Comparative Medicine
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Vol 64, No 2
April 2014
Pages 135–139

Original Research

Craniofacial Trauma as a Clinical Marker of Seizures in a Baboon Colony

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Baboons provide a natural model of epilepsy. However, spontaneous seizures are usually sporadic, brief, and may not be observed. We hypothesized that various types of craniofacial trauma (CFT) may serve as reliable markers for epilepsy. We evaluated the type, demographics, and clinical significance of CFT in a large baboon colony. CFT was categorized according to somatotopic location, propensity to recur, and association with witnessed seizures or abnormal EEG findings. We divided the baboons with CFT into 2 groups: those with known histories of seizures (CFT+Sz, $n = 176$) and those without seizure histories (CFTonly; $n = 515$). In CFT+Sz baboons, the 568 injuries identified included periorbital (57%), scalp (27%), muzzle (12%), and facial (4%) injuries; multiple somatotopic locations or body parts were affected in 21 baboons. The most common CFT injuries associated with seizures were periorbital and scalp lesions (43% for each region). Compared with those in CFTonly animals, EEG abnormalities, including interictal epileptic discharges (IED) and photosensitivity were more prevalent in the CFT+Sz group, particularly among baboons with periorbital or scalp injuries. Compared with CFT+Sz animals, CFTonly baboons tended to have later onset and less frequent recurrence of CFT but higher prevalence of muzzle and tooth injuries. IED and photosensitivity were less prevalent in the CFTonly than the CFT+Sz group, with periorbital injuries carrying the highest and muzzle injuries the lowest association with IED or photosensitivity in both groups. Therefore, CFT in general and periorbital injuries in particular may be markers for seizures in baboons.

Abbreviations: CFT, craniofacial trauma; IED, interictal epileptic discharge; Sz, known history of seizure.

Trauma is a common manifestation of seizures in humans.[7] The prevalence of seizure-related injuries varies among studies, depending on the clinical setting. In one large epidemiologic study, seizure-related injuries occurred in 35% of people with epilepsy who had at least one seizure every year.[3] Seizure-related head injuries were most common (24%), followed by burns (16%), dental injuries (10%), and bone fractures (6%).[3] A more recent study at a tertiary referral center demonstrated seizure-related injuries in 54% of patients, 72% of which were head injuries.[4] Most studies show a strong association of injuries with falls, particularly in the setting of generalized tonic–clonic seizures.[4,8,12] Tongue-biting is commonly associated with generalized tonic–clonic seizures and provides another important clinical indicator of seizure occurrence and severity.[2]

Baboons are a natural model for photosensitive, generalized epilepsy.[6] Although baboons may have seizures related to acquired brain injuries (for example, infections or trauma), most baboons with chronic epilepsy have an inherited form of the disease.[6,10] Baboons have generalized myoclonic or tonic–clonic seizures that tend to occur in the morning.[9] This form of epilepsy similar to a genetically influenced epilepsy that occurs in humans, namely juvenile myoclonic epilepsy.[10]

Received: 05 Jul 2013. Revision requested: 23 Aug 2013. Accepted: 29 Sep 2013.
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Traumatic injuries have been associated with seizures in baboons housed at our institution. Although the prevalence of unprovoked, witnessed seizures in this pedigreed colony was 26%, 57% of baboons with witnessed seizures also had craniofacial trauma (CFT), with CFT frequently occurring as the presenting symptom of chronic epilepsy.[9] Similar to those in humans, seizure-related injuries in baboons tend to affect the head or face because they tend to fall from perches or other elevations in their cages during seizures. Because the colony baboons are not under constant observation, CFT and residual scarring may be the only evidence of seizures for some animals. Seizure presentation and injuries demonstrate various age- and sex-related differences.[9,10] In our colony, injuries affecting the genitals, extremities, or tails generally are due to fighting among male baboons.

The current study was designed to evaluate the clinical association of CFT with seizures. We did this by correlating incidents of CFT with their somatotopic distribution, association with observed seizure activity, and history of seizures and abnormal EEG findings. If CFT affecting particular somatotopic areas are closely associated with seizures or the propensity for epilepsy, veterinarians may be able to identify epileptic animals more promptly. Our ultimate goal was to determine whether certain types of CFT can be used as surrogate markers for seizures or epilepsy for use in both epidemiologic and genetic studies.

Materials and Methods

A retrospective case-detection survey of veterinary records was performed to evaluate the incidence and prevalence of witnessed and suspected seizures in a pedigreed baboon colony housed at the Southwest National Primate Research Center located at the Texas Biomedical Research Institute (Texas Biomed) in San Antonio, TX. Electronic records created between 1980 and 2007 were reviewed (KDK). All baboons were treated in strict accordance with the *Animal Welfare Act* and the *Guide for the Care and Use of Laboratory Animals* and other applicable guidelines and laws.[1,5] This study was approved by the IACUC of the Research Institute at San Antonio and Texas Biomed.

Electronic records were available for 1528 baboons (740 living, 788 dead; 872 female, 586 male; 841 animals who were classified as olive baboons [*Papio hamadryas Anubis*] and 367 animals who were hybrids [that is, traced genetic ancestry to both *Papio hamadryas anubis* and *Papio hamadryas cynocephalus* subspecies]). Electronic records included information about subspecies type, sex, parentage, date of birth, health check data, and medical interventions. The records were screened for craniofacial injuries, particularly brow, scalp, facial or muzzle lacerations, as well as for references to witnessed seizures, whether spontaneous or provoked by ketamine or handling. Ages were rounded to the nearest year or, in baboons 2 y of age or younger, to the nearest half-year. Scalp EEG studies were performed in 671 pedigreed baboons, including 49 CFT+Sz and 100 CFTonly baboons included in this study. The methodology used for the scalp EEGs is described elsewhere.[11]

The prevalence, distribution, and frequency of CFT were compared (χ^2 and Fisher Exact tests, www.vassarstats.net) between baboons with a history of epileptic seizures and craniofacial trauma (CFT+Sz) and those with CFT only (CFTonly). We compared the onset and location of trauma between groups and considered various effects of subspecies, age, sex, and EEG findings, including the prevalence of interictal epileptic discharges (IED) and photosensitivity.

Results

The records of 1098 baboons described a total of 3389 events. Of these, 1537 (45%) were witnessed seizures, 1267 (82%) of which were unprovoked, 212 (14%) of which were associated with ketamine administration for sedation or anesthesia, and 58 (4%) of which were associated with handling. The remaining 1852 events (55%) consisted of traumatic injuries and peri- or postictal behaviors such as transient unresponsiveness, confusion, and lethargy.

CFT was documented in 1455 of 1852 (79%) encounters, affecting a total of 691 animals. CFT included periorbital injuries (brow or eyelid laceration, bruising or swelling as shown in Figure 1), scalp injuries (that is, lacerations or bruising of the forehead, top of the head, or back of the head), injuries affecting the muzzle (that is, tongue or nose bleeding, laceration of the lip or chin, fractured mandibles, broken or loose teeth), facial injuries (facial lacerations or maxillary fractures), and ear lacerations.

We identified 176 (78 female, 98 male; 107 olive baboons, 47 olive×yellow hybrid baboons, and 22 baboons belonging to other subspecies) CFT+Sz baboons that had a combination of epileptic seizures and CFT (Table 1). Data on age of onset, sex, and subspecies classification were available for all of the CFT+Sz baboons, which had a total of 981 witnessed seizures that were spontaneous, provoked by handling or ketamine, or recognized by postictal behavior. The number of reported seizures (mean ± 1 SD) was 5 ±7 seizures (range, 1 to 41; mode, 1). There were 568 reported instances of CFT with a mean number of 3 ± 3 (range, 1 to 16; mode, 1) injuries. Of these, 323 (57%) were periorbital CFT in 140 baboons, 151 (27%) injuries affected the scalp (more often the forehead than the top of the head) in 74 baboons, 24 (4%) affected the face in 17 baboons, and 70 (12%) affected the muzzle or teeth in 44 baboons (Table 2). Brow or scalp lacerations tended to be repetitive, each occurring at a mean frequency of 2 ± 2 per baboon. In addition, 21 baboons presented with a combination of periorbital, scalp, facial or muzzle injuries, and, in a few instances, skull (n = 2), hand, or long bone (n = 3) fractures.

Figure 1. An acute brow laceration after a seizure-related fall in a sedated adult baboon.

In the CFT+Sz group, there were no significant sex-associated differences in recurrence rate or somatotopic location of CFT (Table 1). The age at first seizure (excluding ketamine-induced seizures) and first CFT was 6 ± 5 y old. The first evidence of CFT preceded the first witnessed seizure by more than 6 mo in 76 cases, occurred within 6 mo of the witnessed seizure in another 57 baboons, and followed the first witnessed seizure by more than 6 mo in 42 baboons. The proportion of trauma was relatively stable in all age groups, but recurrence rates were higher in adult (178 CFT in 44 animals) than in adolescent (194 CFT in 58 animals) or preadolescent (196 CFT in 74 animals) baboons (Table 2). The proportion of periorbital trauma remained consistent among preadolescent, adolescent, and adult groups, defined by the age of the first CFT, with an increase of scalp injuries (χ^2 = 7.78, df = 1, P < 0.01) and a decrease of muzzle injuries (χ^2 = 13.20, df = 1, P < 0.001) during adolescence compared with other age groups.

Fifty-seven baboons had 107 craniofacial injuries documented in association with witnessed seizures. Of these, 46 injuries were periorbital or affected the scalp (43% for each location), with only 2 facial and 13 muzzle or tooth injuries associated with seizure activity. There were 51 EEG studies available from 49 baboons with 124 reported injuries. Scalp EEG demonstrated IED in 35 (71%) and photosensitivity in 19 (39%) baboons (Table 1). Of the 39 baboons with 93 periorbital injuries, 30 (68%) had IED, and 28 (41%) were photosensitive (Table 2). Of the 15 baboons with 21 scalp injuries, 11 (65%) had IED, and 6 (35%) were photosensitive. In the 7 baboons with 9 muzzle or tooth injuries, only 2 (29%) had IED, and 1 (14%) was photosensitive. The baboons with muzzle injuries had a significantly lower prevalence of IED (2-tailed Fischer Exact, P < 0.0001) and photosensitivity (2-tailed Fischer Exact, P < 0.0001) than did baboons with periorbital or scalp injuries.

A total of 515 baboons without histories of witnessed or suspected seizures (CFTonly; 265 female, 211 male; 270 olive baboons, 155 olive×yellow hybrid baboons, and 90 baboons belonging to

Table 1. Electroclinical and demographic comparison of CFT groups

	Age (y) at first CFT	No. of CFT events (mean ± SEM, mode)	Male (no. [%])	Female (no. [%])	PHA (no. [%])	PHX (no. [%])	IED (no. affected/ total no. [%]	PS (no. affected/ total no. [%]
CFT+Sz (*n* = 176)	6 ± 5	568[a] (3 ± 3, 1)	98 (55)[b]	78 (46)	107 (61)	47 (26)	35/49 (71)[c]	19/49 (39)[d]
CFT/only (*n* = 515)	7 ± 5	848[a] (2 ± 1, 1)	211 (41)[b]	265 (51)	270 (65)	155 (30)	42/100 (42)[c]	18/100 (18)[d]
Single CFT (*n* = 328)	7 ± 5	NA	120 (37)[e]	184 (56)	172 (52)	98 (29)	21/55 (38)	9/55 (16)
Multiple CFT (*n* = 177)	7 ± 5	NA	91 (51)[e]	79 (40)	98 (55)	56 (32)	19/45 (42)	9/45 (20)

PHA, *Papio h. anubis* (olive baboons); PHX, P*apio h. anubis* × *cynocephalus* crosses (hybrid baboons); PS, photosensitivity, NA, not applicable.
Significant difference ($P_{CFT+Sz} - P_{CFTonly}$ = 0.30, z = –11.0) in the [a]number of lifetime CFT; prevalence of [b]male baboons, [c]IED, and [d]PS; and [e]association of male sex with multiple lifetime CFT ($P < 0.05$, chi-square, 2-tailed).

Table 2. Somatotopic location of CFT and electroclinical features in baboons with known seizure history (CFT+Sz group)

		No. (%) of events per somatotopic location			
		Periorbital	Scalp	Face	Muzzle
No. of trauma events (515 in 176 baboons)		323 (57)	151 (27)	24 (4)	70 (12)
Sex (*n* = 176)	Male (*n* = 98)	177 (55)	85 (26)	16 (5)	44 (14)
	Female (*n* = 78)	146 (59)	66 (27)	8 (3)	26 (11)
Age (*n* = 176)	≤ 3 y (*n* = 74)	109 (56)	52 (27)[a]	4 (2)	31 (16)[b]
	4–7 y (*n* = 58)	108 (56)	66 (34)[a]	10 (5)	10 (5)[b]
	≥ 8 y (*n* = 44)	106 (60)	33 (19)[a]	10 (6)	29 (16)[b]
Scalp EEG (*n* = 49)	IED	68%[c]	65%[c]	NA	29%[c]
	PS	41%[c]	35%[c]	NA	14%[c]

NA, not applicable due to few cases.
[a,b]Significant ($P < 0.05$, chi-square, 2-tailed) [a]increase and [b]decrease in no. of muzzle injuries in adolescent compared with preadolescent and adult baboons.
[c]Significantly ($P < 0.05$, Fisher exact, 2-tailed) increased prevalences of IED and PS in baboons with periorbital and scalp compared with muzzle injuries.

other subspecies) were identified with 848 injuries (Table 1). Data on sex of the baboon was available for 486 animals (94%), on age of onset of CFT for 446 animals (86%), and on subspecies classification for 425 baboons (83%). The mean age at the first injury was 7 ± 5 (mode, 1) years, and the mean number of injures was 2 ± 1 (range, 1 to 11) per baboon. The frequency of multiple injuries did not differ significantly between male and female baboons nor between olive and hybrid baboons. Age at first injury did not differ between baboons with single compared with multiple injuries.

Periorbital injuries were found in 507 (57%) occurrences of CFT in 324 baboons, 207 (23%) scalp injuries were noted in 169 baboons, 30 (3%) facial injuries were noted in 20 baboons, and 143 (16%) injuries affecting the muzzle, including broken teeth or lip laceration or chin abrasions, were found in 96 baboons (Table 3) . Muzzle and tooth injuries were more common (χ^2 = 21.02, df = 1, $P < 0.0001$) among CFTonly male baboons than CFTonly female baboons and were increased (χ^2 = 11.38, df = 1, $P < 0.001$) in CFTonly male baboons compared with CFT+Sz male baboons. The proportion of CFT remained similar over all age periods, as were the recurrence rates in adult (256 CFT in 165 animals), adolescent (235 CFT in 140 animals), and preadolescent (237 CFT in 141 animals) baboons. According to somatotopic distribution, preadolescent baboons had a higher prevalence of scalp injuries (χ^2 = 21.46, df = 1, $P < 0.0001$) and a lower prevalence of periorbital injuries (χ^2 = 13.82, df = 1, $P = 0.0002$) than did adult and adolescent baboons.

EEG studies were available for 100 CFTonly baboons with a total of 120 injuries (Table 1). The prevalences of IED (χ^2 = 10.26, df = 1, $P < 0.002$) and photosensitivity (χ^2 = 6.53, df = 1, $P = 0.0106$) were significantly decreased compared with that of the CFT+Sz group. The prevalences of IED and photosensitivity were similar between baboons with single compared with multiple injuries. IED were identified in 49% and photosensitivity in 19% of 63 baboons with periorbital injuries (Table 3). Scalp injuries were noted in 25 baboons, with prevalences of IED and photosensitivity in 32% and 24%, respectively. Injuries to the muzzle and teeth were noted in 23 baboons, with prevalences of IED and photosensitivity in 26% and 22%, respectively. The prevalences of IED (χ2 = 4.4, df = 1, $P < 0.02$) and photosensitivity (χ^2 = 7.7, df = 1, $P < 0.003$) were significantly decreased among animals with periorbital injuries in the CFTonly group compared with the CFT+Sz group but not for scalp or muzzle injuries.

Discussion

This study is the first to address the relationship between CFT and seizures in a nonhuman primate model of epilepsy. We found that CFT is common in a pedigreed colony of baboons maintained at our facility, particularly among baboons with witnessed seizures (that is, the CFT+Sz group). CFT tends to occur at an earlier age and recur more often in known epileptic baboons than in baboons without a history of epilepsy (the CFTonly group). Acutely witnessed seizures are associated predominantly with periorbital or scalp lacerations and less frequently with those affecting the muzzle or associated with broken teeth. The prevalences of IED and photosensitivity were higher in the CFT+Sz group than in the CFTonly group, and in both groups the prevalence of EEG abnormalities was highest in the baboons with periorbital injuries and lowest in those with muzzle or tooth injuries.

CFT also occurs in humans who have epilepsy. Similar to the baboon experience, human falls usually lead to soft tissue injuries affecting the head and face, whereas tooth avulsions or jaw fractures are less frequent.[3] Although most studies do not describe the somatotopic distributions of craniofacial injuries, we would expect to see forehead, brow, and facial injuries similar to those

Table 3. Somatotopic locations of CFT and electroclinical features of asymptomatic baboons (CFTonly group)

		No. (%) of events per somatotopic location			
		Periorbital	Scalp	Face	Muzzle
No. of trauma events (848 in 515 baboons)		507 (57)	207 (23)	30 (3)	143 (16)
Sex (n = 471)	Male (n = 209)	183 (49)	84 (22)	17 (5)	90 (24)[c]
	Female (n = 262)	258 (65)	87 (22)	9 (2)	45 (11)[c]
Age (n = 446)	≤ 3 y (n = 141)	111 (47)[a]	81 (34)[b]	7 (3)	38 (16)
	4–7 y (n = 140)	135 (57)[a]	49 (21)[b]	12 (5)	39 (17)
	≥ 8 y (n = 165)	168 (65)[a]	41 (16)[b]	4 (2)	43 (17)
EEG abnormalities (n = 100)	IED	49%[d]	37%[d]	not applicable	25%[d]
	Photosensitivity	19%	16%	not applicable	13%

[a]Statistically significant (P < 0.05; chi-squared, 2-tailed test) decrease in periorbital injuries in preadolescent compared with adolescent and adult baboons.
[b]Statistically significant (P < 0.05; chi-squared, 2-tailed test) increase in scalp injuries in preadolescent compared with adolescent and adult baboons.
[c]Statistically significant (P < 0.05; chi-squared, 2-tailed test) increase in male compared with female baboons.
[d]Statistically significant (P < 0.05; chi-squared, 2-tailed test) increase in prevalence of IED and PS in baboons with periorbital compared with scalp or muzzle injuries.

found in baboons. Other common injuries in humans are not necessarily associated with falls (e.g., burns) and injuries due to muscle contractions, including jaw or shoulder dislocations and vertebral fractures.[2]

The most important observation stemming from witnessed seizures that result in CFT is that periorbital, scalp, facial, and muzzle or tooth injuries can all occur with seizures. Nonetheless, the association of periorbital and scalp injuries with seizures is greater than is that with facial or muzzle injuries. The most common CFT injuries in baboons known to have seizures include periorbital and scalp lacerations, although some baboons also had facial injuries, fractured maxillae or mandibles, muzzle wounds, or broken teeth. The large proportion of periorbital injuries is likely due to the baboon's prominent brow, which may even shield the forehead during most falls from elevations. Although several human studies describe head injuries associated with seizures,[3,4,8,12] only one assessed somatotopic differences of CFT injuries differentiating scalp and dental injuries,[3] and none have compared scalp and periorbital injuries. Although CFT did not occur in all baboons with seizures, CFT events were more likely to recur in CFT+Sz than CFTonly baboons. It is unclear whether the recurrence reflects increased seizure frequency or severity, but the similar onset of CFT and seizure activity (with CFT frequently preceding the first seizures) suggests that CFT can serve as a marker for seizure activity. Monitoring CFT in baboons can provide important information regarding the age of onset of epilepsy and yield improved estimates of the number of lifetime seizures. The relative stability of CFT, particularly periorbital trauma, across all ages in epileptic baboons suggests an endogenous (that is, seizure-related) cause rather than exogenous or environmental (for example, fighting) etiology. Although the rate of recurrence of CFT was highest in adult baboons, this is likely due to the prolonged timespan of adulthood as well as the relatively more benign prognosis of adult-onset epilepsy. Furthermore, CFT related to seizures was associated with scalp EEG abnormalities, such as IED and photosensitivity. The closer association between periorbital trauma or scalp injuries and seizures than between muzzle or tooth injuries and seizures was supported by the EEG findings. Therefore, baboons with CFT, particularly periorbital or scalp injuries, need to be followed closely for the appearance of seizures. These animals possibly should be screened by scalp EEG to generate important diagnostic and prognostic information. Such screening could help distinguish between the presence of acquired partial epilepsy and an inherited generalized epilepsy. Accurate diagnostic information will assist the veterinarian in making appropriate treatment and breeding decisions.

Although CFT was common in the CFT+Sz group and had a similar age of onset as that in CFTonly animals, there are important differences in somatopic, sex, and age distribution between the 2 groups of animals. The somatopic distribution favors the muzzle and scalp injuries as compared with a periorbital distribution in CFTonly animals. Some baboons had ear or scalp lacerations that affected the back of the head, and these lesions were not encountered in the CFT+Sz baboons. Male baboons were less prevalent than were female among the CFTonly baboons yet were more likely to have multiple injuries than were female baboons. This difference may reflect a sex-associated bias regarding the presentation of epilepsy, but an increased tendency toward combative behaviors in male baboons cannot be excluded.[9] The CFT recurrence rate is relatively low in adult baboons (relative to their prolonged adulthood), suggesting that adult baboons may be less likely to engage in combat. The increased proportion of periorbital injuries, however, seems to parallel the CFT+Sz baboons more closely, again supporting the notion that periorbital injuries reflect seizure activity. In addition, the age distribution of CFT reveals a higher proportion of scalp injuries in preadolescent CFTonly baboons, whereas muzzle injuries, particularly tooth injuries, are relatively more common in adult baboons. It is likely that scalp injuries are a common feature implicated during both fights and seizures, whereas older baboons are more likely to have tooth injuries because of weakening gums associated with aging.

Like those in CFT+Sz baboons, EEG abnormalities in CFTonly animals showed decreased affinity toward scalp and muzzle injuries. IED and photosensitivity are less prevalent in these groups, and resembled the prevalence of EEG findings in baboons without witnessed seizures.[10] Although the presence of IED or photosensitivity does not necessarily reflect severity of the epilepsy, both of these findings imply seizure susceptibility. Therefore, the EEG findings in the CFT+Sz groups support the inclusion of periorbital injuries and scalp injuries in estimates of seizures frequency. Overall, EEG findings in both CFT+Sz and CFTonly groups favor the inclusion of periorbital injuries into epidemiologic or genetic studies as estimates of seizure prevalence. In contrast, scalp injuries demonstrated an age-dependent presentation, which prompts the question of whether competition and combat play important etiologic roles at young ages. Furthermore, EEG findings were less supportive of a seizure-related etiology in the CFTonly group.

Our current study has several drawbacks. Not all of the baboons with seizure-induced CFT had inherited epilepsy. Some of the baboons may have had meningitis or head injuries leading to focal seizure activity due to a different natural history. Nonetheless, these baboons constituted only a small subset of the animals, most of which rapidly succumbed to the underlying illness. Obviously, not all CFT is a result of seizures, but fighting rarely leads to similar CFT injuries. In addition, injuries associated with seizures may occur during the postictal period when an animal is unable to defend itself against aggressors.

In conclusion, this study demonstrates that CFT injuries provide markers for seizure activity in baboons. Seizures can cause CFT injuries that affect large somatotopic distributions, mainly due to falls from elevations. In animals with a history of epilepsy or in which EEG has confirmed susceptibility to seizures, periorbital and scalp injuries are closely associated with seizures. This pattern is important, because periorbital and scalp injuries may be used as effective markers for seizure activity, both for the early recognition of and for the treatment of epilepsy. CFT in general, and periorbital injuries in particular, should be validated as phenotypes in wild baboon populations to further assess the value of CFT as a stable marker of epilepsy for future epidemiologic and genetic studies.

Acknowledgments

This study was supported by the National Institute of Neurologic Disorders and Stroke (1 R01 NS047755 to JTW), used resources that were supported by a Southwest National Primate Research Center grant (P51 RR013986) from the National Center for Research Resources, NIH, and which currently are supported by the Office of Research Infrastructure Programs (grant P51 OD011133), and was conducted in facilities constructed with support from Research Facilities Improvement Grants (C06 RR013556, C06 RR014578, and C06 RR015456). We are grateful to Dr Sarah Williams-Blangero for her careful review of the manuscript.

The authors declare they have no competing financial interests.

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