Eurasia Specialized Veterinary Publication

International Journal of Veterinary Research and Allied Science
ISSN:3062-357X

2022, Volume 2, Issue 2, Page No: 92-100

Available online at: www.esvpub.com/

Grooming Behavior as a Predictive Biomarker for Dermatitis in Selectively Bred P Rats: Implications for Trichotillomania Research

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ABSTRACT

Trichotillomania (TTM) is a body-focused repetitive behavior disorder that affects approximately 0.5–2% of individuals, with females being four times more likely to develop it than males. The condition causes considerable emotional distress and disruption of normal daily activities. The inbred C57BL/6J mouse strain has been identified as a potential experimental model for TTM because it exhibits behavioral and clinical features similar to those seen in humans with the disorder. Since alcohol-preferring P rats also display comparable behavioral and physiological traits, they were proposed as an additional model organism. In this study, 112 female P rats were video recorded for 15 minutes following exposure to a light water mist, and their grooming activities—including oral, manual, and scratching behaviors—were analyzed. A marked increase in scratching and oral grooming was found to predict later skin lesion formation. These observations indicate that P rats could serve as another suitable model for investigating TTM, offering the benefit of genetic variability (non-inbred), which more accurately represents human populations. Employing this model may contribute to the identification of preventive and therapeutic strategies for TTM and related body-focused repetitive disorders.

Keywords: Animal model, Trichotillomania, Hair-pulling, Body-focused repetitive disorder

Received: 14 March 2022
Revised: 29 May 2022
Accepted: 02 June 2022

How to Cite This Article: Williams E, Johnson E, Brown L. Grooming Behavior as a Predictive Biomarker for Dermatitis in Selectively Bred P Rats: Implications for Trichotillomania Research. Int J Vet Res Allied Sci. 2022;2(1):92-100.
https://doi.org/10.51847/W2rAOURb2f

Introduction

Trichotillomania (TTM), commonly referred to as “hair-pulling disorder,” is classified by the American Psychiatric Association as an obsessive-compulsive disorder [1]. Individuals affected by TTM repeatedly pull out their hair, resulting in visible bald patches and exposed skin, with onset usually in childhood or adolescence. Hair-pulling can occur anywhere hair grows, but the scalp, eyebrows, eyelashes, pubic region, and beard are the most frequent sites [1]. Due to the social stigma associated with the disorder, the actual prevalence is uncertain, though estimates suggest it may affect up to 3% of the population [2]. Women are diagnosed significantly more often than men—representing about 92.5% of adults seeking treatment—although it has been suggested that men may conceal symptoms more easily by shaving or other grooming habits.

Diagnostic features of TTM include persistent hair-pulling leading to noticeable hair loss, repeated efforts to stop or reduce the behavior, and distress or impairment in social, occupational, or functional areas [1]. The condition must also not be explained by another psychiatric or medical condition (e.g., dermatologic disorder). Many individuals also show multiple body-focused repetitive behaviors such as nail biting, skin picking, thumb sucking, knuckle cracking, or nose picking [2–8].

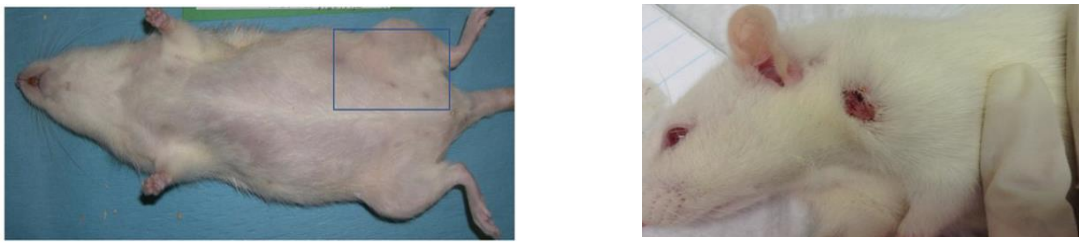
Due to ridicule or embarrassment, many sufferers hide their condition and often develop low self-esteem. They also commonly experience comorbid psychiatric disorders, including depression (57%), generalized anxiety (27%), simple phobia (19%), alcohol misuse (19%), obsessive-compulsive disorder (13%), social anxiety (11%), and eating disorders (11%) [4, 8–15]. Some may ingest pulled hair, leading to serious complications like trichobezoars or intestinal blockage [12].

Treatment remains difficult, with behavioral therapy, nutritional adjustments, and medications showing only limited success [8, 9, 16–21]. Clinical research in humans is hindered by large genetic and environmental variability, long lifespans, and relatively few diagnosed participants. Therefore, establishing animal models that accurately replicate the human form of TTM provides a way to minimize such confounding factors, allowing deeper insights into disease mechanisms and treatment strategies.

Animals also display analogous behaviors: feather-picking in birds [22–31], psychogenic alopecia in cats [32–36] and primates [37–39], acral lick dermatitis in dogs [35, 40–42], tail and ear biting in pigs [43–45], and flank biting in horses [46–48].

The inbred C57BL/6J mouse frequently presents with “barbering” (self-induced hair loss) and idiopathic necrotizing dermatitis, conditions that worsen under stress [49–53]. Historically, such hair loss was attributed to social dominance stress [51, 54], but newer evidence classifies it as a stereotypic, sometimes self-directed, behavior [50–53]. Consequently, the C57BL/6J strain has been proposed as a TTM and dermatotillomania model [50]. Researchers demonstrated that hair loss and lesion development could be predicted through a short behavioral test conducted before symptoms appeared. Specifically, after spraying the mice with water and observing grooming for 15 minutes, higher proportions of scratching time predicted increased risk of future lesions, with an odds ratio of 1.20 [50]. This inbred mouse model has already been utilized to study dietary effects on TTM-like behaviors [50].

At Indiana University’s breeding facility for alcohol-preferring “P” rats, similar patterns of hair loss and ulcerative dermatitis were observed. Symptoms varied, with alopecia affecting regions such as the ventrum, neck, axilla, and groin **(Figure 1a)**, while dermatitis typically appeared around the neck and ears **(Figure 1b)**. Because this rat line is not inbred [55, 56], it offers greater genetic heterogeneity, thus resembling human populations more closely. While tightly controlled inbred models have long aided human disease research, growing evidence indicates that such uniformity may limit applicability to human outcomes [57–59]. For example, vaccine development studies have shown that dependence on inbred mouse strains may misrepresent vaccine effectiveness in genetically diverse humans [60]. Consequently, outbred animal models with broader genetic backgrounds could prove invaluable for advancing translational research on human disorders.



a) b)

Figure 1. Clinical examples showing (a) coat thinning and (b) skin inflammation in P rats. The most pronounced hair loss occurs in the groin area (boxed), continuing along the hind legs, while the entire ventral surface appears sparsely covered (a). Lesions associated with dermatitis typically form around the neck and head (b)

Both C57BL/6J mice and P rats are widely employed as preclinical models in addiction research [61–66]. These strains also tend to exhibit higher anxiety- and depression-like behaviors compared with other laboratory rodents [56]. Because such traits frequently co-occur with trichotillomania (TTM) in humans, their behavioral overlap reinforces their value as translational models for this disorder.

This investigation applied a spray-stimulation test followed by detailed observation of grooming activity to assess whether specific grooming behaviors could forecast later hair loss or lesion formation in P rats, helping determine their suitability as a potential TTM model.

Materials and Methods

Ethical statement

All experimental actions were conducted under the authorization of the Institutional Animal Care and Use Committee (IACUC) of the Indiana University School of Medicine. The animal care program holds AAALAC International accreditation and fully adheres to institutional and federal animal welfare standards.

Animals

The animals utilized were alcohol-preferring (P) rats, developed through selective breeding from a Wistar rat colony at Walter Reed Army Hospital, in contrast to the non-preferring (NP) line [66]. These colonies were later relocated to Indiana University School of Medicine, where maintenance is performed by the Indiana Alcohol Research Center in Indianapolis, USA.

The P phenotype was defined by two criteria:

1. A preference ratio of at least 2:1 for a 10% ethanol solution over water.
2. Daily consumption exceeding 5 g of ethanol per kilogram of body weight [55, 65, 66].

To put this into perspective, this level equals roughly a 70 kg person drinking one-fifth of 90-proof whiskey each day. Alcohol-naïve P and NP rats metabolize ethanol similarly [67]; however, after 6–8 weeks of voluntary intake, P rats show metabolic and functional tolerance to both the aversive and motor-impairing actions of ethanol [68]. They also display withdrawal [69] and relapse-type drinking behavior, termed the alcohol deprivation effect (ADE)—a brief but marked increase in alcohol consumption following abstinence [70].

Relative to NP rats, the P strain shows reduced sensitivity to alcohol's ataxic [71] and hypothermic [72] impacts, and acquires tolerance more rapidly to ataxic [71] and hypnotic [73] effects. During chronic intake or self-administration procedures, P rats reach blood alcohol concentrations (BACs) between 80 and 250 mg%, comparable to values seen in human alcoholism [74, 75]. Together, these findings classify the P rat as a well-established model for studying alcohol dependence [55, 56, 58, 66].

A total of 112 female rats were included in the current study. Power analysis for multiple regression ($\alpha = 0.001$, one predictor, $\rho^2 = 0.1$) suggested approximately 200 rats (100 pairs) would be needed to achieve a power of 0.9183, assuming a low alpha for maximum sensitivity due to the unknown true incidence within the colony. To reduce animal use, the population was divided into two cohorts (~100 rats each), with the second cohort reserved for replication only if the first yielded inconclusive results, which was ultimately unnecessary.

At the beginning of the study, animals averaged six weeks old (range: 4–8 weeks), were bred in-house from P-line parents, and housed with same-sex littermates. Only females were assessed due to the higher rate of this disorder among female subjects in humans.

Rats were maintained in IU facilities under standardized conditions. They were allowed free access to water and Teklad Diet 7001 feed (Envigo, Indianapolis, IN, USA). Ambient temperature and humidity were kept at 21.7 ± 1 °C and 55 ± 5%, with a 12-hour light/12-hour dark cycle (lights on at 07:00). Animals were kept in pairs or trios inside individually ventilated cages (Lab Products, Seaford, DE, USA), built from clear polycarbonate and fitted with filter lids. Bedding consisted of aspen chips (Sani-Chip, PJ Murphy Forest Products, Montville, NH, USA), and each cage was provided with paper towel nesting material.

Health screening was carried out quarterly using indirect sentinel monitoring. At the study's time point, the colony was negative for sialodacryoadenitis virus, parvoviruses (NS1, rat pneumonia virus, Kilham rat virus, H1 virus, rat minute virus), theliovirus, Clostridium piliforme, Mycoplasma pulmonis, pinworms (*Aspicularis tetraptera*, *Syphacia* spp.), and fur mites (*Radfordia ensifer*, *Ornithonyssus bacoti*).

Assessment

Evaluation of grooming patterns was carried out using a modified spray stimulation method as outlined previously [50]. In brief, each rat was transferred from its home cage into a transparent Plexiglass container. After a quiet acclimation period of no less than 5 minutes, the animal's head and shoulders were misted once with water—enough to lightly moisten the fur. Behavior following this exposure was video recorded for 15 minutes, and the test was conducted a single time for each subject. Recordings were later reviewed by one investigator (AP), who measured the percentage of total time the rat spent performing three specific grooming actions within the 15-minute interval **(Table 1)**. Every initiation of each grooming movement was logged continuously throughout the

playback, and its relative frequency was obtained by dividing the total number of initiations by the 15-minute period. All behavioral trials occurred between 1200 and 1700 hours, and the entire data set was collected during a 3-month window. To differentiate animals within shared cages, one tail mark was applied to the second rat ("B"), and two to the third ("C"), using a permanent marker; the first rat ("A") remained unmarked.

Table 1. Grooming categories evaluated.

Grooming Type	Description
Manual Grooming (MG)	The animal cleans its muzzle, face, and head region using its forepaws.
Oral Grooming (OG)	The animal licks its body to groom, typically starting at the upper neck and back, then progressing caudally to the lower body and tail.
Scratching (SCR)	The animal rapidly scratches its head, neck, and back using its hindlimbs; movements are brief and high-speed.

Colony cages were checked by research personnel every two weeks for hair loss and dermatologic lesions, while animal care staff performed daily observations. Tail identifiers were renewed as required. Any rat exhibiting severe dermatitis—defined as a single ulcerated or open wound larger than 2 cm—was euthanized before the planned endpoint. Likewise, individuals with a body condition score ≤ 2 [76] were also euthanized humanely. Because the purpose of the study was to track dermatitis development, no therapeutic treatment was provided; exemption for this was granted prior to the experiment. At roughly 8 months of age, euthanasia was performed via carbon dioxide inhalation, and all bodies were photographed to record lesion status, whether euthanized earlier or at study completion.

Statistical analysis

Relative frequencies of the three grooming behaviors were determined as above. Normality of distributions was tested with the Anderson–Darling method. When data conformed to normality, a one-way ANOVA was used; otherwise, analysis was done using the Kruskal–Wallis test.

Possible confounding from the tail-marking procedure was checked with a chi-square test comparing the presence of lesions between marked and unmarked animals.

For odds-ratio computations, oral and manual grooming values were dichotomized as above or below 50% of the total observation period. Since no rat spent more than 33% of time scratching, this variable was classified as either zero or > 0. Lesion status was incorporated in every odds-ratio estimation. The ratio was first determined by dividing the number of lesioned rats performing the defined level of the behavior by those with lesions who did not; this quotient was then divided by the corresponding value for non-lesioned rats.

Results and Discussion

Two animals were removed from analysis due to incomplete video recordings. Among the 110 remaining subjects, 19 showed evidence of dermatitis (19/110; 17.27%). Numbers of affected animals and their behavioral frequencies are summarized in **Table 2**. There was no significant connection between sharpie marking and lesion occurrence ($\chi^2 = 0.718$; $p = 0.3967$).

Table 2. Frequency of grooming types and incidence of lesions; data used for odds-ratio computation.

Behavior	Number of Animals with Lesions	Number of Animals without Lesions
MG relative frequency < 0.50	11	46
MG relative frequency > 0.50	7	46
OG relative frequency < 0.50	8	51
OG relative frequency > 0.50	10	41
SCR relative frequency = 0	3	6
SCR relative frequency > 0	15	86

Manual grooming and scratching data were non-normally distributed, whereas oral grooming met the normality criteria. Statistical comparisons revealed no significant variation in manual grooming ($p = 0.7147$) or scratching ($p = 0.1324$) between lesioned and lesion-free rats by the Kruskal–Wallis test. However, oral grooming frequency was significantly greater in rats that developed lesions ($p = 0.0448$) based on one-way ANOVA. Summary statistics are shown in **Table 3**.

Table 3. Mean ± SD of relative grooming frequencies for rats with versus without lesions.

Behavior	Animals with Lesions	Animals without Lesions
Manual grooming (MG)	0.51 ± 0.24	0.51 ± 0.19
Oral grooming (OG)	0.60 ± 0.27	0.47 ± 0.23
Scratching (SCR)	0.04 ± 0.10	0.01 ± 0.03

The proportion of time spent scratching predicted the later appearance of dermatitis in females, with an odds ratio of 2.87 (95% CI: 0.65–12.73). Considering oral grooming exceeding 50% of total time as a predictor, the odds ratio was 1.55 (95% CI: 0.56–4.3). Using the same threshold for manual grooming yielded an odds ratio of 0.64 (95% CI: 0.23–1.79).

This investigation proposed that analyzing grooming responses after performing the spray test could forecast which animals would later develop dermatitis. Findings revealed that the relative duration of oral grooming was a reliable indicator of subsequent dermatitis, indicating that this behavioral test could serve as a useful early screening method. Although the proportion of time spent scratching did not differ significantly between affected and unaffected rats, its high odds ratio implies that this action may still strongly correlate with the eventual appearance of skin lesions. Interestingly, the rate of dermatitis within this group was comparable to previously documented frequencies among C57BL/6J mouse colonies [77–79].

The occurrence of lesions among P rats in the present study (approximately 17%) exceeded reported rates in humans (up to 3%) [2]. However, it is widely believed that human prevalence is underestimated, since many individuals conceal symptoms to avoid stigma or ridicule [4, 8–15]. Given that the P strain has been selectively bred for a predisposition toward addictive behaviors [65, 66], its heightened susceptibility could partially account for the elevated rate of dermatitis observed. Nonetheless, an incidence approaching 20% suggests valuable opportunities for further research on behavioral and biological vulnerabilities.

Traditionally, animal studies addressing hair loss and dermatitis have concentrated on testing therapeutic approaches for already-affected subjects. While such studies are valuable, identifying individuals at risk and preventing disease onset would be even more beneficial. The spray test has previously been applied in C57BL/6J mice to detect predisposition and evaluate preventive dietary interventions [50]. Yet, as this mouse strain is genetically uniform, its results may not readily translate to genetically diverse populations like humans. In contrast, the selectively bred P rat line, which retains broader genetic variability, offers a model more reflective of human heterogeneity, thus improving the translational potential of prevention and treatment research.

For instance, prior work from our laboratory demonstrated that trimming nails improved outcomes in P rats suffering from ulcerative dermatitis [80]. However, because participation required naturally occurring dermatitis, the project extended over five years owing to the relatively low spontaneous incidence. The ability to prospectively identify young rats with behavioral indicators of risk would make case–control studies feasible, enabling direct comparisons of potential therapeutic strategies among behaviorally matched individuals.

Future applications of this model include evaluating preventive or therapeutic interventions—such as dietary modification previously proposed in mice [50]—for reducing dermatitis in predisposed animals. Furthermore, investigation of genetic and epigenetic mechanisms may clarify neurochemical or neurophysiological traits distinguishing animals that do or do not exhibit TTM-like behavior. Notably, P rats show several neurochemical distinctions from their non-preferring (NP) counterparts, including altered levels of serotonin and dopamine and differences in receptor and transporter function within meso-corticolimbic circuits [55, 65]. It is well established that disruptions in serotonergic signaling are implicated in disorders such as alcohol dependence, obsessive–compulsive disorder, and depression [81, 82].

Conclusion

Overall, these findings indicate that, akin to the C57BL/6J mouse, the selectively bred P rat may serve as a robust animal model for testing treatments and preventive measures targeting trichotillomania (TTM)-related behaviors. Beyond exhibiting clinical manifestations and grooming characteristics parallel to those reported in women with TTM, the spray test's ability to identify rats showing elevated oral grooming and scratching may facilitate early detection of at-risk individuals. Such identification could enable the design of preventive or early intervention studies. Continued assessment of behavioral and physiological variables will be crucial to establishing the broader relevance of this model for developing strategies to prevent or manage TTM and related body-focused repetitive disorders.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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