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SHORT REPORT

High and variable population prevalence of *HLA-B*56:02* in indigenous Australians and relation to phenytoin-associated drug reaction with eosinophilia and systemic symptoms

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Phenytoin drug reaction with eosinophilia and systemic symptoms (DRESS) in 3 Aboriginal Australians positive for *HLA-B*56:02* has been previously reported. We report the allele frequency of *HLA-B*56:02* in 2 South Australian populations, 1 Aboriginal (4.8%, 95% confidence interval 2.4–7.8%) and the other European (0%). We compared the frequency with publicly available information on *HLA-B*56:02* status in other Indigenous Australian (n = 4) and European Australian cohorts (n = 1). In the Indigenous Australian cohorts, *HLA-B*56:02* allele frequency ranged from 1.3 to 19%. We also describe an additional case of phenytoin DRESS (RegiSCAR DRESS score 7) in an Aboriginal Australian that was associated with *HLA-B*56:02* and with *CYP2C9*1/*3* genotype. In Aboriginal Australians, phenytoin DRESS appears distinctly linked to *HLA-B*56:02* with an allele carriage rate substantially higher than in Europeans, but also with considerable regional variation. Investigations of human leucocyte antigen and other contributing genes and severe adverse drug reactions in understudied non-European populations are required to optimize safe medication use and inform risk mitigation strategies.

KEYWORDS

drug reaction with eosinophilia and systemic symptoms, drug toxicity, human leucocyte antigen, indigenous Australians, phenytoin

1 | INTRODUCTION

Phenytoin has a narrow therapeutic index with common adverse effects including ataxia, nystagmus and agitation that occur predictably with high concentrations. Phenytoin is also associated with uncommon but severe adverse drug reactions (ADR) which appear unrelated to systemic concentrations and may have delayed onset. An example is severe cutaneous adverse reaction (SCAR), including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and drug hypersensitivity syndrome. Phenytoin SJS/TEN has been strongly linked to the *HLA-B*15:02* allele and less commonly to other human leucocyte antigen (HLA)-B alleles of the same B75 serotype (*HLA-B*15:21*, *B*15:11*, *B*15:08*)[1,2] originally reported in Han Chinese from Taiwan but subsequently confirmed in other Asian countries including

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Malaysia, China, Thailand and India, where its frequency can be >10%.[1] In Taiwan where screening for *HLA-B*15:02* is reimbursed, the use of carbamazepine and cases of carbamazepine-related SCAR have declined.[3] In Korean, Japanese and European populations, phenytoin-associated DRESS due to *HLA-B*15:02* is rare due to very low allele frequency (< 0.5%). In a Malay population,[4] a different HLA-B allele in the B75 serotype, *HLA-B*15:13* was associated with phenytoin SJS/TEN and DRESS. *HLA-B*15:13* frequency ranges from 5.5% in Burmese[5] to 13.3% in Javanese[6] subjects, hence showing a high frequency in Southeast Asian populations but not in Han Chinese or Thai populations where frequency is <2%.[6]

CYP2C9 is the major enzyme metabolizing phenytoin with a lesser contribution from CYP2C19.[1] The decreased function *CYP2C9*3* has a higher frequency in South Asian populations (11.3%) compared to Europeans (5.6%) and East Asians (3.4%),[7] and has also been linked to phenytoin associated SCAR in South Asian populations.[8-11]

*HLA-B*15:02* was not carried in 3 cases of phenytoin-associated DRESS reported in Aboriginal Australians in 2012.[12] Two of these were fatal and all carried *HLA-B*56:02*, with 1 being homozygous. *CYP2C9* was not assessed.

We report the allele frequency of *HLA-B*56:02* in 2 South Australian populations, 1 Aboriginal and the other European. We compare this with publicly available information on *HLA-B*56:02* status in other Indigenous Australian (n = 4) and European Australian (n = 1) cohorts. We also describe an additional case of phenytoin DRESS (RegiSCAR DRESS score 7) in an Aboriginal Australian associated with *HLA-B*56:02* and with *CYP2C9*1/*3* genotype, providing further evidence that phenytoin-associated DRESS in Aboriginal Australians is linked to *HLA-B*56:02* and not *B*15:02*.

What is already known about this subject

- Phenytoin hypersensitivity reactions including Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) in Europeans are rare but can be life threatening.
- An association has been found between phenytoin SJS/TEN and *HLA-B*15:02* but only in Southeast Asians.
- Phenytoin associated DRESS has been reported in Aboriginal Australians who carry *HLA-B*56:02*.
- An association has been described between slow metabolism of phenytoin (*CYP2C9*3*) for multiple phenotypes of phenytoin hypersensitivity including maculopapular exanthem >> DRESS >> SJS/TEN.

What this study adds

- *HLA-B*56:02* shows allele frequencies of 1.3–19% in different geographic Indigenous Australian cohorts compared with 0% in Europeans.
- We report an additional case of phenytoin DRESS in an Aboriginal Australian who carried *HLA-B*56:02*.
- There is considerable variability in the frequency of *HLA-B*56:02* within Australia's indigenous populations.
- HLA genotype associated with severe adverse drug reactions may be different in understudied non-European populations.

2 | METHODS

2.1 | HLA frequency in South Australian aboriginal and European populations

This was conducted to ascertain the HLA-B locus allele frequency in a cohort of Aboriginal Australians compared to Europeans living in Australia; we have used the group name European as recommended.[13] Ethics approval was from the Aboriginal Health Council of SA Inc. [Reference No. 04–14-592] and the University of Adelaide: Human Research Ethics Committee [Project No. H-117-2011]. Following informed and signed consent, both groups of participants provided information on age, sex, Aboriginal or European ancestry (parents/grandparents), presence of disease, smoking and alcohol (current/previous/never), residential location, and a saliva sample was collected (Oragene DNA Saliva Kit-DNA Genotek Inc. Canada) for genotyping.

2.2 | Population allele frequency database

A publicly available allele frequency database (http://www.allelefrequencies.net/) was searched to find data on *HLA-B*56:02*, *B*15:02* and *B*15:13* frequencies in different Indigenous Australian communities and Europeans living in Australia.[14]

2.3 | Case report

A 30 year-old Australian Aboriginal woman, of Western Aranda and Pintupi heritage (Figure 1), presented to hospital with hypotension, recent onset of fevers and 1 month of rash, after initially developing acute oedema of her face, arms and legs. Phenytoin had been commenced 7 months previously following multiple seizures, and she had recent influenza B 5 weeks prior to hospitalization, treated with benzylpenicillin and doxycycline. Height was 155 cm, weight 65 kg (body mass index 27.1 kg/m^2) and temperature up to 38.6°C. There was widespread (>50% extent) rash (pruritic, ichthyotic and scaling), which was very severe on the palms (Figure 2), feet and neck. Investigations revealed early severe eosinophilia of 1.22 × 10^9/L (reference: 0.04–0.4 × 10^9/L), acute kidney injury (serum creatinine 231 [reference: 50–100] µmol/L, creatinine clearance [Cockcroft–Gault formula] 32 ml/min) and hypoalbuminaemia of 22 (reference: 34–48) g/L. Gamma-glutamyl transferase was 478 U/L (reference: <60), alkaline phosphatase was also elevated at 717 U/L (reference: 30–110) with

FIGURE 1 Location of the sites (Cape York Peninsula, Groote Eylandt, Kimberley, Yuendumu) of the 4 indigenous Australian cohorts who had been previously tested for *HLA-B* status. Data obtained from http://allelefrequencies.net (HLA & Adverse Drug Reaction Section). West Aranda and Pintupi is the heritage of the subject in the clinical case of DRESS

minor elevation of transaminases (alanine 75 U/L [reference: <55], aspartate 53 U/L [reference: <45]); bilirubin was normal. Coeliac antibodies were negative, imaging showed mediastinal and inguinal lymphadenopathy up to 19 mm, and endoscopy demonstrated normal oesophagus, with minor erosive gastropathy and was positive for *Helicobacter pylori*. Multiple blood cultures were negative as were hepatitis B, C and human immunodeficiency virus, and other viral and infective conditions. Multiple autoimmune serologies were negative.

Medications at admission were phenytoin (300 mg daily) for 7 months, pantoprazole 40 mg orally for 11 weeks and prednisolone, reducing dose commenced at 20 mg daily 3 weeks prior to admission. Plasma phenytoin was 12 (reference: 40–80) μmol/L (albumin corrected phenytoin concentration using the Sheiner–Tozer equation[15] was 22 μmol/L). Clinical features were scored for DRESS using RegiSCAR criteria (Score 7),[16,17] and a clinical diagnosis was made of DRESS associated with phenytoin. Phenytoin was ceased and replaced with levetiracetam. Rechallenge was not done due to disease severity.

Following phenytoin cessation there was a slow resolution of rash over weeks to months (Figure 2). Minor flaking of skin persisted at 5 months; however, at 2 years the abnormalities of skin had resolved completely. Eosinophilia resolved over 5 months. The patient gave written informed consent for reporting the case including photographs, and for research blood taken for genotyping.

2.4 | Genotyping

For the South Australian Aboriginal and European populations and the Case Report patient, HLA-B locus was genotyped (Olerup SBT HLA-B Sequencing Based Typing kit [CareDX Pty Ltd, Fremantle, WA, Australia] with allele calling by Assign SBT v471 [CareDX Pty Ltd] using IMGT database 3.29.0.0 2017-07-10) at the South Australian Transplantation and Immunogenetics Service (Australian Red Cross Blood Service, Adelaide, SA, Australia). *CYP2C9 *2* (rs1799853) and **3* (rs1057910) were assayed using Sanger sequencing. Amplicons surrounding the rs1799853 and rs1057910 loci were amplified separately by polymerase chain reaction (rs1799853 primers: 5′-ATGG GGAGGATGGAAAACAGAGACTT-3′ and 5′-AGTAGAGAAGATAGTA GTCCAGTAAGGTCAGTGATATG-3′; or rs1057910 primers: 5′-CTCT TTAAGTTTGCATATACTTCCAGCAC-3′ and 5′-TGAGTTATGCACTT CTCTCACCCGG-3′; Sigma-Aldrich Pty Ltd, Castle Hill, NSW, Australia). Bidirectional sequencing (BigDye Terminator v3.1 using primers above) was conducted at the Australian Genome Research Facility (Melbourne, VIC, Australia).

2.5 | Statistics

Frequencies (and 95% confidence intervals [for allele $n > 3$]) of *HLA-B*56:02*, *B*15:02* and *B*15:13* alleles within the Indigenous Australian and Europeans cohorts were calculated.

FIGURE 2 Photo of subject's palms at time of DRESS diagnosis (top) and at 2 years and 4 months after phenytoin was ceased

3 | RESULTS

3.1 | HLA frequency in a South Australian aboriginal population

Of the 147 Aboriginal Australians, 33 were non-South Australian being mainly from the Northern Territory (NT) or Western Australia (WA; Figure 1). Median age was 30 (range: 18–67) years, and 69% were female. The European cohort comprised 158 participants residing in South Australia of median age 37 (18–78) years, and 63% were female. In the Aboriginal cohort, 13 individuals (9%) were positive for *HLA-B*56:02*, including 1 homozygous, with an overall *HLA-B*56:02* allele frequency of 4.8%. One of the 13 was from the Tanami Desert region containing Yuendumu (NT). For the European cohort, none (0%) were *HLA-B*56:02* positive (Table 1). For *B*15:02*, only 1 Aboriginal (overall allele frequency 0.3%) was positive compared to none in the European cohort, and no *B*15:13* alleles were detected in either population (Table 1).

3.2 | Population allele frequency database

Data on 4 separate cohorts of indigenous Australians who had been tested for *HLA-B* status were found (n = 41 [Kimberly region] to 191 [Yuendumu]; Figure 1). *HLA-B*56:02* allele frequency ranged from 1.3% (Kimberley) to 19% (Yuendumu; Table 1). For *B*15:02*, none were found in Yuendumu and 0.7% in Groote Eylandt. For *B*15:13*, none were found in Yuendumu, and it was not determined in other indigenous cohorts (Table 1). The database also included a European

TABLE 1 *HLA-B*56:02*, *-B*15:02* and *-B*15:13* allele frequencies in indigenous Australian compared to European cohorts living in Australia

Cohort	*N*	*B*56:02*, % [95% CI] (*n*)	*B*15:02*, % (*n*)	*B*15:13*, % (*n*)
Aboriginal (South Australia)	147	4.8 [2.4–7.2] (14)[a]	0.3 (1)	0 (0)
European (South Australia)	158	0 (0)	0 (0)	0 (0)
European (NSW)[b]	134	0.4 (1)	0 (0)	0 (0)
Aboriginal/Torres Strait Islander (Cape York Peninsula)[b]	103	3 [0.6–5.4] (6)	ND	ND
Aboriginal (Groote Eylandt)[b]	75	2.7 [0.1–5.2] (4)	0.7 (1)	ND
Aboriginal (Kimberly)[b]	41	1.3 (1)	ND	ND
Aboriginal (Yuendumu)[b]	191	19 [15–23] (73)	0 (0)	0 (0)

N = number of individuals; CI = confidence interval; *n* = number of alleles.

[a]includes 1 homozygous individual;

[b]data extracted from http://allelefrequencies.net. ND = not determined.

Note: Australia has 2 distinct indigenous populations, Aboriginals and Torres Strait Islanders.

population (*n* = 134) from New South Wales (Australia). The *B*56:02* allele frequency was 0.4% and was zero percent for *B*15:02* and *B*15:13*.

3.3 | Case report

The patient carried *HLA-B*56:02* and *CYP2C9*1/*3*.

4 | DISCUSSION

We provide further evidence that phenytoin DRESS in Aboriginal Australians is associated with *HLA-B*56:02* and that the carriage of this allele is prevalent, but also variable in different geographic indigenous Australian populations compared to Europeans. This supports previous findings of mitochondrial genome variation in Aboriginal Australians.[18]

In the case report, the diagnosis of DRESS was based on meeting at least 5 of 9 inclusion criteria for a potential case[16] and a validation RegiSCAR score of 7 (definite case) based on fever >38.5°C, lymphadenopathy >1 cm at 2 sites, eosinophilia, extensive rash, involvement of internal organs (liver) and exclusion of other disorders with multiple negative investigations.[16] The time course favoured DRESS with delayed onset after commencement of phenytoin and slow resolution after cessation. In 3 cases reported by Harding et al[12] the onset of symptoms was 2–3 weeks (2 patients) but about 3 months in the other case. In our patient, the onset of symptoms was somewhat atypical in that it occurred 7 months after phenytoin initiation. The presence of early severe eosinophilia was predictive of a severe reaction and systemic disease, although unfortunately formal diagnosis of phenytoin associated DRESS was delayed for some weeks.[19] The occurrence of this ADR was communicated to the patient, the primary care practitioner, other treating clinicians and reported to the hospital drug information service, and the national regulator. The patient was also *CYP2C9*1/*3*, indicative of slower phenytoin metabolism, which has been implicated in phenytoin SCAR in Southeast Asian populations.[8] The mechanism is unclear but Chung et al[8] found that those with SJS/TEN had delayed phenytoin clearance but not those with DRESS.

Phenytoin DRESS has been convincingly associated with *HLA-B*15:02* especially in South Asian populations but not in Europeans as the allele frequency is substantially higher with Asian ancestry.[1] Unlike the association of *HLA-B*15:02* and carbamazepine SJS/TEN in Southeast Asians where the negative predictive value is 100%, a substantial percentage of phenytoin SCAR would not be explained by *HLA-B*15:02* in Southeast Asians. Although the mechanism by which the variant causes this reaction is unknown, it is of interest that slow phenytoin metabolism (*CYP2C9*3* plays a significant role in risk for phenytoin SCAR) and other HLA-B alleles have been associated with phenytoin DRESS. Tassaneeyaku et al[20] identified several other HLA-B variants that were associated with phenytoin SJS/TEN (*13:01*, *38:02*, *51:01*, *56:02*) and DRESS (*51:01*) in Thai patients but when corrected for multiple comparisons, statistical significance was lost. Yampayon et al,[11] in another Thai population, identified that *56:02/04* was associated with phenytoin DRESS, which remained statistically significant after multiple comparison correction.

Our case report supports that of Harding et al[12] in which 2 of the 3 cases were fatal, of phenytoin DRESS in Aboriginal Australians and who were carriers (one was homozygous) for *HLA-B*56:02*. The population frequency of this variant is relatively high, ranging from 1.3 to 4% in Northern Australia, to 4.8% in South Australia to 19% in Central Australia (Yuendumu). The latter is the highest frequency reported for this allele in any location and the reasons for such are unknown, but a founder effect is probable. For most T-cell mediated drug reactions, it is suspected that the drug noncovalently binds to an immune receptor such as HLA and/or TCR in a dose-dependent fashion. It is also possible that the combination of carriage of *HLA-B*56:02* and a slower metabolizing *CYP2C9* genotype are important for the development of phenytoin SCAR (or DRESS) in this population.

The positive and negative predictive values of *HLA-B*56:02* in Indigenous Australian populations cannot be estimated; however, the clinical implications from this finding in Yuendumu have already been addressed. Alice Springs Hospital is the major acute hospital for Central Australia and has reported several cases of serious phenytoin ADRs, such that, since 2014, phenytoin has only been available in the pharmacy for intensive care unit use in status epilepticus. HLA-B

genotyping is not routinely available in clinical practice, but the link to *B*56:02*[12] and the high frequency of this allele in their patient catchment area led to this pragmatic decision (Tsai, Personal Communication). This decision had not been systematically relayed to prescribers in other parts of Australia, as the national warning system is limited. Although of central Australian heritage, our patient could not benefit from this local decision as she was residing outside central Australia at the time of initiation of phenytoin. Although *B*56:02* allele frequency is near zero in Europeans, it can be up to 5% in other Indigenous Australian populations (excluding those in Central Australia). It is incumbent on both national regulatory bodies and pharmaceutical companies to take action when life-threatening adverse drug reactions are affected by regional and not necessarily global pharmacogenetic factors.

The study illustrates the large global diversity in pharmacogenetic variation[13] and highlights the need to investigate life-threatening adverse drug events in understudied indigenous populations[21] including in Oceanians whose pharmacogenetic profile can be very different from Europeans.[22,23]

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

A.A.S.: study design, funding, conduct of experiments, data analyses and interpretation, preparation of manuscript. D.T.B.: study design, conduct of experiments, data analyses, review of manuscript. E.J.P.: data interpretation, review of manuscript. K.M.: case report documentation, review of manuscript. F.I.: case report documentation, patient clinical care, review of manuscript. G.M.B.: patient consent and clinical care, data interpretation, review of manuscript. All authors have approved the final manuscript and have agreed to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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