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REVIEW

Genetically modified laboratory mice with sebaceous glands abnormalities

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Abstract Sebaceous glands (SG) are exocrine glands that release their product by holocrine secretion, meaning that the whole cell becomes a secretion following disruption of the membrane. SG may be found in association with a hair follicle, forming the pilosebaceous unit, or as modified SG at different body sites such as the eyelids (Meibomian glands) or the preputial glands. Depending on their location, SG fulfill a number of functions, including protection of the skin and fur, thermoregulation, formation of the tear lipid film, and pheromone-based communication. Accordingly, SG abnormalities are associated with several diseases such as acne, cicatricial alopecia, and dry eye disease. An increasing number of genetically modified laboratory mouse lines develop SG abnormalities, and their study may provide important clues regarding the molecular pathways regulating SG development, physiology, and pathology. Here, we summarize in tabulated form the available mouse lines with SG abnormalities and, focusing on selected examples, discuss the insights they provide into SG biology and pathology. We hope this survey will become a helpful information source for researchers with a primary interest in SG but also as for researchers from unrelated fields that are unexpectedly confronted with a SG phenotype in newly generated mouse lines.

Keywords Sebaceous gland · Skin · Mouse models

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Introduction

As in many other fields of biomedical research, genetically modified laboratory mice became the mainstay of experimental dermatological research [1]. Such mouse lines are employed to better understand skin development, structure and function, to identify the molecular basis of a disease, to study its pathophysiology, and in some cases even to assess a potential therapeutic approach. Many of the engineered (=transgenic, knockin, knockout, and their several derivatives), but also a number of spontaneous, radiation-induced and chemical mutagenesis-induced mutants exhibit various types and degrees of abnormal cutaneous phenotypes. Such mutant lines have been once carefully compiled in a highly influencing but nowadays not fully up-to-date textbook [2]. More recently, a number of review articles focused on mouse lines with abnormalities in hair follicle morphogenesis, cycling, and/or structure [3, 4] or pigmentation [5]. Because mutant mice provide important clues about the function of gene products, such surveys have proved highly useful to researches with different interests, ranging from skin genetics *aficionados* to investigators from unrelated fields that are confronted with an unexpected skin phenotype in a newly generated or identified mouse line.

The last years witnessed an increased interest in the sebaceous glands (SG) [6–9]. These tiny exocrine glands, most commonly found in the dermis in association with a hair follicle (Fig. 1a), secrete an oily substance with manifold established or putative functions (see below). Recent advances in SG research include the identification of different stem cell pools regulating SG development and homeostasis [10, 11] novel insights into pathways regulating sebaceous lipogenesis [12–15] and a broadening of sebum's functional repertoire [16]. Here, after a brief introduction to SG physiology and pathology, we

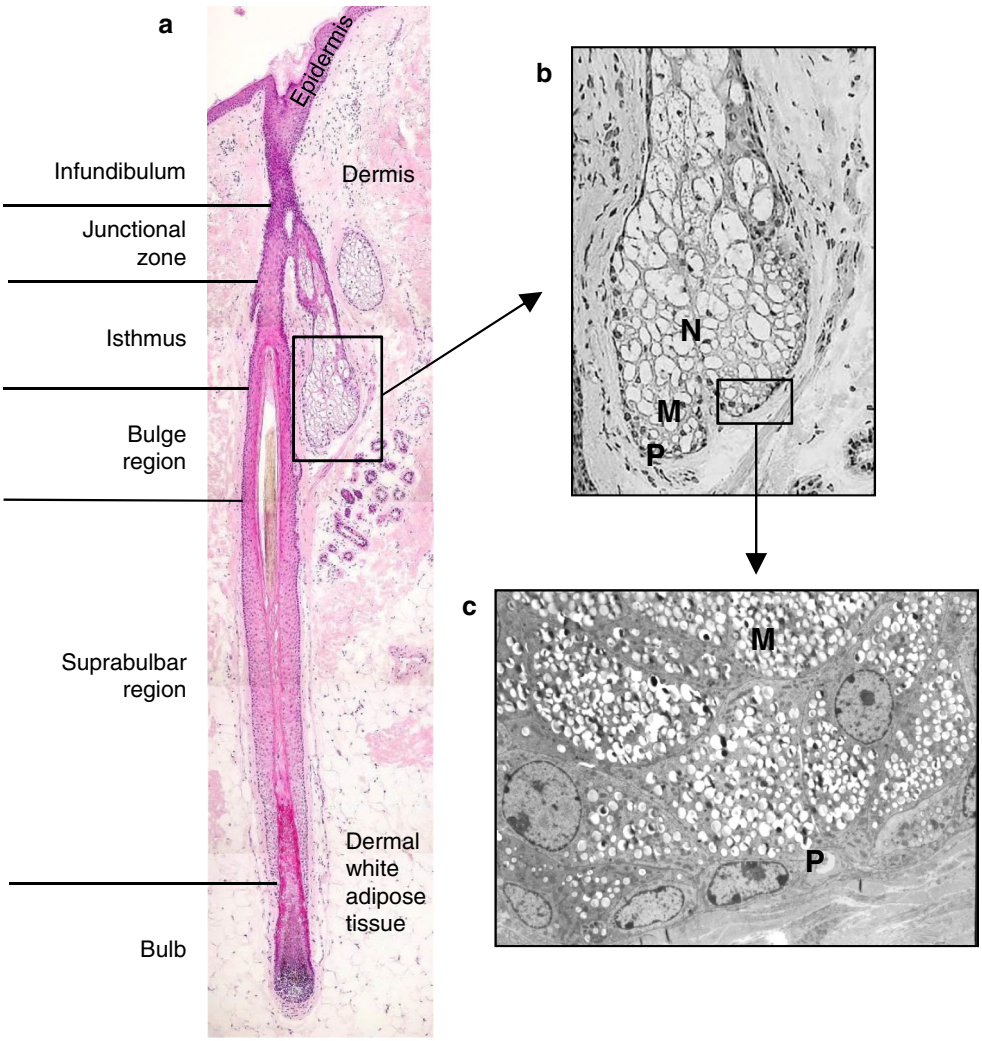

Fig. 1 Morphology of the pilosebaceous unit and fine structure of the sebaceous gland. **a** H&E-stained human scalp hair follicle in sagittal section showing the different follicular compartments. **b** High magnification image of the sebaceous gland. The peripheral (P), maturation (M), and necrosis (N) zones are indicated. **c** Transmission electron micrograph showing flat, undifferentiated sebocytes in the proliferative (P) zone and cells undergoing sebaceous differentiation and bearing numerous lipid droplets (*white spots*) in the cytoplasm in the maturation (M) zone Reproduced with permission from [18]

summarize in tabulated form the available mouse lines with SG abnormalities and, by concentrating on selected examples, discuss the insights they provide into SG biology. Importantly, in addition to providing insights into the role of the targeted gene/protein in sebocyte development or sebaceous lipogenesis, these mouse lines may be suitable for further applications, including pre-clinical studies assessing the effect of novel compounds in decreasing or increasing SG activity.

Morphological and functional diversity of sebaceous glands

SGs are exocrine glands displaying holocrine secretion, meaning that the whole cell forms a secretory product upon disruption of the membrane [8, 17]. Sebocytes, the foremost cell type within SGs, can be distinguished at different stages of differentiation within the same acinus. Sebocytes in the peripheral zone are flattened and mitotically active (Fig. 1b, c). As sebaceous differentiation takes place, these cells accumulate large numbers of cytoplasmic lipid droplets at the expense of other cell structures [18] and are gradually dislodged towards the center of the gland, forming the maturation zone (Fig. 1b, c). Cell disruption and release of lipids and cellular debris eventually take place at the center of the gland, in the necrosis zone (Fig. 1b). Before reaching the skin surface via the infundibulum [19] the SG product passes a glandular excretory duct composed of stratified squamous epithelium. Sebum's classical function is the formation of a protective film that waterproofs and lubricates the skin and the hair shafts. However, several other functions have been proposed for sebum, including antimicrobial and antioxidative properties [8, 9]. Native (=freshly released) human sebum contains squalene, cholesterol, wax esters, and triglycerides [20]. Triglycerides are partially hydrolyzed as sebum passes the hair canal, making superficial sebum to contain free fatty acids as well as lower amounts of mono- and diglycerides. Notably, sebum composition is remarkably species and age-specific.

Sebocytes derive from leucine-rich repeats and immunoglobulin-like domains 1 (LRIG1)-positive cells during the morphogenesis of the pilosebaceous unit [21]. The transmembrane protein LRIG1, an inhibitor of the EGFR/ERBB receptor family, also marks putative SG stem cells at the isthmus of the HF, which renew the SG and the infundibular epithelium [10, 11]. Numerous additional transcription factors and signaling proteins control SG development, growth, and homeostasis, including MYC, BLIMP1, and Indian hedgehog [8, 9]. In adults, sebum production is strongly influenced by steroid and peptide hormones, growth factors, and neuroendocrine regulators [8, 9].

In addition to the hair follicle-associated SG, modified and enlarged SGs (often termed "free" or "ectopic" glands) are found at distinct non-hairy sites such as the nipples, around the genitals, in the oral epithelium, or in the eyelids (Fig. 2). SGs in the latter location are termed Meibomian glands; they secrete a complex mixture of lipids (meibum) that upon delivery to the eye surface form the tear film lipid layer [22]. Another ectopic SG is the preputial gland. This paired gland is located between the skin and the abdominal muscles of male rodents, close to the genital bulb [23–25]. The preputial gland produces a mixture of lipids containing pheromones that have a role in territorial marking and in attracting females [23, 26]. The Harderian gland is located behind the eyeball [27] and is found in all groups of terrestrial vertebrates [28]. The pigment and the lipids with porphyrins produced by this gland reach the surface of the nictitating membrane by a duct and protect the cornea [28]. They are important for the grooming of the fur [27] and seem to facilitate the movement of the third eyelid [29].

The SG is also involved in the pathogenesis of diverse diseases. Meibomian gland dysfunction, for instance, frequently characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion, may result in alteration of the tear film and eye irritation or inflammation [30]. More commonly known is the key role of excessive sebum production in the pathogenesis of acne vulgaris, the most frequent cutaneous disorder during adolescence [31, 32]. Finally, SG degeneration is an early event in many types of cicatricial alopecia in humans and in some animal models for the disease [33, 34]. The *asebia* mouse, for instance, a well-characterized model for primary cicatricial alopecia and one if the earliest mouse mutant lines showing SG abnormalities (Table 1), develops SG atrophy due to a spontaneous mutation in the gene encoding the enzyme stearoyl coenzyme A desaturase 1 [35]. Consequently, normal desquamation of the hair follicle inner root sheath and hair shaft regression are prevented, resulting in inflammatory destruction of the hair follicle [36].

Mouse lines with sebaceous gland abnormalities: the tables

The mouse lines included in the present tables were gathered with the help of a query at PubMed (http://www.ncbi.nlm.nih.gov/pubmed) with the search terms: "mouse" and "sebaceous/sebocyte/Meibomian/preputial/Harderian" and by searching the Mammalian Phenotype browser (http://www.informatics.jax.org/searches/MP_form.shtml) with the search terms abnormal SG morphology (including "absent sebaceous glands", "abnormal skin sebaceous gland morphology", "enlarged sebaceous glands"; "small sebaceous gland", "sebaceous gland atrophy", "sebaceous gland hypoplasia", "abnormal SG number", "absent SG", "abnormal sebocyte morphology"), abnormal preputial gland morphology (including "abnormal male preputial morphology", "squamous metaplasia of the preputial

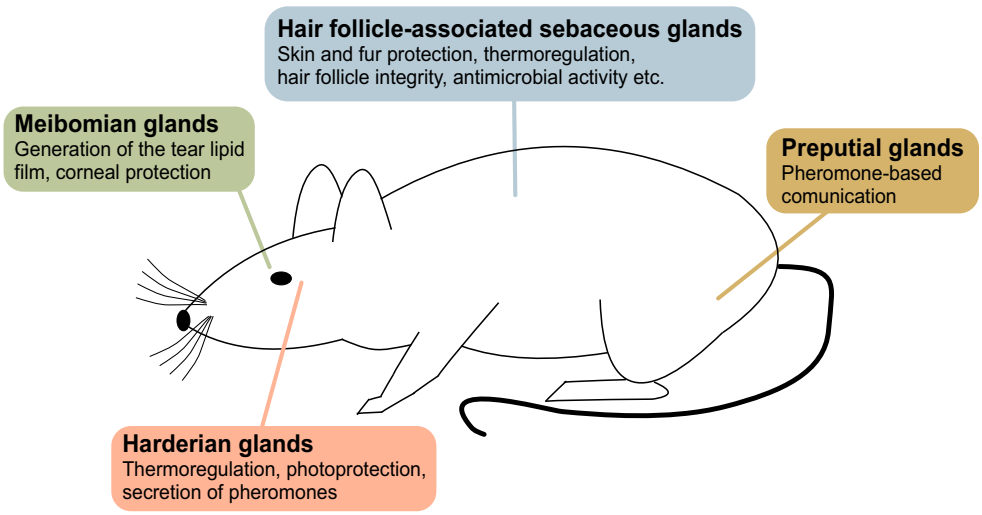

Fig. 2 Major types of sebaceous glands and their localization in mice. See the text for details and references

Table 1 Laboratory mouse lines with abnormalities in the hair follicle-associated sebaceous glands

	Gene symbol	Mutant name (if applicable)	Type	Characteristics/abnormalities	References
Soluble factors					
Amphiregulin (AREG)	*AREG*		tsTg	Enlarged SG producing large amounts of sebum	[51]
Ectodysplasin A1	*Eda*		tsTg	Enlarged SG	[61]
			iTg	Enlarged SG, increased number of sebocytes, excessive sebum production	[62]
Epigen (EPGN)	*EPGN*		itsTg	Enlarged SG, increase in the number of cells per gland, increased sebum production; SG hyperplasia is dependent on continuous epigen supply	[53] [52]
Fatty acid-binding protein, epidermal/fatty acid-binding protein 5 (FABP5)	*Fabp5*		fKO	Reduced size of SG, reduction in the number of sebocytes, altered lipid composition	[63]
Neuregulin-3 (NRG-3)	*Nrg3*		tsTg	Increased number and size of sebocytes, SG are mis-positioned and hyperplastic	[64]
Noggin	*Nog*		tsTg	Hypertrophic SG; pilosebaceous units at the expense of sweat glands in the footpads	[65]
	Nog		tsTg	Ectopic and increased sebocyte differentiation	[66]
Transforming growth factor alpha (TGFA)	*TGFA*		Tg	SG hyperplasia	[50]
Receptors					
Activin receptor type-1B (ACTR-IB)	*Acvr1b*		tsKO	Enlarged SG, increased numbers of SG in the skin	[67]
Fibroblast growth factor receptor 1 and 2 (FGFR 1 + 2)	*Fgfr1* + *Fgfr2*		tsKO	Loss of SG	[68]
Fibroblast growth factor receptor 2b (FGFR 2b)	*Fgfr2*		tsKO	SG atrophy; from postnatal day 6 evident differences in the rate of SG growth between the knockout and control mice, by 3 months: virtual absence of SG	[69]
Glucocorticoid receptor (GR)	*Nr3c1*		tsTg	Hypertrophic SG	[70]
Integrin alpha-V or integrin beta-1	*ITGAV or ITGB1*		tsTg	SG enlargement	[71]
Integrin beta-1	*Itgb1*		tsKO	At 7 weeks of age: no identifiable remnants of SG	[72]
Leucine-rich repeat-containing G protein-coupled receptor 5	*LGR5*		itsTg	LGR5 overexpression during embryogenesis: enlarged SG, increased degradation and accelerated maturation of sebocytes	[73]
Mutated Smoothened	*Smo*		itsTg	Ectopic sebocytes, increase in size and number of SG upon increased hedgehog signaling	[74]
Neurogenic locus notch homolog protein 1 (notch 1)	*Notch1*		itsTg	Enlarged SG	[75]
Peroxisome proliferator-activated receptor gamma	*Pparg*		tsKO	Atrophy of SG, dystrophy of SG	[76]
Tumor necrosis factor receptor superfamily member EDAR/ ectodysplasin-A receptor	*Edar*		tsTg	Enlarged SG	[77]
Vitamin D3 receptor (VDR)	*Vdr*		fKO	Enlarged SG	[78]
Transcription factors					
Catenin beta-1/beta-catenin	*Ctnnb1*		itsTg	Initial SG duplication, then inhibition of sebocyte differentiation and loss of SG	[79]
Delta N87betacat (beta- catenin)	*Ctnnb1*		tsTg	Development of ectopic SG	[80]
CCAAT/enhancer-binding protein alpha and beta (c/EBP alpha and c/EBP beta)	*Cebpa/Cebpb*		itsKO	Blocked sebocyte differentiation, lack of sebum production, unusual looking sebocytes	[81]
Homeobox protein BarH-like 2	*Barx2*		fKO	Enlarged SG	[82]
Homeobox protein DLX-3	*Dlx3*		tsKO	Enlarged SG	[83]
Krüppel-like factor 4	*KLF4*		itsTg	Atrophy of SG at 9 days after Doxycyclin treatment	[46]
Delta lymphoid enhancer-binding factor 1 (LEF-1)	*Lef1*		itsTg	Enlarged and ectopic SG	[84]
Delta N lymphoid enhancer-binding factor 1 (LEF-1)	*Lef1*		tsTg	Development of skin tumors with sebaceous differentiation	[85]
Lymphoid enhancer-binding factor 1 (LEF-1)	*Lef1*		tsTg	Sebaceous tumors, tumors with differentiated sebocytes	[86]

Table 1 continued

	Gene symbol	Mutant name (if applicable)	Type	Characteristics/abnormalities	References
Myc proto-oncogene protein	*MYC*		itsTg	Enlarged SG, increase in cell number	[48]
			itsTg	Enlarged SG, increased number of sebocytes, stimulation of sebaceous differentiation at the expense of hair differentiation	[45]
			itsTg	Enlarged SG, increase in the number of differentiated sebocytes at the expense of hair differentiation	[87]
			tsTg	Enlarged SG	[88]
			itsTg	Enlarged and disorganized SG	[47]
	Myc		tsKO	Impaired SG secretion	[49]
PR domain zinc finger protein 1/B lymphocyte-induced maturation protein 1 (Blimp-1)	*Prdm1*		itsKO	Increased SG size (in some animals)	[89]
			itsKO	SG enlargement	[90]
			tsKO	Enlarged SG, sebum lipids: increase in cholesterol esters, triglycerides and cholesterol, increased sebum production	[91]
Protein C-ets-1/p54	*Ets1*		iTg	In some cases: enlarged SG	[92]
Recombining binding protein suppressor of hairless/RBP-J kappa	*Rbpj*		tsKO	Impaired SG differentiation	[93]
Trans-acting T-cell-specific transcription factor GATA-3/GATA-binding factor 3	*Gata3*		tsKO	Enlarged SG from P7 onwards	[94]
Transcription factor A, mitochondrial (mtTFa)	*Tfam*		tsKO	Lack of SG	[95]
Transcription factor AP-2-alpha and -gamma (AP2-alpha and AP2-gamma)	*Tfap2a and Tfap2c*		tsKO	Defects in SG differentiation	[96]
Transcription factor E2-alpha/transcription factor 3 (TCF-3)	*Tcf3*		itsTg	Impairment of SG development	[97]
Transcription factor SOX-21	*Sox21*		fKO	At P12: enlargement of SG	[98]
Transcription factor SOX-9	*Sox9*		tsKO	SG morphogenesis is blocked, absence of SG progenitor cells	[99]
Transcription factor Sp6/krueppel-like factor 14	*Sp6*		fKO	Increase in SG size	[100]
Tumor protein 63 (p63)	*Trp63*		fKO	Absent SG	[101]
Delta NP63	*Trp63*		itsTg	Absence of SG (no morphogenesis)	[102]
Zinc finger protein GLI1	*GLI1*		tsTg	Differentiation into cells similar to sebaceous glands and epidermal cysts	[103]
Zinc finger protein GLI2	*Gli2*		tsTg	Prominent SG duct, additional pairs of highly branched SGs, elongated and enlarged ducts started at p25, at p45 a second pair of SG appears above the existing one; later: additional SG develop at infundibulum-epidermal junctions, ectopic SG	[104]
	Gli2		tsTg	Deficient/rare SG upon suppression of hedgehog signaling	[74]
Enzymes					
1-Phosphatidylinositol 4,5-bisphosphate phosphodiesterase delta-1/phospholipase C-delta-1	*Plcd1*		fKO	Hyperplasia of SG, increased number of sebocytes, skin tumors with characteristics of interfollicular epidermis and SG	[105]
Acyl-CoA desaturase 1/stearoyl -CoA desaturase 1	*Scd1*	Asebia	Spont	Absence of SG	[37]
			fKO	Degenerated SG	[106]
			tsKO	SG hypoplasia, depletion of sebaceous lipids, paucity of lipid- enriched sebocytes/lack of mature sebocytes; large reduction in sebaceous lipids: reduced wax diester and triglyceride content	[107]
			fKO	SG atrophy	[108]
		Asebia-2J	Spont	Hypoplasia of SG, skin lipids: reduction in sterol esters and cholesterol, loss of diol esters	[36]
		Flake	ENU	Reduced production of sebum, impaired clearance of skin infections	[109]

Table 1 continued

	Gene symbol	Mutant name (if applicable)	Type	Characteristics/abnormalities	References
Bis (5′-adenosyl)-triphosphatase	*Fhit*		fKO	Sebaceous tumors (Fhit±)	[110]
Cathepsin L1	*Ctsl*	nackt	Spont	SG Hyperplasia	[111, 112]
Ceramide synthase 4 (CerS4)	*Cers4*		fKO	Enlarged SG with multiple lobules	[113]
			fKO	Altered lipid composition of SG, enlarged SG	[114]
Cystathionine beta-synthase	*Cbs*		fKO	Hyperplastic SG	[115]
Diacylglycerol *O*-acyltransferase 1	*Dgat1*		fKO	Atrophy of SG (differences in fur lipid content in older mice)	[116]
DNA (cytosine-5)-methyltransferase 1 (Dnmt1)	*Dnmt1*		tsKO	Hyperplastic SG	[117]
Elongation of very long-chain fatty acids protein 3	*Elovl3*		fKO	Hyperplasia of SG, imbalance in the sebum lipid content (increase in the hydrophobic components)	[118]
Exostosin-1	*Ext1*		itsKO	Hyperplasia of SG, increased sebum production from p55, 4- fold increase in SG number (induced from p20 to p55), hyperplastic SG with altered morphology presenting irregular shapes and thickening of the SG canal	[119]
Fatty acid 2-hydroxylase	*Fa2h*		fKO	Hyperproliferation of sebocytes, enlarged SG, dilated hair canals are filled with sebum, altered sebum composition (reduced amount of wax diesters, increased amount of wax monoesters, free fatty acids and cholesterol)	[120]
Focal adhesion kinase (FADK)	*Ptk2*		tsKO	SG hypoplasia	[121]
Gamma secretase	*Psen1/Psen2*		tsKO	Failure to form SG	[122]
Group 2 secretory phospholipase A2	*PLA2G2A*		tsTg	SG hyperplasia	[123]
Group 3 secretory phospholipase A2	*PLA2G3*		Tg	SG hyperplasia in mice older than 9 months of age	[124]
GTPase HRas (H-Ras*G12V*)	*Hras*		KI	Lip skin: more SG than in control mice	[125]
GTPase KRas (kRas *G12d*)	*Kras*		KI	Hyperplasia of SG	[126]
GTPase KRas (kRas *G12D*)	*Kras*		KI	Enlargement of SG, sebaceous cysts, dysplasia of SG	[127]
Histone deacetylases 1 and 2 (HD1 and 2)	*Hdac1 and Hdac2*		tsKO	SG hyperplasia	[128]
Histone deacetylases 1 (HD1)	*Hdac1*		tsKO	SG hyperplasia	[128]
Lysine-specific demethylase hairless	*Hr*		tsTg	Delayed SG differentiation	[129]
N-lysine methyltransferase KMT5A (SETD8)	*Kmt5a*		itsKO	Loss of SG in adult skin	[130]
Ornithine decarboxylase (ODC)	*Odc1*		tsTg	Moderate SG hyperplasia	[131]
	Odc1		tsTg	At p 12: Moderate sebaceous cell hyperplasia	[132]
Palmitoyltransferase ZDHHC13	*Zdhhc13*		Spont	SG hyperplasia	[133]
Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN	*Pten*		tsKO	Enlarged SG, sebaceous carcinomas	[134]
Phospholipase A2, membrane associated/enhancing factor (EF)	*Pla2g2a*		tsTg	Enlarged SG (F2, homozygous)	[135]
Probable palmitoyltransferase ZDHHC21	*Zdhhc21*	Depilated	Spont	SG hyperplasia with an excess of sebum	[136]
Prostaglandin G/H synthase 2/cyclooxygenase 2 (COX-2)	*Ptgs2*		tsTg	Enlargement of SG	[42]
	Ptgs2		tsTg	SG hyperplasia, increased epicutaneous sebum concentration, enlarged gland duct	[40]
	Ptgs2		tsTg	SG hyperplasia	[41]
Protein kinase C lambda	*Prkci*		tsKO	Increased number of differentiated SG cells, enhanced SG differentiation, enlarged SG	[137]
Ras-related C3 botulinum toxin substrate 1	*Rac1*		tsKO	Lack of SG	[138]
			tsKO	Enlarged SG	[139]
			itsKO	7 to 9 days after treatment: enlarged and disorganized SG; early increase in terminally differentiated sebocytes, followed by progressive sebocyte loss	[140]

Table 1 continued

	Gene symbol	Mutant name (if applicable)	Type	Characteristics/abnormalities	References
Receptor tyrosine-protein kinase erbB-2	*Erbb2*		tsTg	Enlargement of SG	[141]
Serine palmitoyltransferase 2	*Sptlc2*		iKO	SG atrophy	[142]
Serine/threonine-protein kinase ATR	*Atr*		iKO	SG cell hypertrophy	[143]
Serine/threonine-protein kinase B-raf (B-Raf$V^{600}E$)	*Braf*		KI	Reduced numbers and size of SG	[144]
Tripeptidyl-peptidase 1 (TPP-1)	*Tpp1*		tsKO	Lack of SG	[145]
Tumor necrosis factor alpha-induced protein 3 (TNF alpha-induced protein 3)	*Tnfaip3*		tsKO	Hyperplasia of SG and sebocytes	[146]
Tyrosine-protein kinase Fyn +Focal adhesion kinase ($Fyn^{-/-}$ + $FAK^{+/-}$)	*Fyn* + *Ptk2*		fKO	Increased number and size of SG	[147]
Others					
14-3-3 protein sigma/stratifin	*Sfn*	Repeated epilation (Er)	Spont	Sfn+/ER (heterozygous dominant- negativ): hyperproliferative SG/enlarged SG	[148]
Acyl-CoA-binding protein (ACBP)	*Dbi*	Nm1054	Spont	Sebocyte hyperplasia, increased number of sebocytes, sebaceous lipids with reduced levels of triacylglycerols	[149]
Apolipoprotein C-I (Apo-CI)	*APOC1*		Tg	Atrophy of SG, lack of sebum	[150]
CD109 antigen	*Cd109*		fKO	Hyperplasia of SG, accumulation of sebum	[151]
Cell death activator CIDE-A	*Cidea*		fKO	Sebocytes accumulate smaller lipid droplets, reduced sebum lipid production	[152]
Corneodesmosin	*Cdsn*		itsKO	Hypertrophic SG	[153]
Disintegrin and metalloproteinase domain-containing protein 10 (ADAM 10)	*Adam10*		tsKO	Absence of SG, reduced lipid production	[154]
			itsKO	Deletion from P21 on: no significant loss of sebocytes, decreased lipid production	[154]
Gap junction beta-2 protein (Cx26-G45E)	*GJB2*		itsTg	Atrophy of SG in animals maintained on doxycycline for 10 weeks	[155]
Gasdermin-A3	*Gsdma3*	Rim3	Spont	Abnormal SG differentiation	[156, 157]
		Defolliculated (Dfl)	Spont	Sebocytes produce little or no sebum, abnormal differentiation of SG	[158]
		Defolliculated (Dfl)	Spont	Abnormal differentiation of SG, reduced sebum production	[159]
		Finnegan (Fgn)	ENU	Abnormal SG differentiation	[160]
		Reduced coat 2 (RCo2)	ENU	Absent SG	[161]
		Bare skin (Bsk)	ENU	Absent SG	[161]
		Rex denuded (Re den)	ENU	Absent SG	[161]
			ENU	Absence of SG	[162]
Golgi pH regulator	*Gpr89*		tsKO	Enlargement of SG at 1 month after birth	[163]
Insulin-induced gene 1 and 2 protein (INSIG-1 and 2)	*Insig1 and Insig2*		tsKO	Enlarged SG	[164]
Keratin, type I cytoskeletal 10/keratin-10 (K10)	*Krt10*		fKO	SG started to enlarge at the age of four weeks due to a stronger turnover of sebocytes, increased sebum production	[165]
Keratin, type I cytoskeletal 25	*Krt25*	Rex	Spont	Enlargement of SG	[166]
			ENU	M100573, enlargement of SG	[166]
Keratin, type II cytoskeletal 71	*Krt71*	Caracul Rinshoken	Spont	Enlarged SG	[167]
Long-chain fatty acid transport protein 4/Fatty acid transport protein 4 (FATP4)	*Slc27a4*	Wrinkle-free	Spont	Dystrophic SG, sebum: reduced level of type II diester wax	[168]

Table 1 continued

	Gene symbol	Mutant name (if applicable)	Type	Characteristics/abnormalities	References
Mothers against decapentaplegic homolog 4/SMAD family member 4 (SMAD 4)	*Smad4*		tsKO	Enlarged SG, increased sebocyte differentiation	[169]
			tsKO	Enlarged SG	[170]
			tsKO	Enlarged SG, sebaceous adenoma	[171]
			tsKO	One squamous papilloma accompanied by sebaceous hyperplasia	[172]
Mothers against decapentaplegic homolog 7	*Smad7*		itsTg	Accelerated SG morphogenesis, rapid growth of SG, hypertrophic enlarged SG, premature SG development	[173]
Mothers against decapentaplegic homolog 7 and E3 ubiquitin-protein ligase SMURF2	*Smad7 and SMURF2*		itsTg	Hypertrophic SG (more than in Smad7 alone)	[173]
Myelin protein zero-like protein 3 (predicted)	*Mpzl3*	Rough Coat (rc)	spont	SG hypertrophy, sebocyte hyperplasia	[174]
Nuclear receptor coactivator 1	Ncoa1		fKO	Heterozygous: enlarged SG	[175]
Perilipin-2	*Plin2*		fKO	Reduced size of SG, glands contain fewer cells, reduced proliferation	[12]
Prelamin-A/C (LMNA C1824T)	*LMNA*		itsTg	Disorganized SG, alterations of SG	[176]
	LMNA		itsTg	Initial hyperplasia is followed by hypoplasia of SG	[177]
	Lmna	Disheveled hair and ear (Dhe)	Spont	Hypoplastic SG	[178]
			KI	Reduced numbers of SG	[179]
	LMNA		itsTg	Displaced and hyperplastic SG, enlarged and abnormal differentiation	[180]
Protein Mpv17 (Mpv-17)	*Mpv17*		fKO	2-year-old mice: reduction in number and size of SG	[181]
Retinoblastoma-like protein 1 (p107) and retinoblastoma- like protein 2 (p130)	*Rbl1* and *Rbl2*		fKO	Hyperplastic SG	[182]
RING finger LIM domain-binding protein	*Rlim*		tsTg	Enlarged SG	[183]
Sonic hedgehog protein (SHH)	*Shh*		itsTg	Enlarged SG in the Tabby backround	[184]
			fKO	Failure to produce SG	[185]
SV40 large T antigen (SV40T)	*SV40 Tag*		tsTg	Enlarged SG	[186]
Telomeric repeat-binding factor 1	*Terf1*		tsKO	Absence of SG	[187]
TNF receptor-associated factor 6	*Traf6*		fKO	Impairment of SG	[188]
Unknown					
		Alopecia-1	ENU	Lack of SG, at two weeks of age SG are rarely found	[189]
		Alopecia-2	ENU	Lack of SG, at two weeks of age SG are rarely found	[189]
		Bareskin (Bsk)	ENU	SG consisted of rudimentary buds, cells at site of SG were undergoing abnormal cornification rather than sebaceous differentiation	[2]
		Curly bare (cub)	Spont	Enlarged SG	[190]
		Hairless	Spont	SG hypertrophy (2 months after birth), atrophy (after 1 year of age)	[191]
		Hairless-Rhino	Spont	SG hypertrophy (2 months after birth), atrophy (after 1 year of age)	[191]
		Harlequin Ichthyosis (ichq)	Spont	Small, immature SG	[192]
		Rhino	Spont	SG hypertrophy (2 months after birth), atrophy after 1 year of age	[191]
		Rough-fur (ruf)	ENU	Enlarged SG, lipid droplets are denser, irregular shape of SG	[193]
		Soft coat (soc)	Spont	SG Hyperplasia	[2]

Table 1 continued

	Gene symbol	Mutant name (if applicable)	Type	Characteristics/abnormalities	References
		Uncovered (Uncv)	Spont	SG hyperplasia	[194]

Spont spontaneous, *Tg* transgen, *i* induced, *ts* tissue specific, *fKO* full knockout, *KI* knockin, *SG* sebaceous gland, *PG* preputial gland, *MG* Meibomian gland, *HG* Harderian gland

Table 2 Laboratory mouse lines with abnormalities in Meibomian glands

	Gene symbol	Mutant name (if applicable)	Type	Characteristics/abnormalities	References
Soluble factors					
Noggin	*Nog*		tsTg	Formation of pilosebaceous units at the expense of MG/suppression of the induction of MG	[65]
Transforming growth factor alpha (TGFA)	*TGFA*		itsTg	Abnormal MG morphogenesis, atrophy, and anomalies with a variation of severity	[54]
	Tgfa		fKO	Absence/hypoplasia of MG	[55]
Receptors					
Epidermal growth factor receptor	*Egfr*		tsKO	Hypoplastic MG	[195]
Glucocorticoid receptor (GR)	*Nr3c1*		tsTg	Lack of MG	[70]
Neurogenic locus notch homolog protein 1 (Notch1)	*Notch1*		tsKO	MG dysfunction, abnormal morphology of MG, lack of lipids	[196]
Tumor necrosis factor receptor superfamily member EDAR/ectodysplasin-A receptor	*Edar*		tsTg	Enlarged MG	[77]
Transcription factors					
CCAAT/enhancer-binding protein alpha and beta (c/EBP alpha and c/EBP beta)	*Cebpa and Cebpb*		itsKO	Reduced lobule size and diminished numbers of differentiated meibocytes with clear vacuolated cytoplasm	[81]
Homeobox protein BarH-like 2	*Barx2*		fKO	Defects in MG development and structure	[197]
Krueppel-like factor 5	*Klf5*		tsKO	Malformed MG with disorganized acini, lipid accumulation in the meibomian ducts	[198]
Myc proto-oncogene protein	*MYC*		itsTg	Enlarged MG	[45]
NF-kappaB super-repressor	*IkBaDN*		KI	Lack of MG	[199]
PR domain zinc finger protein 1/B lymphocyte-induced maturation protein 1 (Blimp-1)	*Prdm1*		tsKO	Enlarged MG	[91]
Transcription factor AP-1/proto-oncogene c-jun	*Jun*		tsKO	Hypoplastic MG	[195]
Transcription factor SOX-9	*Sox9*		tsKO	Reduced number of MG, 40 % fewer glands in the upper and the lower eyelids, most MG had fewer acini	[200]
Twist-related protein 2	*Twist2*		fKO	Absent/hypoplastic MG	[201]
Enzymes					
Acetyl-CoA acetyltransferase, mitochondrial	*Acat1*		fKO	Atrophy of Meibomian gland	[202]
Acyl-CoA desaturase 1/Stearoyl-CoA desaturase 1	*Scd1*	Asebia-2J	Spont	Small MG, rudimentary duct and glandular structures	[36]
			fKO	Atrophy of MG, lack of foamy appearance due to depletion of meibum lipids	[108]
Histone deacetylases 1 and 2 (HD1 and 2)	*Hdac1 and Hdac2*		tsKO	MG hyperplasia	[128]

Table 2 continued

	Gene symbol	Mutant name (if applicable)	Type	Characteristics/abnormalities	References
Mitogen-activated protein kinase kinase kinase 1	*Map3k1*		fKO	Hypoplastic MG	[195]
Superoxide dismutase (Cu–Zn)	*Sod1*		fKO	MG alterations including increase in periglandular inflammatory infiltrates, decrease in MG glandular acinar density, increase in periglandular fibrosis	[203]
Others					
14-3-3 protein sigma/stratifin	*Sfn*	Repeated epilation (Er)	Spont	MG atrophy and reduced lipid content in aged heterozygotes	[204]
Apolipoprotein C-I (Apo-CI)	*APOC1*		Tg	MG atrophy	[150]
Basigin (CD147)	*Bsg*		fKO	MG malformation, impaired meibocyte function, secretory acini of MG were poorly developed, small MG, cells in secretory acini failed to produce lipids	[205]
Cell death activator CIDE-A	*Cidea*		fKO	Meibocytes accumulate a larger number of smaller-size lipid droplets	[152]
Gasdermin-A3	*Gsdma3*	Defolliculated (Dfl)	Spont	Decreased lipid production	[158]
Insulin-induced gene 1 and 2 protein (INSIG-1 and 2)	*Insig1 and Insig2*		tsKO	Abnormalities in MG	[164]
Long-chain fatty acid transport protein 4/Fatty acid transport protein 4 (FATP4)	*Slc27a4*	Wrinkle-free	Spont	Abnormal development of MG (dystrophic MG), defective meibocyte differentiation	[168]
TNF receptor-associated factor 6	*Traf6*		fKO	Impairment of MG development	[188]
Unknown					
		ARMGD	n.r.	MG atrophy	[206]
		crinkled	Chem.	Absence of MG	[207]
		Rhino (hrrhhrrh)	Spont	Progressive loss or atrophy of MG	[208]
		Rhino hrrh		Loss of acini and atrophy of MG	[2]
		Tabby	Spont	Lack of MG	[209]
		Tabby	Spont	Lack of MG	[2]
		Waved with open eyelids 2 (woe2)	Spont	Absence of MG	[210]
		Waved with open eyes (woe)	Spont	Absence of MG	[211]

Spont spontaneous, *Tg* transgen, *i* induced, *ts* tissue specific, *fKO* full knockout, *KI* knockin, *SG* sebaceous gland, *PG* preputial gland, *MG* meibomian gland, *HG* Harderian Gland, *n.r.* not reported, *chem.* chemically

gland"), abnormal Harderian gland morphology (including "abnormal Harderian gland development", "abnormal Harderian gland pigmentation", "abnormal Harderian gland size", "absent Harderian gland"), and abnormal Meibomian gland morphology (including "abnormal Meibomian gland acinus morphology", "abnormal Meibomian gland development", "absent Meibomian gland", "enlarged Meibomian gland", "Meibomian gland atrophy", "Meibomian gland cyst", "small Meibomian gland"). For reasons of clarity and comprehensibility, we present the mouse lines in four tables, depending on whether they show abnormalities in skin SG (Table 1), Meibomian glands (Table 2), preputial glands (Table 3), or Harderian glands (Table 4). In each table, the genes and gene products responsible for the SG abnormalities are grouped in categories ("soluble factors", "receptors", "transcription factors", "enzymes", "adhesion molecules", "others" and "unknown"). After indicating whether there is a classical, mostly spontaneous mouse mutation for the gene in question, we list the type of genetic modification, provide a summary of the SG phenotype, and indicate the relevant publication. Although we made every effort to include all known mouse lines with a SG phenotype, we cannot exclude having missed important lines. We apologize for

Table 3 Laboratory mouse lines with abnormalities in the preputial glands

	Gene symbol	Mutant name (if applicable)	Type	Characteristics/abnormalities	References
Receptors					
Glucocorticoid receptor (GR)	*Nr3c1*		tsTg	Underdeveloped PG	[70]
Gonadotropin-releasing hormone receptor (GnRH-R)	*Gnrhr*		fKO	Reduced size of PG	[212]
KiSS-1 receptor (KiSS-1R)/G protein-coupled receptor 54	*Kiss1r*		fKO	Lacked preputial separation, small PG	[213]
			fKO	Reduced development of PG	[214]
			fKO	PG were frequently not identifiable	[215]
		GKirKO mouse	tsKO	Failure to exhibit PG separation	[216]
Transcription factors					
Catenin beta-1/beta-catenin	*Ctnnb1*		KI	Keratinized squamos metaplasia of PG	[217]
	Ctnnb1		KI	Hyperplasia and squamous metaplasia of PG	[218]
CCAAT/enhancer-binding protein alpha and beta (c/EBP alpha and c/EBP beta)	*Cebpa/Cebpb*		itsKO	Atrophy of PG lobules and decreased numbers of finely vacuolated sebocytes	[81]
Helix-loop-helix protein 2 (HEN-2)	*Nhlh2*		fKO	Absent or reduced PG	[219]
Homeobox protein Hox-D13	*Hoxd13*	Synpolydactyly homolog (spdh)	Spont	Lack of PG	[24]
		Digit in Y and carpe ("Dyc")	Spont	Absent PG	[220]
PR domain zinc finger protein 1/B lymphocyte-induced maturation protein 1 (Blimp-1)	*Prdm1*		tsKO	Enlarged PG	[91]
Transcription factor GATA-5/GATA-binding factor 5	*Gata5*		fKO	Hypoplastic clitoral glands	[221]
Enzymes					
Cathepsin L1	*Ctsl*	Nackt	Spont	Furunculosis and abscesses of PG (mouse maintained non-SPF)	[112]
Ornithine decarboxylase (ODC)	*ODC1*		tsTg	Abnormal PG, increased amount of glandular tissue, thicker ducts, metaplastic change	[222]
Others					
Adenomatous polyposis coli protein (APC1638T)	*Apc*		KI	Absence of PG	[23]
Autophagy protein 5	*Atg5*		tsKO	Aberrant differentiation of PG	[223]
DNA cross-link repair 1A protein/SNM1 homolog A	*Dclre1a*		fKO	Frequent infection of PG	[224]
DNA repair protein RAD51 homolog 3	*Rad51c*		tsKO	Increased keratinization of preputial sebocytes	[225]
DNA repair protein RAD51 homolog 3 + cellular tumor antigen p53	*Rad51c + Trp53*		tsKO	Increased incidence of PG tumors	[225]
Gasdermin-A3	*Gsdma3*	Defolliculated (Dfl)	Spont	Decreased PG lipid production	[158]
GTPase KRas and catenin beta-1	*Kras and Ctnnb1*		KI	Keratinized squamos metaplasia of PG	[217]
Metastasis-suppressor KiSS-1	*Kiss1*		fKO	Lacked preputial separation, small PG	[213]
			fKO	Poor PG development	[226]
SV40 large T antigen (SV40T)	*SV40 Tag*		tsTg	Small PG	[186]
Protein mab-21-like 1	*Mab21l1*		fKO	Reduction in overall size of PG	[227]
TNF receptor-associated factor 6	*Traf6*		fKO	Impairment of PG	[188]

Table 3 continued

	Gene symbol	Mutant name (if applicable)	Type	Characteristics/abnormalities	References
Uveal autoantigen with coiled-coil domains and ankyrin repeats/nuclear membrane-binding protein (nucling)	*Uaca*		fKO	PG swelling and pathological alterations including keratinization, inflammation and granulomatous lesions	[228]
			fKO	High prevalence of PG abscess, frequent inflammatory lesions of PG in some males younger than 1 year	[229]
Unknown					
		Diabetes	Spont	Small PG	[230]
		Downless	Spont	Absent PG	[2]
		Mesenchymal dysplasia (mes)	Spont	Small PG	[231]

Spont spontaneous, *Tg* transgen, *i* induced, *ts* tissue specific, *fKO* full knockout, *KI* knockin, *SG* sebaceous gland, *PG* preputial gland, *MG* Meibomian gland, *HG* Harderian Gland

Table 4 Laboratory mouse lines with abnormalities in the Harderian glands

	Gene symbol	Mutant name (if applicable)	Type	Characteristics/abnormalities	References
Soluble factors					
Fibroblast growth factor 10 (FGF-10)	*Fgf10* (*rat*)		tsTg	Ectopic HG in cornea	[232]
	Fgf10		fKO	Lack of HG	[232]
	Fgf10		fKO	Absent HG epithelium	[233]
	Fgf10	*Aey17*	ENU	HG atrophy (gland replaced by fibrotic pigmented mass)	[234]
Receptors					
Proto-oncogene tyrosine-protein kinase receptor Ret	*Ret*		tsTg	HG tumors with hyperplastic and dysplastic lesions	[235]
Receptor tyrosine-protein kinase erbB-2/proto-oncogene Neu	*Erbb2/Neu* (*rat*)		tsTg	HG tumors	[236]
Receptor tyrosine-protein kinase erbB-2/tyrosine kinase-type cell surface receptor HER2	*ERBB2/HER2*		tsTg	HG enlargement	[29]
Retinoid acid receptor alpha (RAR alpha)	*Rara*		fKO	HG agenesis	[237]
Retinoid acid receptor (RAR gamma)	*Rarg*		fKO	Monolateral or bilateral absence of the HG epithelium	[238]
Retinoid acid receptor (RAR alpha/gamma)	*Rara/Rarg*		fKO	Agenesis of the HG	[239]
Retinoid acid receptor (RAR beta/gamma)	*Rarb/Rarg*		fKO	Agenesis of the HG	[239]
	Rarb/Rarg		fKO	Unilateral or bilateral absence of HG	[240]
Transcription factors					
Catenin beta-1/beta-catenin	*Ctnnb1*		KI	Squamos metaplasia with keratinization of the glandular epithelium of HG	[241]
Homeobox protein BarH-like 2	*Barx2*		fKO	Absence of the HG	[197]
Microphthalmia-associated transcription factor	*Mitf*		Spont	No melanocytes in HG	[242]
NF-kappaB super-repressor	*IkBaDN*		KI	Lack of HG	[199]
Transcription factor SOX-10	*Sox10*		tsKO	No evidence of secretory acini in HG	[200]
Transcription factor SOX-9	*Sox9*		tsKO	Epithelial component of HG is absent	[200]

Table 4 continued

	Gene symbol	Mutant name (if applicable)	Type	Characteristics/abnormalities	References
Enzymes					
Acyl-CoA desaturase 1/stearoyl-CoA desaturase 1	*Scd1*		tsKO	HG atrophy	[107]
Aldehyde dehydrogenase family 1 member A3/ retinaldehyde dehydrogenase 3 (RALDH-3)	*Aldh1a3*		fKO	HG agenesis	[243]
GTPase HRas/c-Ha-ras	*HRAS*	rasH2	Tg	HG adenoma	[244]
			Tg	Some mice developed HG adenocarcinomas	[245]
GTPase KRas	*Kras*		KI	Hyperplastic HG	[246]
GTPase NRas	*Nras*		tsTg	Hyperplasia, degeneration and destruction of HG	[247]
	Nras		tsTg	HG tumors and HG hypertrophy	[248]
Proto-oncogene serine/threonine-protein kinase mos	*Mos*		Tg	HG hyperplasia in one line	[249]
Retinal dehydrogenase 1 (RALDH 1) and Aldehyde dehydrogenase family 1 member A3/retinaldehyde dehydrogenase 3 (RALDH-3)	*Aldh1a3 and Aldh1a1*		fKO	Agenesis of HG	[250]
Serine/threonine-protein phosphatase 2A catalytic subunit alpha isoform (PP2A-alpha)	*PPP2CA*		tsTg	SG hypoplasia	[251]
Others					
Acyl-CoA-binding protein (ACBP)	*Dbi*		fKO	Enlarged HG, hypertrophy of acinar cells, vesicles and lumen contain more lipid	[27]
Dickkopf-related protein 2 (Dkk-2)	*Dkk2*		fKO	HG hypoplasia	[195]
Human F8B	*F8*		Tg	HG tumors	[252]
Neurogenic locus notch homolog protein 4 (Notch 4)/one of three chains: Transforming protein Int-3	*Notch4/ Int3*		tsTg	HG hyperplasia	[253]
Transforming growth factor beta regulator 1/nuclear interactor of ARF and Mdm2	*Tbrg1*		fKO	HG adenoma	[254]
v-Ha-ras	*Hras*		tsTg	Benign hyperplasia of HG	[255]
	Hras		tsTg	Hyperplasia of individual HG	[256]
	Hras		tsTg	Bilateral hyperplasia of HG	[257]
v-Ha-ras and c-myc	*Hras* and *Myc*		tsTg	Benign hyperplasia of HG	[255]
v-Ha-ras/cyclin-dependent kinase inhibitor 1A (P21)	*Hras/ Cdkn1a*		tsTg	HG hyperplasia	[258]
Unknown					
		Ichthyosis (ic)	Spont	Absent HG	[259]
		Ocular retardation (or)	Spont	Hypertrophy of HG	[260]
		White-footed mice (two inbred lines: GS109A, GS16A1)	Spont	Harderian adenocarcinomas	[261]

Spont spontaneous, *Tg* transgen, *i* induced, *ts* tissue specific, *fKO* full knockout, *KI* knockin, *SG* sebaceous gland, *PG* preputial gland, *MG* Meibomian gland, *HG* Harderian gland

any unintended omission and would be grateful for input in this regard from our readers.

While it would go beyond the scope of the present review to analyze in detail the phenotype and the significance of each mouse line, glancing through the table immediately reveals some gene products that seem to be of special importance for the SG. A classic model for studying the SG is a mouse line named asebia. Gates and Karasek described in 1965 a spontaneous mouse mutation that is characterized by impaired sebum production due to the absence of SG [37]. Several groups investigated this line in detail [35]. Another enzyme whose expression influences the SG is cyclooxygenase 2 (COX2), also known as prostaglandin endoperoxide H synthase 2. This enzyme uses arachidonic acid to produce prostaglandin H2 [38, 39]. Transgenic mice with overexpression of COX2 in the skin

show enlarged SG [40–42], with increased sebum accumulation and SG duct enlargement. These changes support the observation that COX2 inhibits apoptosis [43] and leads to the enlargement of the SG. Another protein whose overexpression increases the size of the SG is the transcription factor myc [44], whose overexpression enhances proliferation and differentiation of the sebocytes at the expense of the hair differentiation [45]. Several groups developed mice with overexpression of myc and observed enlargement of the SG as a consequence [45–49]. Finally, several ligands of the epidermal growth factor receptor (EGFR) influence SG size and sebaceous lipogenesis: Overexpression of transforming growth factor alpha [50], amphiregulin [51], or epigen [52, 53] resulted in enlarged SGs. Mice with inducible expression of transforming growth factor alpha in the eyelid resulted in atrophic MG due to malformation of the eyelid [54]. Conversely, transforming growth factor alpha-deficient mice have hypoplastic MG [55].

Conclusions and outlook

During the compilation of these annotated tables, it became evident that the description and analysis of SG abnormalities differ substantially depending on the laboratory involved. As many reports come from groups whose primary interest is not the SG, the phenotype description is often vague or superficial. For instance, SG enlargement is frequently reported without distinguishing whether it arises from hyperplasia, hypertrophy, or a combination of both events. In addition, dissimilarities in genetic background (different inbreed strains, mixed backgrounds) and environmental differences (nutrition, pathogen status) may result in substantial variations in histological and clinical aspects of the SG abnormality. Finally, the fact that no SG abnormality was reported for a specific mouse line should not lead to the assumption that that such abnormality is not present, as mild changes in SG structure and function may not result in a readily detectable phenotype. These limitations should be kept in mind when consulting the tables provided here.

Genetically modified mouse lines, in association with sebocyte cell culture models [56] significantly contributed to our understanding of SG development, physiology, and pathology. Until now, regulatory sequences of genes encoding keratins or other structural proteins have been used for targeting genes in the epithelial compartment of the skin, including the sebocytes [1]. This approach has the disadvantage that various cell types in the epidermis and in the pilosebaceous unit are targeted concomitantly, potentially causing unspecific phenotypes and side effects. In this regard, the recent report of a mouse line allowing sebocyte-specific gene targeting [57] will allow more precise studies on several aspects of SG biology. We also anticipate that the availability of the CRISPR/Cas9 technology, a novel tool allowing efficient and reliable targeted changes in the genome [58], will further increase the number of genetically modified mouse lines, including those with a SG phenotype. As a detailed guide for SG analysis is now available [59] we also expect future studies to provide a more professional description of the SG alterations.

Although considerable progress has been made in understanding SG biology and pathology, several pathways and processes remain poorly characterized. For instance, while a role for specific enzymes in sebaceous lipogenesis has been demonstrated, our knowledge in this area (particularly in comparison to adipocytes) remains unsatisfactory. Thus, future studies should focus on the systematic characterization of the role played by enzymes as elongases and desaturases [60] in sebum synthesis as well as their regulation. Another worthwhile field for future research is defining the SG stem cells and studying how sebaceous differentiation takes place. Finally, a better understanding of the molecular processes underlying holocrine secretion, in particular the role played by apoptotic pathways, may reveal novel targets for treating SG-associated diseases.

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Compliance with ethical standards

Conflict of interest There are no conflicts of interest to declare.

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