zinc finger protein 777	1.11421619	0.001176301	0.024210904
1647	GADD45A	growth arrest and DNA damage inducible alpha	1.112275952	0.000350672	0.013454179
100170841	EPOP	elongin BC and polycomb repressive complex 2 associated protein	1.10901666	0.002603285	0.035554998
6697	SPR	sepiapterin reductase	1.106427276	0.001739081	0.029471545

2961	GTF2E2	general transcription factor IIE subunit 2	1.106054019	0.001962199	0.030892812
4794	NFKBIE	NFKB inhibitor epsilon	1.104717754	0.003831069	0.043644852
150962	PUS10	pseudouridylate synthase 10	1.104422146	0.002437124	0.034302226
115572	FAM46B	family with sequence similarity 46 member B	1.102159694	0.000575608	0.016938968
5936	RBM4	RNA binding motif protein 4	1.101841373	0.001569818	0.027483352
3337	DNAJB1	DnaJ heat shock protein family (Hsp40) member B1	1.100890879	0.001182371	0.024210904
55831	EMC3	ER membrane protein complex subunit 3	1.099593266	0.000324364	0.013005997
22849	CPEB3	cytoplasmic polyadenylation element binding protein 3	1.099012807	0.003717012	0.042872243
6095	RORA	RAR related orphan receptor A	1.09843787	0.000680865	0.018347544
80223	RAB11FIP1	RAB11 family interacting protein 1	1.09635408	0.0000932	0.0074074
22889	KHDC4	KH domain containing 4, pre-mRNA splicing factor	1.096330027	0.000628384	0.017741304
403313	PLPP6	phospholipid phosphatase 6	1.089616154	0.001921284	0.030599186
80237	ELL3	elongation factor for RNA polymerase II 3	1.087509326	0.000329729	0.013084735
51271	UBAP1	ubiquitin associated protein 1	1.08609144	0.000154851	0.009179272
29074	MRPL18	mitochondrial ribosomal protein L18	1.083402026	0.000742594	0.019289439
57693	ZNF317	zinc finger protein 317	1.080494016	0.001070388	0.022891564
80314	EPC1	enhancer of polycomb homolog 1	1.078664672	0.001321579	0.025240743
55039	TRMT12	tRNA methyltransferase 12 homolog	1.077973546	0.00080448	0.020057246
91603	ZNF830	zinc finger protein 830	1.077853449	0.000757704	0.019429455
163087	ZNF383	zinc finger protein 383	1.0751688	0.003994783	0.044725292
219699	UNC5B	unc-5 netrin receptor B	1.074639182	0.004177211	0.046046011
26577	PCOLCE2	procollagen C-endopeptidase enhancer 2	1.073337014	0.004108466	0.045652767
100506778	NA	NA	1.072869114	0.00369073	0.042831656
55659	ZNF416	zinc finger protein 416	1.071621999	0.003039007	0.038488695
2717	GLA	galactosidase alpha	1.069233156	0.000356303	0.013465999
55328	RNLS	renalase, FAD dependent amine oxidase	1.067504499	0.000565544	0.016898736
7298	TYMS	thymidylate synthetase	1.066192187	0.002197537	0.03248105
22863	ATG14	autophagy related 14	1.065942747	0.001989277	0.031168298
91862	MARVELD3	MARVEL domain containing 3	1.065734969	0.00078767	0.019881022
3727	JUND	JunD proto-oncogene, AP-1 transcription factor subunit	1.065352169	0.001096684	0.02320743
9510	ADAMTS1	ADAM metalloproteinase with thrombospondin type 1 motif 1	1.064070414	0.002524182	0.03494363

4601	MXI1	MAX interactor 1, dimerization protein	1.058873955	0.00256976	0.035274257
55432	YOD1	YOD1 deubiquitinase	1.056382241	0.004608254	0.048447975
4645	MYO5B	myosin VB	1.050804941	0.001036771	0.022786467
90441	ZNF622	zinc finger protein 622	1.048491731	0.001422705	0.026191703
51646	YPEL5	yippee like 5	1.047259674	0.002117656	0.031979445
54807	ZNF586	zinc finger protein 586	1.043927444	0.000758899	0.019429455
10001	MED6	mediator complex subunit 6	1.043654601	0.001163368	0.023982496
26993	AKAP8L	A-kinase anchoring protein 8 like	1.036552729	0.001550752	0.027368962
91746	YTHDC1	YTH domain containing 1	1.034030634	0.003432809	0.041038591
100505905	NA	NA	1.033891125	0.000997713	0.022503611
23099	ZBTB43	zinc finger and BTB domain containing 43	1.029904744	0.002802423	0.03720763
200424	TET3	tet methylcytosine dioxygenase 3	1.025982026	0.001041549	0.022786467
91445	RNF185	ring finger protein 185	1.025761806	0.00141732	0.026182357
140459	ASB6	ankyrin repeat and SOCS box containing 6	1.025583791	0.003716165	0.042872243
57132	CHMP1B	charged multivesicular body protein 1B	1.020978998	0.001135286	0.023642409
1540	CYLD	CYLD lysine 63 deubiquitinase	1.020631503	0.004218641	0.046252884
80219	COQ10B	coenzyme Q10B	1.020187953	0.004238841	0.046403125
51651	PTRH2	peptidyl-tRNA hydrolase 2	1.018768387	0.000886108	0.020771655
7553	ZNF7	zinc finger protein 7	1.017772451	0.003764791	0.043265295
51307	FAM53C	family with sequence similarity 53 member C	1.017363317	0.000579349	0.016961605
8480	RAE1	ribonucleic acid export 1	1.013066762	0.000269902	0.011756407
79983	POF1B	POF1B, actin binding protein	1.012933656	0.001546235	0.02735535
79056	PRRG4	proline rich and Gla domain 4	1.00732089	0.000434275	0.014819822
401152	C4orf3	chromosome 4 open reading frame 3	1.005156102	0.001377907	0.025859381
26524	LATS2	large tumor suppressor kinase 2	1.003219236	0.001355205	0.025562765
56652	TWINK	twinkle mtDNA helicase	0.999306137	0.003573099	0.042164184
2125	EVPL	envoplakin	0.998675446	0.003920241	0.044202495
55181	SMG8	SMG8, nonsense mediated mRNA decay factor	0.998552994	0.004615546	0.048447975
57661	PHRF1	PHD and ring finger domains 1	0.993636575	0.001209688	0.024374625
55905	RNF114	ring finger protein 114	0.991919072	0.000405521	0.014395639
90637	ZFAND2A	zinc finger AN1-type containing 2A	0.990860574	0.00348817	0.041423103

84950	PRPF38A	pre-mRNA processing factor 38A	0.989490986	0.001201823	0.024353539
2055	CLN8	CLN8, transmembrane ER and ERGIC protein	0.988424883	0.00108263	0.02304986
10189	ALYREF	Aly/REF export factor	0.986575542	0.001284592	0.02496828
1198	CLK3	CDC like kinase 3	0.985227552	0.001765512	0.029629817
51103	NDUFAF1	NADH:ubiquinone oxidoreductase complex assembly factor 1	0.984878112	0.002379342	0.033923428
6016	RIT1	Ras like without CAAX 1	0.982293663	0.001236644	0.024615274
57109	REXO4	REX4 homolog, 3'-5' exonuclease	0.980205797	0.00246652	0.034516132
3074	HEXB	hexosaminidase subunit beta	0.978028331	0.003251562	0.039804464
56957	OTUD7B	OTU deubiquitinase 7B	0.97627326	0.001820826	0.0298467
10869	USP19	ubiquitin specific peptidase 19	0.974939832	0.001414453	0.026174712
26012	NSMF	NMDA receptor synaptonuclear signaling and neuronal migration factor	0.974879431	0.003250337	0.039804464
94241	TP53INP1	tumor protein p53 inducible nuclear protein 1	0.971613076	0.001993998	0.031192953
57180	ACTR3B	ARP3 actin related protein 3 homolog B	0.968441792	0.002067564	0.031468129
55608	ANKRD10	ankyrin repeat domain 10	0.968266417	0.00060387	0.017323057
23016	EXOSC7	exosome component 7	0.96798257	0.000693313	0.018478862
650	BMP2	bone morphogenetic protein 2	0.960730823	0.003137787	0.039081145
1824	DSC2	desmocollin 2	0.960042474	0.000927325	0.021367355
54805	CNNM2	cyclin and CBS domain divalent metal cation transport mediator 2	0.959212997	0.003226518	0.039667845
90338	ZNF160	zinc finger protein 160	0.957625721	0.003443656	0.041065172
1387	CREBBP	CREB binding protein	0.955835266	0.00403791	0.044996553
51447	IP6K2	inositol hexakisphosphate kinase 2	0.95417299	0.000386622	0.014162269
3312	HSPA8	heat shock protein family A (Hsp70) member 8	0.952192624	0.003869274	0.043974901
63934	ZNF667	zinc finger protein 667	0.950334781	0.002185252	0.03248105
10507	SEMA4D	semaphorin 4D	0.945212671	0.001124448	0.023485179
10765	KDM5B	lysine demethylase 5B	0.943856321	0.002246611	0.03275008
84844	PHF5A	PHD finger protein 5A	0.943179061	0.000901385	0.021075598
23352	UBR4	ubiquitin protein ligase E3 component n-recogin 4	0.942867143	0.00255454	0.035192056
9775	EIF4A3	eukaryotic translation initiation factor 4A3	0.937237711	0.000621777	0.01760244
9943	OXS1	oxidative stress responsive 1	0.936606204	0.004592266	0.048345702

221393	ADGRF4	adhesion G protein-coupled receptor F4	0.929436888	0.001989744	0.031168298
6882	TAF11	TATA-box binding protein associated factor 11	0.928027573	0.003718235	0.042872243
84159	ARID5B	AT-rich interaction domain 5B	0.926176099	0.002509927	0.034846281
9150	CTDP1	CTD phosphatase subunit 1	0.92516799	0.003067599	0.038679366
54149	C21orf91	chromosome 21 open reading frame 91	0.919959451	0.004014119	0.044906581
54927	CHCHD3	coiled-coil-helix-coiled-coil-helix domain containing 3	0.919394292	0.001756266	0.029612453
	MAPKAPK5-				
51275	AS1	MAPKAPK5 antisense RNA 1	0.917830185	0.003663775	0.042657447
5430	POLR2A	RNA polymerase II subunit A	0.915017037	0.002358177	0.033756432
9489	PGS1	phosphatidylglycerophosphate synthase 1	0.914953921	0.002098024	0.031784063
9807	IP6K1	inositol hexakisphosphate kinase 1	0.914155658	0.003725711	0.042889208
10963	STIP1	stress induced phosphoprotein 1	0.910825059	0.00252497	0.03494363
201164	PLD6	phospholipase D family member 6	0.910548309	0.004656209	0.0487673
3420	IDH3B	isocitrate dehydrogenase 3 (NAD(+)) beta	0.908832689	0.001101403	0.02320743
22824	HSPA4L	heat shock protein family A (Hsp70) member 4 like	0.906566392	0.002286576	0.03305139
2730	GCLM	glutamate-cysteine ligase modifier subunit	0.905199977	0.002808818	0.037257916
1211	CLTA	clathrin light chain A	0.899544918	0.000391446	0.014209703
23764	MAFF	MAF bZIP transcription factor F	0.895427106	0.004171161	0.046046011
4520	MTF1	metal regulatory transcription factor 1	0.893628468	0.001418532	0.026182357
54980	C2orf42	chromosome 2 open reading frame 42	0.890962467	0.002117562	0.031979445
51126	NAA20	N(alpha)-acetyltransferase 20, NatB catalytic subunit	0.890089452	0.004019483	0.044931409
114789	SLC25A25	solute carrier family 25 member 25	0.889911144	0.004198908	0.046203426
1104	RCC1	regulator of chromosome condensation 1	0.886989779	0.000685286	0.018355928
2065	ERBB3	erb-b2 receptor tyrosine kinase 3	0.883951984	0.002177766	0.03248105
30827	CXXC1	CXXC finger protein 1	0.880336437	0.001281977	0.024951404
29080	CCDC59	coiled-coil domain containing 59	0.878938641	0.002427028	0.034277902
7268	TTC4	tetratricopeptide repeat domain 4	0.878620862	0.001245401	0.024688313
5184	PEPD	peptidase D	0.87700482	0.002037085	0.031335479
23171	GPD1L	glycerol-3-phosphate dehydrogenase 1 like	0.876128649	0.002018564	0.031335479
1374	CPT1A	carnitine palmitoyltransferase 1A	0.875668693	0.003032954	0.038488695
301	ANXA1	annexin A1	0.874524865	0.001569423	0.027483352

6533	SLC6A6	solute carrier family 6 member 6	0.872555201	0.001379312	0.025859381
9533	POLR1C	RNA polymerase I subunit C	0.869692009	0.003716096	0.042872243
54442	KCTD5	potassium channel tetramerization domain containing 5	0.866423119	0.001942208	0.030692908
130576	LYPD6B	LY6/PLAUR domain containing 6B	0.865219496	0.00193506	0.030613813
85450	ITPRIP	inositol 1,4,5-trisphosphate receptor interacting protein	0.864343132	0.002034479	0.031335479
64768	IPPK	inositol-pentakisphosphate 2-kinase	0.8627447	0.004719803	0.049111778
6903	TBCC	tubulin folding cofactor C	0.862743172	0.002040894	0.031335479
11128	POLR3A	RNA polymerase III subunit A	0.861263832	0.003501674	0.041516937
83860	TAF3	TATA-box binding protein associated factor 3	0.857862704	0.001007675	0.022599138
2288	FKBP4	FK506 binding protein 4	0.854832708	0.000829937	0.020337023
55178	MRM3	mitochondrial rRNA methyltransferase 3	0.8539633	0.003586201	0.042226054
2632	GBE1	1,4-alpha-glucan branching enzyme 1	0.853142809	0.002204684	0.03248105
80131	LRR8E	leucine rich repeat containing 8 VRAC subunit E	0.85028891	0.003568487	0.042164184
100499467	LINC00673	long intergenic non-protein coding RNA 673	0.849974397	0.00204563	0.031335479
10140	TOB1	transducer of ERBB2, 1	0.848353232	0.000917407	0.02120724
54764	ZRANB1	zinc finger RANBP2-type containing 1	0.847451819	0.003010039	0.038360826
5514	PPP1R10	protein phosphatase 1 regulatory subunit 10	0.84636361	0.001546716	0.02735535
4097	MAFG	MAF bZIP transcription factor G	0.846234315	0.004768209	0.049432967
57696	DDX55	DEAD-box helicase 55	0.84089827	0.002058811	0.031423261
83786	FRMD8	FERM domain containing 8	0.839350317	0.003154325	0.039150899
51507	RTFDC1	replication termination factor 2 domain containing 1	0.833780718	0.00200899	0.031264092
8848	TSC22D1	TSC22 domain family member 1	0.833512648	0.002432368	0.034277902
100506584	NA	NA	0.831162475	0.002870375	0.0376018
26098	EDRF1	erythroid differentiation regulatory factor 1	0.828790801	0.003182464	0.039329306
9904	RBM19	RNA binding motif protein 19	0.827727899	0.002586257	0.035416214
55313	CPPED1	calcineurin like phosphoesterase domain containing 1	0.825817508	0.002878996	0.0376018
26118	WSB1	WD repeat and SOCS box containing 1	0.825286059	0.00139609	0.025935693
84172	POLR1B	RNA polymerase I subunit B	0.822251824	0.003378996	0.040599105
10482	NXF1	nuclear RNA export factor 1	0.81841057	0.001226159	0.024549578
1845	DUSP3	dual specificity phosphatase 3	0.814168163	0.003310302	0.040179249
5429	POLH	DNA polymerase eta	0.812177893	0.000992359	0.022467265

7266	DNAJC7	DnaJ heat shock protein family (Hsp40) member C7	0.805355582	0.002913587	0.037742954
9885	OSBPL2	oxysterol binding protein like 2	0.80469853	0.001351929	0.025547166
56902	PNO1	partner of NOB1 homolog	0.801044244	0.003594165	0.042226054
476	ATP1A1	ATPase Na <sup>+</sup> /K <sup>+</sup> transporting subunit alpha 1	0.795665716	0.004462428	0.047681566
55802	DCP1A	decapping mRNA 1A	0.795430957	0.002711124	0.03643717
26574	AATF	apoptosis antagonizing transcription factor	0.792591068	0.004565415	0.048208126
55783	CMTR2	cap methyltransferase 2	0.782201674	0.004512789	0.048001592
23762	OSBP2	oxysterol binding protein 2	0.781040392	0.002039125	0.031335479
7328	UBE2H	ubiquitin conjugating enzyme E2 H	0.780812152	0.002199636	0.03248105
9330	GTF3C3	general transcription factor IIIC subunit 3	0.780589689	0.001867785	0.030048624
339230	CCDC137	coiled-coil domain containing 137	0.767957538	0.003595595	0.042226054
6835	SURF2	surfeit 2	0.765580928	0.003361	0.040454568
79720	VPS37B	VPS37B, ESCRT-I subunit	0.765077855	0.003441564	0.041065172
79066	METTL16	methyltransferase like 16	0.761354939	0.003778535	0.04328801
51324	SPG21	SPG21, maspardin	0.761087127	0.002932698	0.037811947
10978	CLP1	cleavage and polyadenylation factor I subunit 1	0.759727275	0.003783724	0.043290651
51204	TACO1	translational activator of cytochrome c oxidase I	0.753431509	0.003222684	0.039654833
8724	SNX3	sorting nexin 3	0.749591175	0.00237871	0.033923428
56912	IFT46	intraflagellar transport 46	0.74052332	0.004408049	0.047277314
54708	MARCH5	membrane associated ring-CH-type finger 5	0.739600642	0.002194575	0.03248105
4953	ODC1	ornithine decarboxylase 1	0.728675942	0.004744535	0.049223256
26156	RSL1D1	ribosomal L1 domain containing 1	0.72676921	0.001907039	0.030474223
64771	C6orf106	chromosome 6 open reading frame 106	0.726728806	0.00346693	0.041225962
406	ARNTL	aryl hydrocarbon receptor nuclear translocator like	0.724242175	0.002062651	0.031448269
55030	FBXO34	F-box protein 34	0.709357031	0.004561082	0.048208126
57103	TIGAR	TP53 induced glycolysis regulatory phosphatase	0.708417483	0.003615371	0.042266115
7088	TLE1	transducin like enhancer of split 1	0.687781494	0.004257257	0.046429726
51606	ATP6V1H	ATPase H <sup>+</sup> transporting V1 subunit H	0.670702046	0.002486831	0.034592858
3735	KARS	lysyl-tRNA synthetase	0.667597884	0.003135402	0.039081145
7555	CNBP	CCHC-type zinc finger nucleic acid binding protein	0.666769935	0.003987259	0.044711127
9794	MAML1	mastermind like transcriptional coactivator 1	0.658821068	0.004274112	0.046468771

192111	PGAM5	PGAM family member 5, mitochondrial serine/threonine protein phosphatase	0.65496305	0.003301681	0.040108683
51202	DDX47	DEAD-box helicase 47	0.653320714	0.004025013	0.044958041
26994	RNF11	ring finger protein 11	0.653105101	0.00300763	0.038360826

## Substrate softness promotes a reversible switch from proliferation to terminal differentiation in human keratinocytes

Archives of Dermatological Research

Choua Ya, Mariana Carrancá, Dominique Sigauco-Roussel, Philippe Faure, Bérengère Fromy, Romain Debret

Corresponding author: Romain Debret  
LBTI, UMR5305 CNRS/UCBL  
7, passage du Vercors  
F-69367 LYON cedex 7  
[romain.debret@ibcp.fr](mailto:romain.debret@ibcp.fr)

**ESM 2:** List of genes significantly down-regulated in Soft PAH conditions (FDR < 0.05)

ENTREZID	SYMBOL	GENENAME	logFC	P.Value	adj.P.Val
10561	IFI44	interferon induced protein 44	-4.403489707	0.003361303	0.040454568
100505479	NA	NA	-4.263788942	0.000876961	0.020771655
3429	IFI27	interferon alpha inducible protein 27	-4.010372709	0.0000354	0.004829526
290	ANPEP	alanyl aminopeptidase, membrane	-3.922708897	0.00000716	0.002272774
7980	TFPI2	tissue factor pathway inhibitor 2	-3.690718473	0.0000809	0.006960369
4549	RNR1	s-rRNA	-3.66027128	0.0000481	0.0055457
154075	SAMD3	sterile alpha motif domain containing 3	-3.621697519	0.000549544	0.016657922
2537	IFI6	interferon alpha inducible protein 6	-3.579040293	0.0000587	0.006200796
8862	APLN	apelin	-3.49199537	0.000139502	0.00884638
60676	PAPPA2	pappalysin 2	-3.340846149	0.001266397	0.024951404
56134	PCDHAC2	protocadherin alpha subfamily C, 2	-3.262664981	0.004136537	0.045774261
219285	SAMD9L	sterile alpha motif domain containing 9 like	-3.25490979	0.001107271	0.023262466
2335	FN1	fibronectin 1	-3.186931391	0.000000139	0.000331905

7052	TGM2	transglutaminase 2	-3.184410431	0.00040705	0.014395639
84848	MIR503HG	MIR503 host gene	-3.18414089	0.000408108	0.014395639
3009	HIST1H1B	histone cluster 1 H1 family member b	-3.156481868	0.000401583	0.014395639
3037	HAS2	hyaluronan synthase 2	-3.042308427	0.000678527	0.018347544
2124	EVI2B	ecotropic viral integration site 2B	-2.950271165	0.001462675	0.02648387
4512	COX1	cytochrome c oxidase subunit I	-2.864726402	0.000295236	0.012285888
50863	NTM	neurotrimin	-2.803678893	0.000191864	0.010148185
22989	MYH15	myosin heavy chain 15	-2.716476383	0.0000119	0.002709607
160428	ALDH1L2	aldehyde dehydrogenase 1 family member L2	-2.709941396	0.00017917	0.009769532
4550	RNR2	l-rRNA	-2.674528736	0.00022372	0.0110209
5452	POU2F2	POU class 2 homeobox 2	-2.661778752	0.0000054	0.001930073
4514	COX3	cytochrome c oxidase III	-2.637016071	0.001811965	0.029828366
79132	DHX58	DExH-box helicase 58	-2.627518701	0.002046479	0.031335479
4508	ATP6	ATP synthase F0 subunit 6	-2.621831873	0.001795651	0.029828366
100129940	LOC100129940	uncharacterized LOC100129940	-2.618491303	0.000612512	0.017500697
90853	SPOCD1	SPOC domain containing 1	-2.618092275	0.003078925	0.038787941
3430	IFI35	interferon induced protein 35	-2.617215328	0.0000238	0.003785391
6546	SLC8A1	solute carrier family 8 member A1	-2.615117793	0.00000367	0.001749452
100462981	MTRNR2L2	MT-RNR2-like 2	-2.604065074	0.000294556	0.012285888
7431	VIM	vimentin	-2.601854911	0.000373408	0.013819969
100216001	LINC00704	long intergenic non-protein coding RNA 704	-2.59796754	0.00000452	0.00185843
284756	C20orf197	chromosome 20 open reading frame 197	-2.576736076	0.000557526	0.016732805
6586	SLIT3	slit guidance ligand 3	-2.575441689	0.0000178	0.003308299
1295	COL8A1	collagen type VIII alpha 1 chain	-2.512413705	0.0000963	0.0074319
3956	LGALS1	galectin 1	-2.504052852	0.0000968	0.0074319
100131897	FAM196B	family with sequence similarity 196 member B	-2.465770734	0.0000916	0.0074074
1440	CSF3	colony stimulating factor 3	-2.460741195	0.002624785	0.035780227
56978	PRDM8	PR/SET domain 8	-2.459904225	0.0000865	0.007333706
100505562	NA	NA	-2.435420438	0.001814423	0.029828366
114801	TMEM200A	transmembrane protein 200A	-2.435322377	0.00035485	0.013454179
4541	ND6	NADH dehydrogenase, subunit 6 (complex I)	-2.434519899	0.004728463	0.049145072

84940	CORO6	coronin 6	-2.434008015	0.003245435	0.039804464
22854	NTNG1	netrin G1	-2.424911298	0.0000107	0.002611285
8771	TNFRSF6B	TNF receptor superfamily member 6b	-2.420730433	0.0000395	0.004965955
133396	IL31RA	interleukin 31 receptor A	-2.412631198	0.001061075	0.022821411
4513	COX2	cytochrome c oxidase subunit II	-2.41161744	0.00017894	0.009769532
1002	CDH4	cadherin 4	-2.372874145	0.0000082	0.002434283
8346	HIST1H2BI	histone cluster 1 H2B family member i	-2.340039735	0.001289311	0.025025943
4509	ATP8	ATP synthase F0 subunit 8	-2.339123306	0.002020212	0.031335479
4540	ND5	NADH dehydrogenase, subunit 5 (complex I)	-2.310877621	0.002440461	0.034315376
55107	ANO1	anoctamin 1	-2.303933312	0.00000296	0.001563969
5947	RBP1	retinol binding protein 1	-2.299755313	0.001599069	0.027892912
1289	COL5A1	collagen type V alpha 1 chain	-2.258760678	0.000567786	0.016898736
100463486	MTRNR2L8	MT-RNR2-like 8	-2.247984978	0.003092053	0.03882044
3909	LAMA3	laminin subunit alpha 3	-2.23674644	0.000000921	0.000939896
8829	NRP1	neuropilin 1	-2.235032703	0.0000696	0.006576086
10610	ST6GALNAC2	ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 2	-2.215934956	0.000225185	0.011035795
8728	ADAM19	ADAM metallopeptidase domain 19	-2.209142914	0.000134972	0.008764586
3918	LAMC2	laminin subunit gamma 2	-2.183187629	0.00000243	0.001453041
4538	ND4	NADH dehydrogenase, subunit 4 (complex I)	-2.17879287	0.003198982	0.039440987
4539	ND4L	NADH dehydrogenase, subunit 4L (complex I)	-2.155582235	0.00079155	0.019891991
8358	HIST1H3B	histone cluster 1 H3 family member b	-2.125551332	0.003723421	0.042889208
5106	PCK2	phosphoenolpyruvate carboxykinase 2, mitochondrial	-2.11820777	0.000197548	0.010337643
7058	THBS2	thrombospondin 2	-2.114375223	0.0000868	0.007333706
100506850	NA	NA	-2.10952707	0.000615401	0.01751319
4939	OAS2	2'-5'-oligoadenylate synthetase 2	-2.101386433	0.000129826	0.008545701
114879	OSBPL5	oxysterol binding protein like 5	-2.078051692	0.000810647	0.020115597
309	ANXA6	annexin A6	-2.050351874	0.00000326	0.001664914
100131754	NA	NA	-2.048564615	0.00269874	0.036406236
25890	ABI3BP	ABI family member 3 binding protein	-2.03876358	0.000675473	0.018347544
80380	PDCD1LG2	programmed cell death 1 ligand 2	-2.034011655	0.00000688	0.002233961
1808	DPYSL2	dihydropyrimidinase like 2	-2.012784055	0.000282629	0.01201676

79739	TLL7	tubulin tyrosine ligase like 7	-2.005779069	0.000543977	0.016657922
2014	EMP3	epithelial membrane protein 3	-2.00270888	0.001813238	0.029828366
8091	HMG2	high mobility group AT-hook 2	-1.99275529	0.000125066	0.008427801
150759	LINC00342	long intergenic non-protein coding RNA 342	-1.991868716	0.003010114	0.038360826
5744	PTHLH	parathyroid hormone like hormone	-1.986073099	0.0000667	0.006558963
25878	MXRA5	matrix remodeling associated 5	-1.97520359	0.000281304	0.01201676
10411	RAPGEF3	Rap guanine nucleotide exchange factor 3	-1.964975249	0.000147888	0.00904275
25758	KIAA1549L	KIAA1549 like	-1.963389351	0.00007	0.006576086
11174	ADAMTS6	ADAM metalloproteinase with thrombospondin type 1 motif 6	-1.956086221	0.0000928	0.0074074
2863	GPR39	G protein-coupled receptor 39	-1.952905249	0.000319129	0.01287727
3371	TNC	tenascin C	-1.951156126	0.000886932	0.020771655
643783	USP46-AS1	USP46 antisense RNA 1	-1.942724073	0.002879488	0.0376018
3624	INHBA	inhibin beta A subunit	-1.940017663	0.000851637	0.020615005
4053	LTBP2	latent transforming growth factor beta binding protein 2	-1.929741452	0.00000227	0.001453041
60489	APOBEC3G	apolipoprotein B mRNA editing enzyme catalytic subunit 3G	-1.929458113	0.000781934	0.019841389
199964	TMEM61	transmembrane protein 61	-1.914900668	0.003468683	0.041225962
100507248	NA	NA	-1.91060054	0.001208252	0.024374625
256691	MAMDC2	MAM domain containing 2	-1.901651974	0.000532317	0.016528079
4131	MAP1B	microtubule associated protein 1B	-1.895363325	0.003427756	0.041012503
643314	KIAA0754	KIAA0754	-1.894660345	0.000184837	0.00991605
100506918	NA	NA	-1.890839601	0.000263161	0.011607762
57094	CPA6	carboxypeptidase A6	-1.878695763	0.001324589	0.025264454
5803	PTPRZ1	protein tyrosine phosphatase, receptor type Z1	-1.878004906	0.001438369	0.026300607
404550	C16orf74	chromosome 16 open reading frame 74	-1.871334981	0.000415006	0.014567013
343099	CCDC18	coiled-coil domain containing 18	-1.864560389	0.001769669	0.029629817
55972	SLC25A40	solute carrier family 25 member 40	-1.856374089	0.000485977	0.015601495
131566	DCBLD2	discoidin, CUB and LCCL domain containing 2	-1.851828087	0.0000024	0.001453041
80184	CEP290	centrosomal protein 290	-1.849678568	0.001149917	0.023842694
348110	ARPIN	actin related protein 2/3 complex inhibitor	-1.8490157	0.000201293	0.010414046
3007	HIST1H1D	histone cluster 1 H1 family member d	-1.841095593	0.002339781	0.03359933
80212	CCDC92	coiled-coil domain containing 92	-1.83200373	0.000183702	0.009903247

8727	CTNNAL1	catenin alpha like 1	-1.831961904	0.000358316	0.013470798
5270	SERPINE2	serpin family E member 2	-1.826463527	0.0000266	0.004045436
285512	FAM13A-AS1	FAM13A antisense RNA 1	-1.825501285	0.002875307	0.0376018
23046	KIF21B	kinesin family member 21B	-1.823302979	0.001077972	0.022990725
3694	ITGB6	integrin subunit beta 6	-1.815243476	0.001429728	0.026228184
8340	HIST1H2BL	histone cluster 1 H2B family member I	-1.783258821	0.004629636	0.048560188
3955	LFNG	acetylglucosaminyltransferase	-1.775511173	0.001053911	0.022821411
3718	JAK3	Janus kinase 3	-1.774890931	0.002721779	0.036544487
642587	MIR205HG	MIR205 host gene	-1.771665198	0.0000756	0.006793366
83468	GLT8D2	glycosyltransferase 8 domain containing 2	-1.76766246	0.001314345	0.025218207
83648	FAM167A	family with sequence similarity 167 member A	-1.767538966	0.002756751	0.036772124
64750	SMURF2	SMAD specific E3 ubiquitin protein ligase 2	-1.764655378	0.001330377	0.025307281
147372	CCBE1	collagen and calcium binding EGF domains 1	-1.763841091	0.00210774	0.031897432
118429	ANTXR2	anthrax toxin receptor 2	-1.756574048	0.000129705	0.008545701
2491	CENPI	centromere protein I	-1.75094627	0.001062274	0.022821411
11098	PRSS23	protease, serine 23	-1.743924845	0.000138177	0.00884638
6941	TCF19	transcription factor 19	-1.736329467	0.0000105	0.002611285
6487	ST3GAL3	ST3 beta-galactoside alpha-2,3-sialyltransferase 3	-1.720296654	0.000552949	0.016657922
677	ZFP36L1	ZFP36 ring finger protein like 1	-1.712543442	0.001185441	0.024210904
93663	ARHGAP18	Rho GTPase activating protein 18	-1.709824494	0.0000137	0.002803363
857	CAV1	caveolin 1	-1.700622363	0.001430194	0.026228184
388591	RNF207	ring finger protein 207	-1.700439222	0.000745779	0.019301094
10019	SH2B3	SH2B adaptor protein 3	-1.695477607	0.000101003	0.007578672
100507010	NA	NA	-1.686746512	0.000477451	0.015399024
768211	RELL1	RELT like 1	-1.683845878	0.000220568	0.010941087
727738	NA	NA	-1.683614525	0.000440244	0.014857064
162461	TMEM92	transmembrane protein 92	-1.670598281	0.004840813	0.049824106
2250	FGF5	fibroblast growth factor 5	-1.669812223	0.00086508	0.02071664
3691	ITGB4	integrin subunit beta 4	-1.667383393	0.0000738	0.006670581
11015	KDELRS	KDEL endoplasmic reticulum protein retention receptor 3	-1.661314298	0.003954661	0.044515256

84142	ABRAXAS1	abraxas 1, BRCA1 A complex subunit	-1.656546443	0.002201524	0.03248105
494470	RNF165	ring finger protein 165	-1.652783614	0.004844838	0.049829634
100507624	NA	NA	-1.645291169	0.001732056	0.029387352
1978	EIF4EBP1	eukaryotic translation initiation factor 4E binding protein 1	-1.639113651	0.003017402	0.038419433
1062	CENPE	centromere protein E	-1.637805649	0.004218563	0.046252884
11346	SYNPO	synaptopodin	-1.635609924	0.000462222	0.015183806
153769	SH3RF2	SH3 domain containing ring finger 2	-1.634698013	0.000874006	0.020771655
5827	PXMP2	peroxisomal membrane protein 2	-1.624225296	0.002280475	0.033041441
80034	CSRNP3	cysteine and serine rich nuclear protein 3	-1.620834569	0.002613242	0.035656906
1294	COL7A1	collagen type VII alpha 1 chain	-1.619278335	0.00038991	0.014209703
83695	RHNO1	RAD9-HUS1-RAD1 interacting nuclear orphan 1	-1.612696652	0.0000362	0.004829526
375033	PEAR1	platelet endothelial aggregation receptor 1	-1.61005648	0.003097632	0.03882044
79148	MMP28	matrix metalloproteinase 28	-1.608157565	0.003607968	0.042248718
84958	SYTL1	synaptotagmin like 1	-1.598890547	0.00126083	0.024947672
730102	CRYZL2P	crystallin zeta like 2, pseudogene	-1.596778436	0.000248519	0.011342969
57730	ANKRD36B	ankyrin repeat domain 36B	-1.586149907	0.001330372	0.025307281
91663	MYADM	myeloid associated differentiation marker	-1.583217396	0.002561493	0.035253842
440	ASNS	asparagine synthetase (glutamine-hydrolyzing)	-1.569828011	0.000396961	0.014356941
6121	RPE65	RPE65, retinoid isomerohydrolase	-1.569319598	0.000829244	0.020337023
5328	PLAU	plasminogen activator, urokinase	-1.557591067	0.0000136	0.002803363
3714	JAG2	jagged 2	-1.54934785	0.000683377	0.018350998
11278	KLF12	Kruppel like factor 12	-1.539238157	0.00410958	0.045652767
148641	SLC35F3	solute carrier family 35 member F3	-1.538276824	0.0000949	0.0074074
435	ASL	argininosuccinate lyase	-1.538259737	0.001007323	0.022599138
1909	EDNRA	endothelin receptor type A	-1.534586243	0.002939512	0.037832313
360132	FKBP9P1	FK506 binding protein 9 pseudogene 1	-1.533864128	0.000421409	0.014625328
84441	MAML2	mastermind like transcriptional coactivator 2	-1.53385997	0.0000585	0.006200796
2273	FHL1	four and a half LIM domains 1	-1.532323092	0.001949646	0.030742438
27303	RBMS3	RNA binding motif single stranded interacting protein 3	-1.531075807	0.001391901	0.025935693
283143	LINC00900	long intergenic non-protein coding RNA 900	-1.527055104	0.004269312	0.046451934
875	CBS	cystathionine-beta-synthase	-1.524056222	0.00187168	0.0300681

1806	DPYD	dihydropyrimidine dehydrogenase	-1.51930123	0.004634859	0.048579305
554202	MIR31HG	MIR31 host gene	-1.517692329	0.000192814	0.010148185
79915	ATAD5	ATPase family, AAA domain containing 5	-1.506880643	0.000783382	0.019842893
11344	TWF2	twinfilin actin binding protein 2	-1.505952986	0.00099869	0.022503611
3978	LIG1	DNA ligase 1	-1.504536322	0.0016707	0.028640461
196993	CT62	cancer/testis antigen 62	-1.502391382	0.002894935	0.037607316
128239	IQGAP3	IQ motif containing GTPase activating protein 3	-1.500724076	0.0000669	0.006558963
10379	IRF9	interferon regulatory factor 9	-1.50033481	0.0000804	0.006958628
143888	KDEL2	KDEL motif containing 2	-1.492047687	0.00085508	0.020615005
57531	HACE1	HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1	-1.489776258	0.002405827	0.034164663
55902	ACSS2	acyl-CoA synthetase short chain family member 2	-1.487316682	0.0005098	0.016156899
1745	DLX1	distal-less homeobox 1	-1.484751071	0.002284045	0.03305139
51559	NT5DC3	5'-nucleotidase domain containing 3	-1.484664366	0.000814881	0.020115597
84542	KIAA1841	KIAA1841	-1.484095582	0.003100527	0.03882044
80023	NRSN2	neurensin 2	-1.482499313	0.00237572	0.033923428
7476	WNT7A	Wnt family member 7A	-1.481301599	0.000727413	0.019173104
1611	DAP	death associated protein	-1.480911174	0.000534507	0.016528079
4897	NRCAM	neuronal cell adhesion molecule	-1.477123806	0.002895705	0.037607316
100506831	NA	NA	-1.470663338	0.00029121	0.012285888
3730	ANOS1	anosmin 1	-1.467986648	0.000141557	0.008889455
340371	NRBP2	nuclear receptor binding protein 2	-1.466211713	0.001725376	0.029378695
3552	IL1A	interleukin 1 alpha	-1.466148779	0.001527502	0.027175457
9732	DOCK4	dedicator of cytokinesis 4	-1.459933349	0.0000391	0.004965955
675	BRCA2	BRCA2, DNA repair associated	-1.455515402	0.002408255	0.03416518
92689	FAM114A1	family with sequence similarity 114 member A1	-1.45124562	0.0000389	0.004965955
9651	PLCH2	phospholipase C eta 2	-1.450016235	0.000916879	0.02120724
145553	MDP1	magnesium dependent phosphatase 1	-1.447981489	0.004035109	0.044996553
6196	RPS6KA2	ribosomal protein S6 kinase A2	-1.447475003	0.000743068	0.019289439
55771	PRR11	proline rich 11	-1.445789446	0.000420624	0.014625328
5034	P4HB	prolyl 4-hydroxylase subunit beta	-1.443868694	0.00000443	0.00185843

200150	PLD5	phospholipase D family member 5	-1.442657486	0.000530639	0.016528079
55450	CAMK2N1	calcium/calmodulin dependent protein kinase II inhibitor 1	-1.441050978	0.000293926	0.012285888
10123	ARL4C	ADP ribosylation factor like GTPase 4C	-1.438468777	0.001659302	0.02852561
7498	XDH	xanthine dehydrogenase	-1.436931769	0.004261257	0.046435025
93034	NT5C1B	5'-nucleotidase, cytosolic IB	-1.436142393	0.003798047	0.043337779
79979	TRMT2B	tRNA methyltransferase 2 homolog B	-1.426139674	0.000313449	0.012796079
79875	THSD4	thrombospondin type 1 domain containing 4	-1.423651479	0.000142891	0.008909595
2202	EFEMP1	EGF containing fibulin extracellular matrix protein 1	-1.422442337	0.000509728	0.016156899
116496	FAM129A	family with sequence similarity 129 member A	-1.420113829	0.000706931	0.018771772
10630	PDPN	podoplanin	-1.417914772	0.000567653	0.016898736
11078	TRIOBP	TRIO and F-actin binding protein	-1.416220076	0.002707572	0.03643717
57577	CCDC191	coiled-coil domain containing 191	-1.411512436	0.002825987	0.037324564
79827	CLMP	CXADR like membrane protein	-1.408119612	0.000246484	0.011342969
80005	DOCK5	dedicator of cytokinesis 5	-1.405945431	0.0000188	0.003318628
5654	HTRA1	HtrA serine peptidase 1	-1.402325649	0.00000896	0.002457072
163732	CITED4	Cbp/p300 interacting transactivator with Glu/Asp rich carboxy-terminal domain 4	-1.400673197	0.000962918	0.021974827
9048	ARTN	artemin	-1.400301154	0.001184184	0.024210904
860	RUNX2	runt related transcription factor 2	-1.398956473	0.001654016	0.028477157
55612	FERMT1	fermitin family member 1	-1.39383382	0.000462338	0.015183806
347240	KIF24	kinesin family member 24	-1.393446035	0.001101189	0.02320743
27086	FOXP1	forkhead box P1	-1.389774491	0.000656582	0.018073091
3688	ITGB1	integrin subunit beta 1	-1.388861798	0.000160702	0.009486745
1594	CYP27B1	cytochrome P450 family 27 subfamily B member 1	-1.384856009	0.0000927	0.0074074
57594	HOMEZ	homeobox and leucine zipper encoding	-1.378910827	0.000363202	0.013547526
23531	MMD	monocyte to macrophage differentiation associated	-1.372720838	0.000786459	0.019881022
5054	SERPINE1	serpin family E member 1	-1.372138828	0.00010929	0.007918819
84951	TNS4	tensin 4	-1.370753557	0.001395314	0.025935693
146857	SLFN13	schlafen family member 13	-1.367339615	0.001964393	0.030892812
7045	TGFBI	transforming growth factor beta induced	-1.366752025	0.001110187	0.023289476
115704	EVI5L	ecotropic viral integration site 5 like	-1.35744799	0.001780192	0.029629817

26147	PHF19	PHD finger protein 19	-1.350253402	0.002631883	0.035842783
23586	DDX58	DExD/H-box helicase 58	-1.349284745	0.002534923	0.035023126
10120	ACTR1B	ARP1 actin related protein 1 homolog B	-1.346610873	0.002089974	0.031763163
162394	SLFN5	schlafen family member 5	-1.345947104	0.002472409	0.034557523
134429	STARD4	StAR related lipid transfer domain containing 4	-1.344603248	0.000545006	0.016657922
9672	SDC3	syndecan 3	-1.342391768	0.000465163	0.015241545
64129	TINAGL1	tubulointerstitial nephritis antigen like 1	-1.341520165	0.000509027	0.016156899
1308	COL17A1	collagen type XVII alpha 1 chain	-1.340298999	0.00017181	0.009744936
646329	NA	NA	-1.339849625	0.00124516	0.024688313
257144	GCSAM	germinal center associated signaling and motility	-1.338494413	0.002274867	0.032993652
10635	RAD51AP1	RAD51 associated protein 1	-1.337343048	0.001114405	0.023309509
8291	DYSF	dysferlin	-1.336259008	0.002983403	0.038225014
6307	MSMO1	methylsterol monooxygenase 1	-1.333223079	0.003037676	0.038488695
51088	KLHL5	kelch like family member 5	-1.332661845	0.002526723	0.03494363
901	CCNG2	cyclin G2	-1.328742798	0.002137862	0.032115131
2122	MECOM	MDS1 and EVI1 complex locus	-1.328181629	0.001347358	0.025494515
286144	TRIQK	triple QxxK/R motif containing	-1.32436065	0.000663747	0.018165305
1826	DSCAM	DS cell adhesion molecule	-1.324005776	0.001315103	0.025218207
84985	FAM83A	family with sequence similarity 83 member A	-1.320926563	0.001930217	0.030613813
11113	CIT	citron rho-interacting serine/threonine kinase	-1.320429743	0.001356333	0.025562765
678	ZFP36L2	ZFP36 ring finger protein like 2	-1.318611499	0.001217557	0.024429799
79703	C11orf80	chromosome 11 open reading frame 80	-1.316686916	0.000225841	0.011035795
9700	ESPL1	extra spindle pole bodies like 1, separase	-1.315265975	0.001588629	0.027744694
115825	WDFY2	WD repeat and FYVE domain containing 2	-1.314206555	0.000124142	0.008405145
3157	HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1	-1.311186014	0.0000708	0.006607755
220074	LRTOMT	leucine rich transmembrane and O-methyltransferase domain containing	-1.310453492	0.003269921	0.039960723
55075	UACA	uveal autoantigen with coiled-coil domains and ankyrin repeats	-1.307272944	0.000828286	0.020337023
6241	RRM2	ribonucleotide reductase regulatory subunit M2	-1.305150648	0.000457071	0.015080192
2067	ERCC1	ERCC excision repair 1, endonuclease non-catalytic subunit	-1.304948438	0.001930119	0.030613813

10024	TROAP	trophinin associated protein	-1.303485656	0.004281509	0.046513788
84978	FRMD5	FERM domain containing 5	-1.302400691	0.00138365	0.025894296
79817	MOB3B	MOB kinase activator 3B	-1.301815008	0.001462384	0.02648387
3833	KIFC1	kinesin family member C1	-1.300799033	0.000884941	0.020771655
27347	STK39	serine/threonine kinase 39	-1.298723072	0.000740874	0.019289439
84953	MICALCL	MICAL C-terminal like	-1.298573413	0.001033386	0.022786467
65065	NBEAL1	neurobeachin like 1	-1.296288862	0.004117108	0.045685782
55364	IMPACT	impact RWD domain protein	-1.292135521	0.001149292	0.023842694
6451	SH3BGR1	SH3 domain binding glutamate rich protein like	-1.287920366	0.000581092	0.016976451
5091	PC	pyruvate carboxylase	-1.287722776	0.000716336	0.01891603
1854	DUT	deoxyuridine triphosphatase	-1.287117975	0.000404546	0.014395639
55764	IFT122	intraflagellar transport 122	-1.287104147	0.001932775	0.030613813
4597	MVD	mevalonate diphosphate decarboxylase	-1.286688903	0.003985935	0.044711127
25938	HEATR5A	HEAT repeat containing 5A	-1.279132943	0.001215682	0.024426494
3151	HMGN2	high mobility group nucleosomal binding domain 2	-1.279102054	0.004285503	0.046521809
4486	MST1R	macrophage stimulating 1 receptor	-1.275344954	0.001098189	0.02320743
10903	MTMR11	myotubularin related protein 11	-1.274982857	0.001226963	0.024549578
51643	TMBIM4	transmembrane BAX inhibitor motif containing 4	-1.274788522	0.000144212	0.008909595
54558	SPATA6	spermatogenesis associated 6	-1.274354089	0.003626498	0.042302503
261729	STEAP2	STEAP2 metalloredutase	-1.273503125	0.000600342	0.017256508
57547	ZNF624	zinc finger protein 624	-1.273041561	0.001604441	0.027952487
344787	ZNF860	zinc finger protein 860	-1.26535217	0.001563914	0.027481036
65250	C5orf42	chromosome 5 open reading frame 42	-1.265131809	0.00067489	0.018347544
9407	TMPRSS11D	transmembrane protease, serine 11D	-1.264574726	0.001296101	0.025055609
3339	HSPG2	heparan sulfate proteoglycan 2	-1.264280288	0.000469638	0.015287201
22807	IKZF2	IKAROS family zinc finger 2	-1.264185349	0.001556944	0.027392245
126282	TNFAIP8L1	TNF alpha induced protein 8 like 1	-1.261988596	0.001830163	0.0298467
128077	LIX1L	limb and CNS expressed 1 like	-1.259026107	0.00177045	0.029629817
89795	NAV3	neuron navigator 3	-1.258887338	0.000247966	0.011342969
54821	ERCC6L	ERCC excision repair 6 like, spindle assembly checkpoint helicase	-1.258243552	0.002685586	0.036339026

323	APBB2	amyloid beta precursor protein binding family B member 2	-1.255825376	0.0001632	0.00955524
4668	NAGA	alpha-N-acetylgalactosaminidase	-1.252628652	0.000352165	0.013454179
255738	PCSK9	proprotein convertase subtilisin/kexin type 9	-1.252511103	0.00018051	0.009805201
1902	LPAR1	lysophosphatidic acid receptor 1	-1.252042953	0.000575753	0.016938968
728730	LOC728730	uncharacterized LOC728730	-1.250222903	0.003501884	0.041516937
64375	IKZF4	IKAROS family zinc finger 4	-1.249906852	0.003406772	0.040898437
10983	CCNI	cyclin I	-1.24908541	0.000325013	0.013005997
344595	DUBR	DPPA2 upstream binding RNA	-1.247366573	0.000467022	0.015267454
89796	NAV1	neuron navigator 1	-1.245876065	0.000516571	0.016227506
26011	TENM4	teneurin transmembrane protein 4	-1.244682522	0.000229539	0.011035795
55526	DHTKD1	dehydrogenase E1 and transketolase domain containing 1	-1.243914001	0.000649516	0.018044661
57761	TRIB3	tribbles pseudokinase 3	-1.242744866	0.003897705	0.044153154
138050	HGSNAT	heparan-alpha-glucosaminide N-acetyltransferase	-1.2373197	0.000294512	0.012285888
23767	FLRT3	fibronectin leucine rich transmembrane protein 3	-1.23702068	0.001505575	0.026885807
55835	CENPJ	centromere protein J	-1.233641079	0.002187702	0.03248105
51616	TAF9B	TATA-box binding protein associated factor 9b	-1.232637128	0.001039035	0.022786467
4907	NT5E	5'-nucleotidase ecto	-1.228639258	0.000553158	0.016657922
11284	PNKP	polynucleotide kinase 3'-phosphatase	-1.225939094	0.001311913	0.025218207
285203	EOGT	EGF domain specific O-linked N-acetylglucosamine transferase	-1.225936982	0.000204905	0.01045454
284111	SLC13A5	solute carrier family 13 member 5	-1.223808956	0.003166687	0.039253342
757	TMEM50B	transmembrane protein 50B	-1.222916827	0.001014482	0.022602605
6591	SNAI2	snail family transcriptional repressor 2	-1.221702085	0.003633597	0.042340598
377677	CA13	carbonic anhydrase 13	-1.220454185	0.001276024	0.024951404
23649	POLA2	DNA polymerase alpha 2, accessory subunit	-1.218589387	0.004403017	0.047277314
3653	IPW	imprinted in Prader-Willi syndrome (non-protein coding)	-1.217004587	0.00076865	0.019573855
266977	ADGRF1	adhesion G protein-coupled receptor F1	-1.215940761	0.000388937	0.014209703
2752	GLUL	glutamate-ammonia ligase	-1.210719526	0.001366426	0.025685214
5939	RBMS2	RNA binding motif single stranded interacting protein 2	-1.207953835	0.000150571	0.009055347
594	BCKDHB	branched chain keto acid dehydrogenase E1 subunit beta	-1.205775487	0.00165449	0.028477157
56034	PDGFC	platelet derived growth factor C	-1.204147306	0.001191645	0.024271159
222171	PRR15	proline rich 15	-1.202406885	0.00425078	0.046429726

100130938	NA	NA	-1.200742745	0.001635115	0.028279963
118980	SFXN2	sideroflexin 2	-1.200410248	0.001484508	0.026707724
85019	TMEM241	transmembrane protein 241	-1.200265622	0.0000738	0.006670581
64764	CREB3L2	cAMP responsive element binding protein 3 like 2	-1.195281088	0.0000768	0.006811171
2621	GAS6	growth arrest specific 6	-1.194503693	0.002703521	0.036436321
51435	SCARA3	scavenger receptor class A member 3	-1.191471057	0.002432997	0.034277902
201799	TMEM154	transmembrane protein 154	-1.190194326	0.00028059	0.01201676
54841	BIVM	basic, immunoglobulin-like variable motif containing	-1.187980885	0.000661804	0.018146906
134728	IRAK1BP1	interleukin 1 receptor associated kinase 1 binding protein 1	-1.187115102	0.002299092	0.033109702
285704	RGMB	repulsive guidance molecule family member b microtubule associated monooxygenase, calponin and LIM domain containing 2	-1.18437206	0.000294921	0.012285888
9645	MICAL2	domain containing 2	-1.183676049	0.0000923	0.0074074
558	AXL	AXL receptor tyrosine kinase	-1.182698322	0.004720039	0.049111778
54541	DDIT4	DNA damage inducible transcript 4	-1.181206123	0.004405	0.047277314
6319	SCD	stearoyl-CoA desaturase	-1.181187164	0.000169333	0.009697752
10643	IGF2BP3	insulin like growth factor 2 mRNA binding protein 3	-1.180504725	0.000173925	0.009744936
122953	JDP2	Jun dimerization protein 2	-1.17600312	0.000354475	0.013454179
79174	CRELD2	cysteine rich with EGF like domains 2	-1.174600139	0.001652687	0.028477157
51466	EVL	Enah/Vasp-like	-1.172741321	0.00368822	0.042831656
3914	LAMB3	laminin subunit beta 3	-1.172726039	0.000201924	0.010414046
114327	EFHC1	EF-hand domain containing 1	-1.166293488	0.000731115	0.019235199
114880	OSBPL6	oxysterol binding protein like 6	-1.165100683	0.000260271	0.011607762
9203	ZMYM3	zinc finger MYM-type containing 3	-1.162531654	0.002153716	0.032285395
22822	PHLDA1	pleckstrin homology like domain family A member 1	-1.159556047	0.0000431	0.005135249
6281	S100A10	S100 calcium binding protein A10	-1.157275417	0.000547647	0.016657922
8853	ASAP2	ArfGAP with SH3 domain, ankyrin repeat and PH domain 2	-1.156611515	0.000109209	0.007918819
9871	SEC24D	SEC24 homolog D, COPII coat complex component	-1.156434669	0.000101325	0.007578672
3959	LGALS3BP	galectin 3 binding protein	-1.156029582	0.003767466	0.043265295
2069	EREG	epiregulin	-1.155371545	0.000681965	0.018347544
84866	TMEM25	transmembrane protein 25	-1.153660913	0.00123673	0.024615274
220134	SKA1	spindle and kinetochore associated complex subunit 1	-1.15225153	0.003694816	0.042844275

57337	SENP7	SUMO1/sentrin specific peptidase 7	-1.15116747	0.00371616	0.042872243
2121	EVC	EvC ciliary complex subunit 1	-1.14985039	0.000263259	0.011607762
3655	ITGA6	integrin subunit alpha 6	-1.148903523	0.004028727	0.044964371
9830	TRIM14	tripartite motif containing 14	-1.14876689	0.001140613	0.023718783
64847	SPATA20	spermatogenesis associated 20	-1.148255432	0.003420438	0.04099361
10741	RBBP9	RB binding protein 9, serine hydrolase	-1.148025526	0.001451707	0.0263856
4439	MSH5	mutS homolog 5	-1.147462558	0.003676716	0.042738462
6237	RRAS	RAS related	-1.147234699	0.001069837	0.022891564
51750	RTEL1	regulator of telomere elongation helicase 1	-1.146330299	0.001032752	0.022786467
6653	SORL1	sortilin related receptor 1	-1.1416096	0.000583311	0.017006489
57451	TENM2	teneurin transmembrane protein 2	-1.141558626	0.003562947	0.042135983
9415	FADS2	fatty acid desaturase 2	-1.138690549	0.000819331	0.020180964
285671	RNF180	ring finger protein 180	-1.137934386	0.00229516	0.033086429
1956	EGFR	epidermal growth factor receptor	-1.137791555	0.000954989	0.021898836
10013	HDAC6	histone deacetylase 6	-1.137171106	0.001292827	0.025026186
10972	TMED10	transmembrane p24 trafficking protein 10	-1.135028994	0.003795797	0.043337779
41	ASIC1	acid sensing ion channel subunit 1	-1.134083232	0.003750418	0.043138866
730091	LINC00886	long intergenic non-protein coding RNA 886	-1.133613359	0.004670589	0.048846296
8089	YEATS4	YEATS domain containing 4	-1.132798724	0.004175735	0.046046011
80321	CEP70	centrosomal protein 70	-1.131799689	0.001690178	0.028882635
9401	RECQL4	RecQ like helicase 4	-1.131628435	0.002220343	0.032566553
55973	BCAP29	B-cell receptor associated protein 29	-1.130785208	0.001575238	0.027544497
51014	TMED7	transmembrane p24 trafficking protein 7	-1.12959619	0.004393346	0.047225986
1303	COL12A1	collagen type XII alpha 1 chain	-1.128066662	0.000355049	0.013454179
9601	PDIA4	protein disulfide isomerase family A member 4	-1.126923809	0.00204506	0.031335479
95681	CEP41	centrosomal protein 41	-1.125641393	0.000866955	0.02071664
84056	KATNAL1	katanin catalytic subunit A1 like 1	-1.12453554	0.000441539	0.014857064
4001	LMNB1	lamin B1	-1.121222031	0.003994448	0.044725292
144165	PRICKLE1	prickle planar cell polarity protein 1	-1.11937255	0.004215947	0.046252884
374443	LOC374443	C-type lectin domain family 2 member D pseudogene	-1.118869735	0.001839868	0.029945785
25766	PRPF40B	pre-mRNA processing factor 40 homolog B	-1.116374313	0.004370735	0.047053751

22955	SCMH1	Scm polycomb group protein homolog 1	-1.114258526	0.000597036	0.017244398
51659	GINS2	GINS complex subunit 2	-1.110280113	0.000234659	0.011063845
7048	TGFBR2	transforming growth factor beta receptor 2	-1.106004202	0.000345244	0.013439115
641	BLM	Bloom syndrome RecQ like helicase	-1.104932572	0.002523047	0.03494363
9117	SEC22C	SEC22 homolog C, vesicle trafficking protein	-1.103162473	0.001321021	0.025240743
5833	PCYT2	phosphate cytidyltransferase 2, ethanolamine	-1.101960893	0.002865998	0.0376018
100506156	NA	NA	-1.100848	0.004520254	0.048001592
5829	PXN	paxillin	-1.100742148	0.001822814	0.0298467
81928	CABLES2	Cdk5 and Abl enzyme substrate 2	-1.100305479	0.001889257	0.030290461
130574	LYPD6	LY6/PLAUR domain containing 6	-1.095670807	0.002826906	0.037324564
3709	ITPR2	inositol 1,4,5-trisphosphate receptor type 2	-1.094923966	0.002993388	0.038318579
114788	CSMD3	CUB and Sushi multiple domains 3	-1.094017051	0.004523775	0.048001592
25934	NIPSNAP3A	nipsnap homolog 3A cell proliferation regulating inhibitor of protein phosphatase	-1.093817228	0.004325416	0.046883833
57650	CIP2A	2A	-1.092765941	0.002969472	0.038086132
22864	R3HDM2	R3H domain containing 2	-1.088769555	0.001015741	0.022602605
1787	TRDMT1	tRNA aspartic acid methyltransferase 1	-1.087565738	0.000633027	0.017767036
2222	FDFT1	farnesyl-diphosphate farnesyltransferase 1	-1.083244761	0.001113478	0.023309509
80179	MYO19	myosin XIX	-1.079813539	0.001303544	0.025165446
202	CRYBG1	crystallin beta-gamma domain containing 1	-1.079229138	0.000231435	0.011035795
1911	PHC1	polyhomeotic homolog 1	-1.077918602	0.003367683	0.040497242
51752	ERAP1	endoplasmic reticulum aminopeptidase 1	-1.07042715	0.00076297	0.019463922
3673	ITGA2	integrin subunit alpha 2	-1.070404422	0.000401606	0.014395639
26227	PHGDH	phosphoglycerate dehydrogenase	-1.066720513	0.002288102	0.03305139
2054	STX2	syntaxin 2	-1.066637956	0.001845937	0.029952483
7057	THBS1	thrombospondin 1	-1.064991111	0.001434283	0.026269443
56937	PMEPA1	prostate transmembrane protein, androgen induced 1	-1.0635491	0.000476979	0.015399024
1606	DGKA	diacylglycerol kinase alpha	-1.062568125	0.001337765	0.025413973
27242	TNFRSF21	TNF receptor superfamily member 21	-1.06187144	0.00017594	0.009769532
4796	TONSL	tonsoku like, DNA repair protein	-1.055236692	0.002817943	0.037302225
55848	PLGRKT	plasminogen receptor with a C-terminal lysine	-1.054028507	0.003090501	0.03882044

5427	POLE2	DNA polymerase epsilon 2, accessory subunit	-1.050841772	0.000357385	0.013470798
23621	BACE1	beta-secretase 1	-1.047336004	0.001276195	0.024951404
64792	IFT22	intraflagellar transport 22	-1.046487625	0.002392363	0.034075066
23184	MESD	mesoderm development LRP chaperone	-1.044783895	0.000681864	0.018347544
10989	IMMT	inner membrane mitochondrial protein	-1.04424258	0.00360417	0.042238863
8438	RAD54L	RAD54 like	-1.043595333	0.00437635	0.047078714
50650	ARHGEF3	Rho guanine nucleotide exchange factor 3	-1.04134716	0.003920193	0.044202495
22821	RASA3	RAS p21 protein activator 3	-1.040530512	0.004836592	0.04981655
378938	MALAT1	metastasis associated lung adenocarcinoma transcript 1 (non-protein coding)	-1.036918936	0.00181056	0.029828366
84513	PLPP5	phospholipid phosphatase 5	-1.035479993	0.002484378	0.034592858
4288	MKI67	marker of proliferation Ki-67	-1.035167829	0.003105118	0.03884388
960	CD44	CD44 molecule (Indian blood group)	-1.033633508	0.001811032	0.029828366
440145	MZT1	mitotic spindle organizing protein 1	-1.032851663	0.003425378	0.041012503
493869	GPX8	glutathione peroxidase 8 (putative)	-1.032598963	0.002999212	0.038358766
55785	FGD6	FYVE, RhoGEF and PH domain containing 6	-1.03151216	0.002234867	0.032646609
23322	RPGRIP1L	RPGRIP1 like	-1.027908762	0.000313515	0.012796079
2194	FASN	fatty acid synthase	-1.026656496	0.001780108	0.029629817
100129034	LOC100129034	uncharacterized LOC100129034	-1.025208333	0.003288562	0.040051492
4750	NEK1	NIMA related kinase 1	-1.025163422	0.003195553	0.039440987
51514	DTL	denticleless E3 ubiquitin protein ligase homolog	-1.023509571	0.003940112	0.04439151
58505	OSTC	oligosaccharyltransferase complex non-catalytic subunit	-1.023010081	0.000852455	0.020615005
29904	EEF2K	eukaryotic elongation factor 2 kinase	-1.022146257	0.000254246	0.0115571
79867	TCTN2	tectonic family member 2	-1.021730976	0.002418501	0.034242519
5327	PLAT	plasminogen activator, tissue type	-1.021339836	0.001278885	0.024951404
4628	MYH10	myosin heavy chain 10	-1.02072616	0.000679114	0.018347544
3912	LAMB1	laminin subunit beta 1	-1.020719497	0.004118948	0.045685782
85414	SLC45A3	solute carrier family 45 member 3	-1.019251766	0.004421994	0.047355773
11168	PSIP1	PC4 and SFRS1 interacting protein 1	-1.018296674	0.003574186	0.042164184
10616	RBCK1	RANBP2-type and C3HC4-type zinc finger containing 1	-1.014755922	0.004699335	0.049037411
54780	NSMCE4A	NSE4 homolog A, SMC5-SMC6 complex component	-1.013531227	0.000336322	0.013199701

119392	SFR1	SWI5 dependent homologous recombination repair protein 1	-1.009613958	0.002360636	0.033757797
133418	EMB	embigin	-1.008925002	0.001209638	0.024374625
56938	ARNTL2	aryl hydrocarbon receptor nuclear translocator like 2	-1.005955497	0.003043466	0.038511031
4047	LSS	lanosterol synthase	-1.005350225	0.000452983	0.015049569
92912	UBE2Q2	ubiquitin conjugating enzyme E2 Q2	-1.004293499	0.001183286	0.024210904
54704	PDP1	pyruvate dehydrogenase phosphatase catalytic subunit 1	-1.003099159	0.000281393	0.01201676
2182	ACSL4	acyl-CoA synthetase long chain family member 4	-1.002161644	0.000876661	0.020771655
1717	DHCR7	7-dehydrocholesterol reductase	-0.999359578	0.000686131	0.018355928
159090	FAM122B	family with sequence similarity 122B	-0.998009296	0.003291823	0.040057052
200844	C3orf67	chromosome 3 open reading frame 67	-0.996200068	0.001920851	0.030599186
55812	SPATA7	spermatogenesis associated 7	-0.99333637	0.002952286	0.037962518
26268	FBXO9	F-box protein 9	-0.991194036	0.001062315	0.022821411
9706	ULK2	unc-51 like autophagy activating kinase 2	-0.986789578	0.003784826	0.043290651
4174	MCM5	minichromosome maintenance complex component 5	-0.984546851	0.001395032	0.025935693
9814	SFI1	SFI1 centrin binding protein	-0.983216088	0.004251913	0.046429726
11123	RCAN3	RCAN family member 3	-0.979059364	0.004331877	0.046918269
1763	DNA2	DNA replication helicase/nuclease 2	-0.977519664	0.002838578	0.03740952
6764	ST5	suppression of tumorigenicity 5	-0.975645884	0.002642594	0.035893985
84632	AFAP1L2	actin filament associated protein 1 like 2	-0.975109964	0.002484489	0.034592858
205717	USF3	upstream transcription factor family member 3	-0.975020326	0.002843276	0.037436907
143	PARP4	poly(ADP-ribose) polymerase family member 4	-0.974388345	0.000428426	0.014748178
5990	RFX2	regulatory factor X2	-0.968946788	0.002858429	0.037596125
84937	ZNRF1	zinc and ring finger 1	-0.968822367	0.002122114	0.031979445
89782	LMLN	leishmanolysin like peptidase	-0.967196511	0.004298138	0.046623535
642273	FAM110C	family with sequence similarity 110 member C	-0.961619756	0.001061456	0.022821411
2314	FLII	FLII, actin remodeling protein	-0.958341741	0.00064217	0.01795312
10625	IVNS1ABP	influenza virus NS1A binding protein	-0.955817315	0.002736951	0.036672339
7515	XRCC1	X-ray repair cross complementing 1	-0.954206165	0.002927527	0.037811947
60481	ELOVL5	ELOVL fatty acid elongase 5	-0.953644562	0.002004477	0.031261963
6678	SPARC	secreted protein acidic and cysteine rich	-0.953290062	0.000915284	0.02120724
3992	FADS1	fatty acid desaturase 1	-0.952507931	0.001281898	0.024951404

2004	ELK3	ELK3, ETS transcription factor	-0.94988437	0.002695678	0.036399293
5562	PRKAA1	protein kinase AMP-activated catalytic subunit alpha 1	-0.949530156	0.001012452	0.022599838
55884	WSB2	WD repeat and SOCS box containing 2	-0.948123498	0.002819992	0.037302225
65987	KCTD14	potassium channel tetramerization domain containing 14	-0.946562196	0.00186225	0.030012167
8496	PPFIBP1	PPFIA binding protein 1	-0.94591209	0.001776372	0.029629817
26499	PLEK2	pleckstrin 2	-0.943922247	0.000838838	0.020449901
9695	EDEM1	ER degradation enhancing alpha-mannosidase like protein 1	-0.943915053	0.001828132	0.0298467
4061	LY6E	lymphocyte antigen 6 family member E	-0.941999066	0.001412472	0.026171944
8458	TTF2	transcription termination factor 2	-0.940510576	0.000737525	0.019267384
2305	FOXM1	forkhead box M1	-0.938779995	0.003260128	0.039875161
54820	NDE1	nudE neurodevelopment protein 1	-0.936808944	0.001684541	0.028820781
171423	PDIA3P1	protein disulfide isomerase family A member 3 pseudogene 1	-0.934716009	0.002261978	0.032873463
55331	ACER3	alkaline ceramidase 3	-0.933108795	0.004489151	0.047859712
9644	SH3PXD2A	SH3 and PX domains 2A	-0.931073612	0.000314486	0.012796079
29	ABR	active BCR-related	-0.928233681	0.001078243	0.022990725
84230	LRR8C	leucine rich repeat containing 8 VRAC subunit C	-0.916405829	0.003038407	0.038488695
54557	SGTB	small glutamine rich tetratricopeptide repeat containing beta	-0.915669571	0.003902247	0.044153154
4940	OAS3	2'-5'-oligoadenylate synthetase 3	-0.914922166	0.001345904	0.025494515
6747	SSR3	signal sequence receptor subunit 3	-0.914865262	0.001776133	0.029629817
79968	WDR76	WD repeat domain 76	-0.913625321	0.002686127	0.036339026
55062	WIPI1	WD repeat domain, phosphoinositide interacting 1	-0.912710297	0.004503914	0.047945538
1912	PHC2	polyhomeotic homolog 2	-0.908653679	0.003417887	0.04099361
8609	KLF7	Kruppel like factor 7	-0.907823555	0.001934818	0.030613813
6464	SHC1	SHC adaptor protein 1	-0.907279558	0.000449438	0.014966608
51199	NIN	ninein	-0.90057794	0.000807676	0.020101854
1639	DCTN1	dynactin subunit 1	-0.898591193	0.00293294	0.037811947
1284	COL4A2	collagen type IV alpha 2 chain	-0.895203759	0.002166148	0.032437721
811	CALR	calreticulin	-0.888567721	0.001752329	0.029612453
2201	FBN2	fibrillin 2	-0.88667937	0.004248828	0.046429726
6382	SDC1	syndecan 1	-0.881032807	0.001863311	0.030012167
81563	C1orf21	chromosome 1 open reading frame 21	-0.880103104	0.001316939	0.025219557

2771	GNAI2	G protein subunit alpha i2	-0.879523587	0.000751573	0.019415865
9181	ARHGEF2	Rho/Rac guanine nucleotide exchange factor 2	-0.87917224	0.002773694	0.036894776
4957	ODF2	outer dense fiber of sperm tails 2	-0.87657735	0.003862839	0.043954842
9388	LIPG	lipase G, endothelial type	-0.876174968	0.002126798	0.032016259
824	CAPN2	calpain 2	-0.875855455	0.000548632	0.016657922
84061	MAGT1	magnesium transporter 1	-0.875279545	0.001046703	0.022794514
87	ACTN1	actinin alpha 1	-0.874344612	0.003296014	0.040073915
55013	MCUB	mitochondrial calcium uniporter dominant negative beta subunit	-0.873391576	0.003671723	0.042715177
51232	CRIM1	cysteine rich transmembrane BMP regulator 1	-0.869578833	0.00179809	0.029828366
10484	SEC23A	Sec23 homolog A, coat complex II component	-0.868636538	0.000913737	0.02120724
266655	BRD3OS	BRD3 opposite strand	-0.867487677	0.002402229	0.034164663
5836	PYGL	glycogen phosphorylase L	-0.867426832	0.003702511	0.042863912
30844	EHD4	EH domain containing 4	-0.865960825	0.001157421	0.023894394
146057	TTBK2	tau tubulin kinase 2	-0.863387801	0.003597166	0.042226054
3949	LDLR	low density lipoprotein receptor	-0.862344062	0.001465113	0.026494432
55714	TENM3	teneurin transmembrane protein 3	-0.859584778	0.002120799	0.031979445
65244	SPATS2	spermatogenesis associated serine rich 2	-0.85845915	0.00075669	0.019429455
158	ADSL	adenylosuccinate lyase	-0.857966332	0.001897913	0.030362361
93627	TBCK	TBC1 domain containing kinase	-0.857216221	0.004819224	0.04981655
6242	RTKN	rhotekin	-0.853801552	0.003029227	0.038488695
90488	TMEM263	transmembrane protein 263	-0.8530291	0.004149755	0.045884985
6602	SMARCD1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1	-0.851664635	0.003199783	0.039440987
93643	TJAP1	tight junction associated protein 1	-0.851117891	0.002860632	0.037596125
7453	WARS	tryptophanyl-tRNA synthetase	-0.850341293	0.001229796	0.024571831
8243	SMC1A	structural maintenance of chromosomes 1A	-0.847991726	0.001616308	0.028080569
4026	LPP	LIM domain containing preferred translocation partner in lipoma	-0.847438328	0.001266972	0.024951404
5621	PRNP	prion protein	-0.843763417	0.003097977	0.03882044
64866	CDCP1	CUB domain containing protein 1	-0.84202829	0.000802157	0.020034288

10644	IGF2BP2	insulin like growth factor 2 mRNA binding protein 2	-0.841404805	0.002590707	0.035417075
4924	NUCB1	nucleobindin 1	-0.840930461	0.00134364	0.025491679
152503	SH3D19	SH3 domain containing 19	-0.840824778	0.001471036	0.026567911
50814	NSDHL	NAD(P) dependent steroid dehydrogenase-like	-0.838918591	0.001811027	0.029828366
991	CDC20	cell division cycle 20	-0.833617872	0.00328638	0.040051492
9926	LPGAT1	lysophosphatidylglycerol acyltransferase 1	-0.828281154	0.00209692	0.031784063
30001	ERO1A	endoplasmic reticulum oxidoreductase 1 alpha	-0.827044618	0.004460348	0.047681566
10376	TUBA1B	tubulin alpha 1b	-0.825565446	0.00404527	0.045043431
11328	FKBP9	FK506 binding protein 9	-0.823578642	0.004659685	0.048767957
11161	ERG28	ergosterol biosynthesis 28 homolog	-0.8232607	0.002205289	0.03248105
79863	RBFA	ribosome binding factor A	-0.822184981	0.002868398	0.0376018
55711	FAR2	fatty acyl-CoA reductase 2	-0.821965514	0.004342791	0.046952418
57646	USP28	ubiquitin specific peptidase 28	-0.820735347	0.004485829	0.047859712
55198	APPL2	adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 2	-0.818347435	0.001474336	0.026593897
374	AREG	amphiregulin	-0.81785038	0.004559405	0.048208126
64785	GINS3	GINS complex subunit 3	-0.817675832	0.003900535	0.044153154
5756	TWF1	twinfilin actin binding protein 1	-0.815683032	0.001481975	0.026697973
81839	VANGL1	VANGL planar cell polarity protein 1	-0.813900349	0.001515752	0.027000038
7468	NSD2	nuclear receptor binding SET domain protein 2	-0.81362965	0.002588165	0.035416214
253832	ZDHHC20	zinc finger DHHC-type containing 20	-0.810939993	0.003961193	0.044523689
79680	RTL10	retrotransposon Gag like 10	-0.809928072	0.003595031	0.042226054
135228	CD109	CD109 molecule	-0.807160107	0.002252363	0.03280046
646	BNC1	basonuclin 1	-0.805355913	0.00264318	0.035893985
129787	TMEM18	transmembrane protein 18	-0.801653079	0.004234091	0.046386674
2030	SLC29A1	solute carrier family 29 member 1 (Augustine blood group)	-0.801447546	0.002575194	0.035306359
24149	ZNF318	zinc finger protein 318	-0.800332369	0.001848216	0.029952483
64343	AZI2	5-azacytidine induced 2	-0.799601824	0.00119691	0.024288422
8935	SKAP2	src kinase associated phosphoprotein 2	-0.79249461	0.002095928	0.031784063
55959	SULF2	sulfatase 2	-0.786618978	0.004828726	0.04981655
8148	TAF15	TATA-box binding protein associated factor 15	-0.784330572	0.002200319	0.03248105

63939	FAM217B	family with sequence similarity 217 member B	-0.777944981	0.00162895	0.028207484
151011	sept-10	septin 10	-0.777087989	0.001613219	0.028071197
91404	SESTD1	SEC14 and spectrin domain containing 1	-0.774477248	0.003627367	0.042302503
2119	ETV5	ETS variant 5	-0.773662462	0.002456564	0.0344440116
4641	MYO1C	myosin IC	-0.770486844	0.00249924	0.03473165
23589	CARHSP1	calcium regulated heat stable protein 1	-0.769703951	0.003008654	0.038360826
5217	PFN2	profilin 2	-0.764762883	0.002008391	0.031264092
55893	ZNF395	zinc finger protein 395	-0.757850266	0.003586856	0.042226054
9674	KIAA0040	KIAA0040	-0.757449977	0.003280175	0.040017571
493	ATP2B4	ATPase plasma membrane Ca <sup>2+</sup> transporting 4	-0.752494428	0.004416376	0.047331095
133619	PRRC1	proline rich coiled-coil 1	-0.751383263	0.002356127	0.033756432
894	CCND2	cyclin D2	-0.750143058	0.002920545	0.03775829
11057	ABHD2	abhydrolase domain containing 2	-0.747736992	0.003916625	0.044202495
55705	IPO9	importin 9	-0.746092338	0.004577675	0.048246669
57415	C3orf14	chromosome 3 open reading frame 14	-0.742184419	0.004127121	0.045740928
7289	TULP3	tubby like protein 3	-0.736855919	0.002914595	0.037742954
81688	C6orf62	chromosome 6 open reading frame 62	-0.736007735	0.002340147	0.03359933
50809	HP1BP3	heterochromatin protein 1 binding protein 3	-0.732994855	0.002543413	0.035106471
5058	PAK1	p21 (RAC1) activated kinase 1	-0.730124955	0.002892829	0.037607316
25782	RAB3GAP2	RAB3 GTPase activating non-catalytic protein subunit 2	-0.728500328	0.004338372	0.046952418
50807	ASAP1	ArfGAP with SH3 domain, ankyrin repeat and PH domain 1	-0.726652461	0.003613192	0.042266115
23175	LPIN1	lipin 1	-0.714777476	0.002051257	0.031375004
23051	ZHX3	zinc fingers and homeoboxes 3	-0.704799632	0.003957327	0.044515256
23380	SRGAP2	SLIT-ROBO Rho GTPase activating protein 2	-0.678649982	0.004499098	0.047929993
5859	QARS	glutaminyl-tRNA synthetase	-0.672335642	0.004570778	0.048226091
51582	AZIN1	antizyme inhibitor 1	-0.630683927	0.00362595	0.042302503

## Substrate softness promotes a reversible switch from proliferation to differentiation in human keratinocytes

Archives of Dermatological Research

Choua Ya, Mariana Carrancá, Dominique Sigaudou-Roussel, Philippe Faure, Bérengère Fromy, Romain Debret

Corresponding author: Romain Debret  
LBTI, UMR5305 CNRS/UCBL  
7, passage du Vercors  
F-69367 LYON cedex 7  
[romain.debret@ibcp.fr](mailto:romain.debret@ibcp.fr)

**ESM 3:** Table summarizing substrate stiffness effect on keratinocyte behaviour

	<b>Stifness</b>	<b>Proliferation</b>	<b>Early differentiation</b>	<b>Late differentiation</b>
<b>Glass/plastic</b>	> 1 Gpa	+	++	(+/-) restricted
<b>Rigid hydrogel</b>	40 kPa	+	+	++
<b>Medium hydrogel</b>	15 kPa	+	(+/-) fast transition	++
<b>Soft hydrogel</b>	4 kPa	-	(+/-) fast transition	++