

Risk-taking: Behind the 'warrior' gene story

Tony Merriman

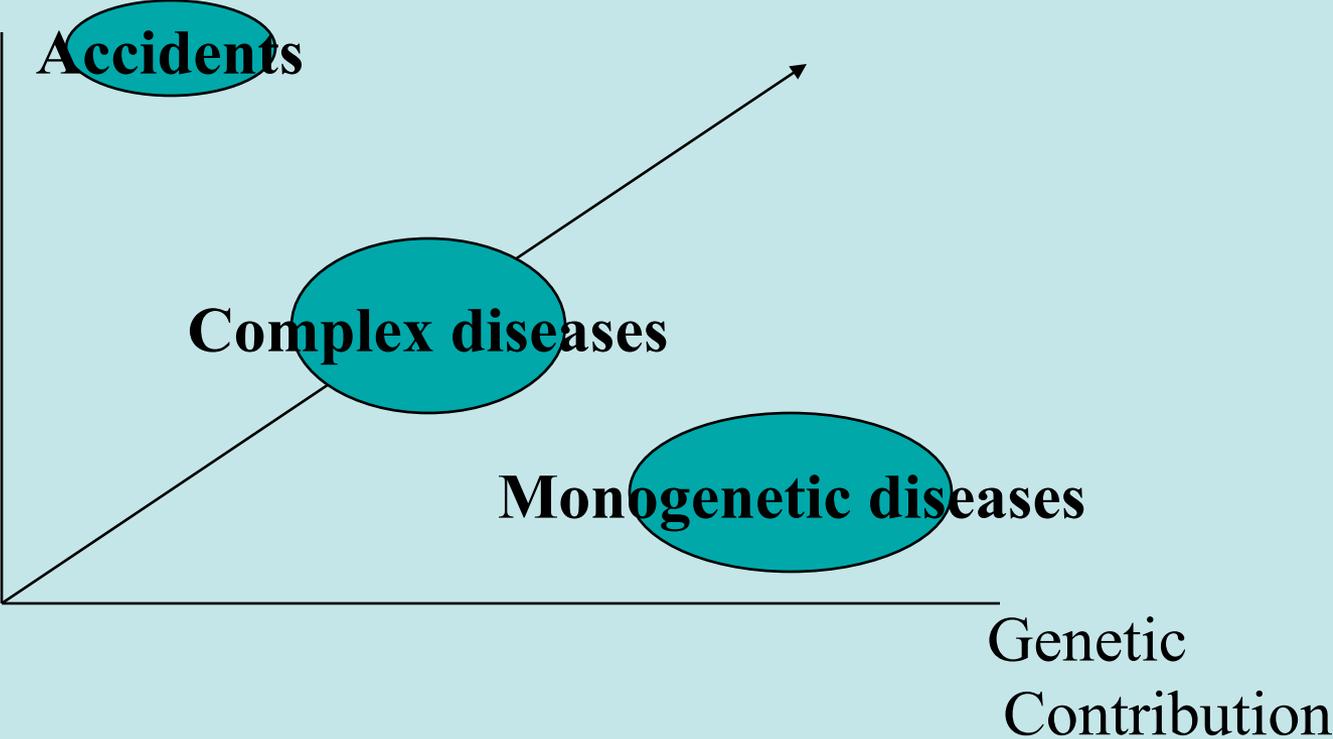
Biochemistry Department

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Presented by Phillip Wilcox

Aetiology of health

Environmental
Contribution





Otago D

Wednesday, Aug

Happily married...
...for 72 years



Slip, sliding away
Houses teeter on edge

General 2

Warrior gene link in Maori violence

■ NZ study's controversial findings
Brisbane: Maori carry a be more likely to be criminals



Above (from left): Graffiti on a Carlyle St building
graffi

Residents





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'Warrior gene' blamed for Maori violence

August 8, 2006 - 4:59PM



BREAKING NEWS

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'Warrior' gene blamed for Maori violence

By Tamara McLean

08aug06

NEW Zealand Maori carry a "warrior" gene which makes them more prone to violence, criminal acts and risky behaviour, a scientist has controversially claimed.

Dr Rod Lea (ESR)

Quotes in NZ papers 8 August

- Maori men have a “striking overrepresentation” of the monoamine oxidase gene that is “strongly associated with risk taking and aggressive behaviour”
- “Maori, being very adventurous individuals as they crossed the Pacific, have carried this gene forward and it was partly responsible for them arriving in NZ and surviving”
- “Obviously this means [modern Maori] are going to be more aggressive and violent and more likely to get involved in risk-taking behaviour”
- “It is controversial, because it has implications suggesting links with criminality among Maori”
- “it definitely predisposes people to be more likely to be criminals”
- “There are lots of lifestyle, upbringing-related exposures that could be relevant here so, obviously, the gene won’t automatically make you a criminal”

Dr Lea studies monoamine oxidase A in a health context (addiction)

- “In terms of alcohol-metabolising genes, we’ve found that Maori have a very unique genetic signature”
- “That influences their drinking behaviour so they’re much more likely to binge drink than other groups which are more likely to moderate their drinking”

Radio NZ: Dr Lea attempted to ‘set the story straight’

Radio NZ 9 August

- “We’ ve been looking at finding better ways to treat tobacco dependence using information about genetics, and we’ re focusing on a lot of different, what we call candidate genes. One of these genes is called the monoamine oxidase gene, which has been [associated] in other studies overseas to behavioural traits such as aggressive behaviour and risk-taking, as well as addiction. The goals of our research is to find better treatment strategies for [Maori].”
- “Because there was [association] to aggressive behaviour it’ s been dubbed the ‘warrior gene’ by researchers overseas.”
- “At this stage we’ ve just found that there are differences in genetic frequencies and we haven’ t [associated] this to any particular trait, certainly not criminality.”
- “This gene has been [associated] to different anti-social behaviours but the link that has been made has usually been quite weak, and often is only present in association with other non-genetic factors eg upbringing. This gene may increase the tendency for aggression but only in combination with a lot of other genes, as well as lifestyle”

NZ Herald Readers Views

“What racist garbage, Dr Lea has based his conclusions on small numbers and unpublished (and therefore unverifiable) work. If Maori are more violent than Pakeha how does he explain the colonisation of New Zealand (not to mention the rest of the world)? Maybe he would be better off trying to find the "crusader" gene that seems to drive Europeans to want to colonise, control and categorise the rest of humanity.”

- Tim Rochford

Kia ora, I would like to thank the all-wise researchers for uncovering the Maori Warrior Gene. I always wondered why I said naughty words whenever I hit my thumb with a hammer! I am also relieved to know that the reason I kick my truck in the tyre whenever it won't start is because of this gene too! I will now be able to distinguish between my Maori and non-Maori brethren much easier... the Maori is the angry one :-) Please pass on my thanks to the people involved in this research and let them know that the next time we put a hangi down, we'll put a couple of packs aside for them as a token of our gratitude... unless of course we get angry and end up killing each other! PS... all sarcasm intended :-)

- Shane Nikora

Tze Ming Mok

- “Well now I’ m terrified. By my calculation, about 900,000 people in this country have an ingrained racial genetic predisposition towards violence and criminality.”
- “You know who I’ m talking about. **White women.**”
- “A whopping 30% of all Pakeha are lumbered with a so-called ‘warrior’ gene which rides on the X chromosome.”
- “Everything we ever knew about white women has suddenly clicked into place. Crazy white chicks, they’ re bung from the start.”
- “Is it right to entrust care of our most vulnerable people to a population from whom one in three is genetically-predisposed to giving them a serious whack if really pushed?”
- “There are increasing numbers of white middle-class women in my street. I’ m considering moving to a safer area.”

Simon Cunliffe, Sunday Times

- “The subsequent furore was all about Maori and criminality and the genetic predisposition of the one towards the other. **All heat and very little light.** In the age of the sound-bite, that, unfortunately, is the predictable level of the debate.”
- “It is all too easy to imagine that the trite connection has taken hold in the minds of many.”
- “The Director of the Christchurch School of Medicine’s Maori Indigenous Health Unit, Suzanne Pitama, said Lea’s comments were “dangerous”. It just reinforces stereotypes she said. Amen to that.”

Tariana Turia

- “The ESR study was focussed into study of genetics of tobacco dependence and, as such, study of this candidate gene may be of help.”
- “Clearly the lead researchers comments have not been at all helpful and I would suggest that ESR need to review their practices.”
- “But I would also challenge the media to look in more depth into stories such as this, to ensure a balanced interpretation.”

WELLINGTON MEDICAL RESEARCH FOUNDATION

RESEARCH REVIEW

2005

Victoria University of Wellington

**Genomic Patterns in the Maori Population: Relevance to Alcohol
Dependence**

RA Lea,^{1,2} GK Chambers ¹

¹School of Biological Sciences, ²The Institute of Environmental Science and
Research, Porirua

- “This gene has also been dubbed the warrior gene which is interesting in the context of Maori males.”
- “In conclusion, our analysis of this gene has provided evidence for positive selection perhaps associated with risk-taking and aggressive behaviour in Maori.”

Abstract for presentation at [11th International Congress of Human Genetics](#)

Tracking the evolutionary history of the Warrior gene across the South Pacific: Implications for genetic epidemiology of behavioral disorders

- Dr Rod **Lea**, Institute of Environmental Science and Research, New Zealand
- Mr David **Hall**, Institute of Environmental Science and Research, New Zealand
- Dr Geoffrey **Chambers**, Victoria University of Wellington, New Zealand
- Prof Lyn **Griffiths**, Griffith University, Australia

Historically, the New Zealand Maoris were extremely adventurous risk takers and fearsome warriors. A DNA repeat polymorphism in the neuronal Monoamine Oxidase (MAO) gene on the X chromosome is strongly associated with risk taking and aggressive behaviour. Hence, the gene has been dubbed the "Warrior" gene. The MAO gene is known to be highly polymorphic in human populations and there is new evidence that the full spectrum sequence variation across MAO exhibits unusual patterns of linkage disequilibrium (LD) indicative of positive selection.

Interestingly, our unpublished studies have revealed striking over-representation of the MAO repeat polymorphism in the Maori male population compared to Caucasian males. We have also characterised LD among SNPs spanning the entire gene in Maori and identified 2-tagging SNPs that signify the common haplotype. This MAO haplotype is associated with the Warrior allele in Maori males suggesting that variation in the MAO gene has been under the influence of positive selection during the risky Polynesian voyages and wars.

Cultural, linguistic and genetic evidence points to Formosa (Taiwan) as the staging post of Maori (Polynesian) voyages between 5000-10000 years ago. In light of this, we will also present full comparative genomic data of the MAO gene in Taiwan aboriginal tribes in an effort to elucidate the evolutionary history of the Warrior gene in the South Pacific. Understanding the evolution of the MAO gene will also be useful for studies of human behavioral disorders such as alcohol and tobacco dependence.

Tony reviewed the science behind the ‘warrior’ gene story

The science did not undergo the (sometimes) rigorous peer review associated with publication in reputable scientific journals.

1. Is the gene “strongly associated” with aggressive behaviour?
2. If the gene is associated with aggressive behaviour, is this the case in Maori men, either ancestral or modern?
3. Why is it called the ‘warrior’ gene?

Monoamine oxidases

- Genes A and B encoded on the X chromosome
- Enzymes that catalyse the oxidative deamination of many biological amines
- Play a role in regulation of many neurotransmitters (serotonin, dopamine)
- Degrade exogenous compounds (eg phenylethylamine)
- In smoking there is ‘growing evidence’ that non-nicotinic components of tobacco smoke inhibit MAO levels

Table 1
Therapeutic monoamine oxidase inhibitors

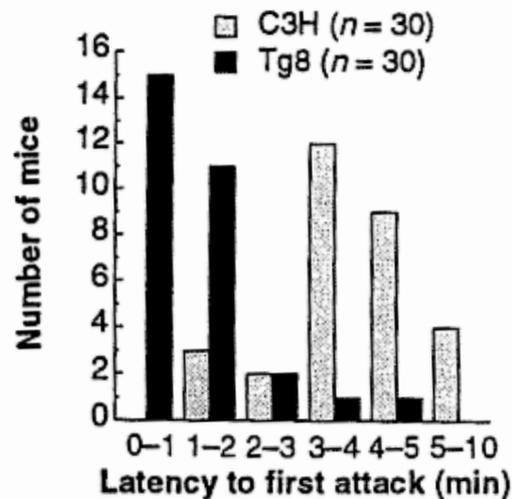
Inhibitor	Inhibition	Clinical application
Phenylzine	Non-selective, irreversible	Antidepressant
Tranlycypromine	Non-selective, irreversible	Antidepressant
Clorgyline	MAO-A, irreversible	
Moclobemide	MAO-A, reversible	Antidepressant, Alzheimer's disease, smoking cessation?
Deprenyl (selegiline)	MAO-B, irreversible	Parkinson's disease, Alzheimer's disease
Pargyline	MAO-B, irreversible	

Mice with a knocked out MAO-A gene exhibit aggressive behaviour

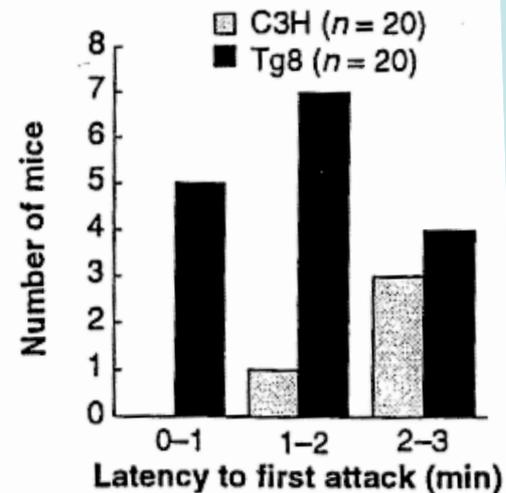
Science 1995

Aggressive Behavior and Altered Amounts of Brain Serotonin and Norepinephrine in Mice Lacking MAOA

Olivier Cases, Isabelle Seif,* Joseph Grimsby, Patricia Gaspar, Kevin Chen, Sandrine Pournin, Ulrike Müller, Michel Aguet, Charles Babinet, Jean Chen Shih, Edward De Maeyer



Breeding



Non-breeding

A Dutch family with a mutant MAO-A allele exhibit antisocial behaviour

Science 1993

Abnormal Behavior Associated with a Point Mutation in the Structural Gene for Monoamine Oxidase A

H. G. Brunner,* M. Nelen, X. O. Breakefield, H. H. Ropers, B. A. van Oost

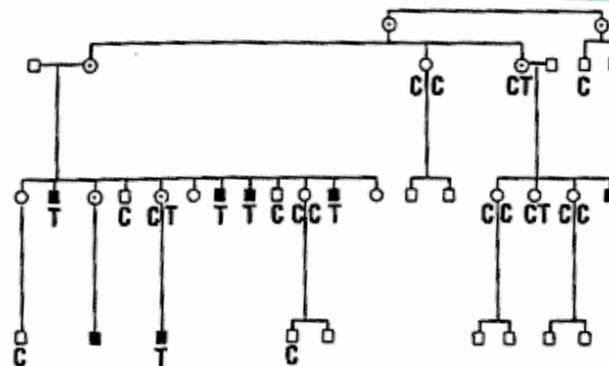


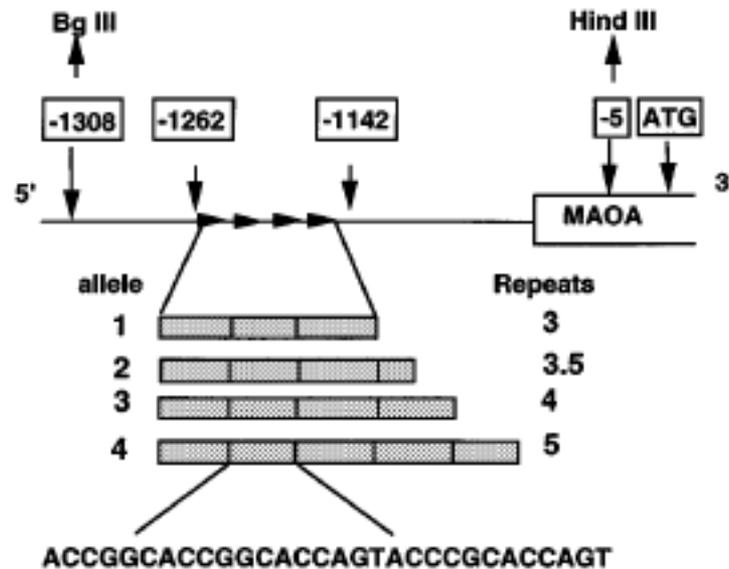
Fig. 1. Segregation of a mutation in the MAOA structural gene in a family with X-linked borderline mental retardation and prominent behavioral disturbance. All affected males and obligate carriers have a C to T mutation at nucleotide position 936. In 12 normal males, only the normal C is present.

- By 1995, mutant forms of MAO-A had been implicated in aggressive behaviour in human and mouse
- What about more common genetic variants and aggressive behaviour in the wider population?

RAPID COMMUNICATION

Sue Z. Sabol · Stella Hu · Dean Hamer

A functional polymorphism in the monoamine oxidase A gene promoter



The allele with fewer repeats is associated with 'low' MAO-A activity

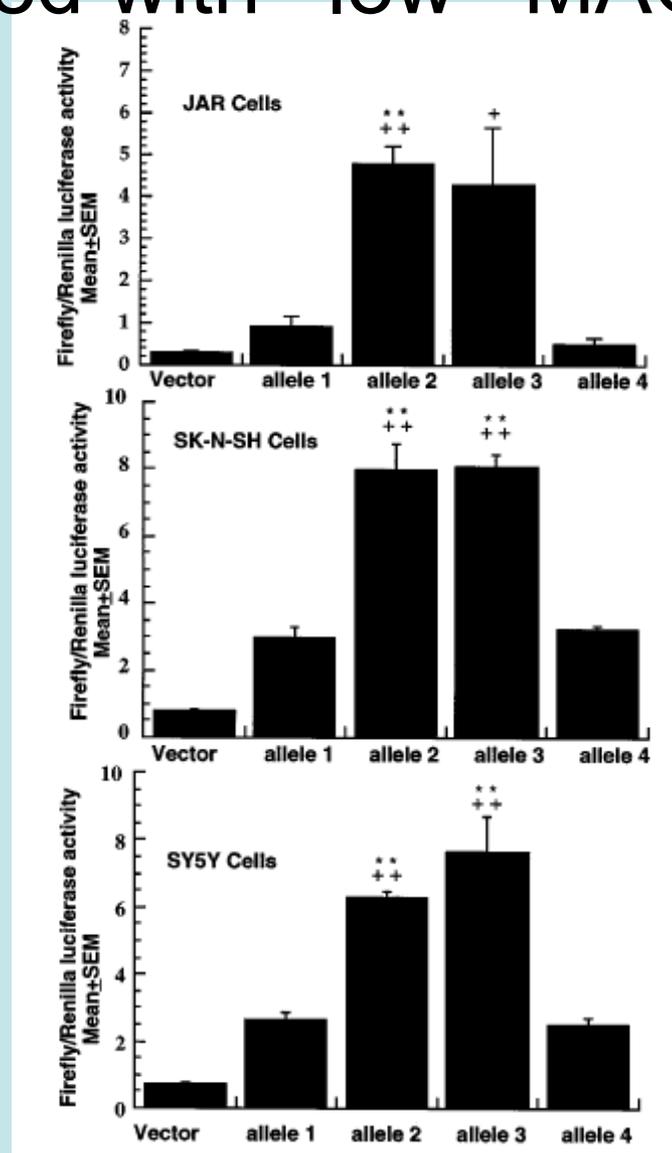


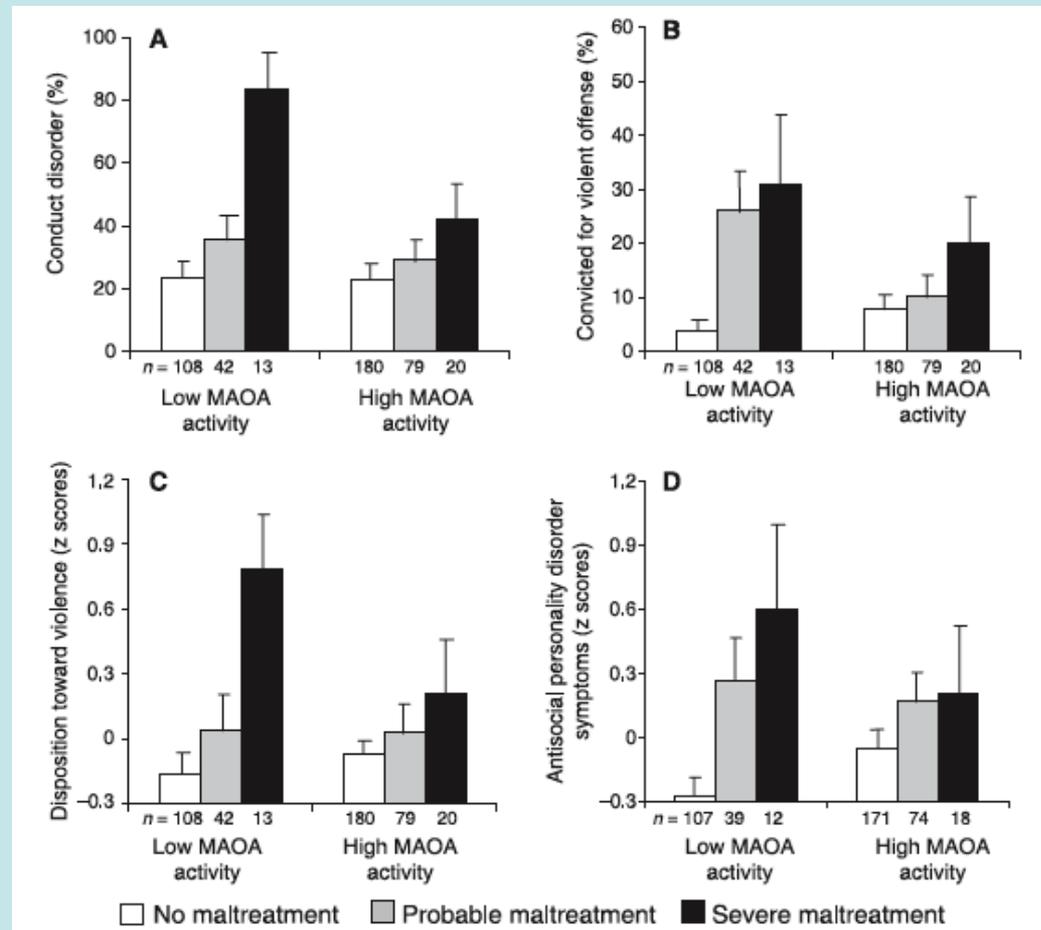
Table 1 MAOA-uVNTR allele frequencies

Population	MAOA-uVNTR allele			
	1 (low)	2	3 (high)	4
Total				
<i>n</i>	768	12	1345	31
%	35.6	0.4	62.4	1.4
White/Non-Hispanic				
<i>n</i>	539	8	1056	26
%	33.1	0.5	64.8	1.6
Asian/Pacific Islander				
<i>n</i>	50	1	31	–
%	61.0	1.2	37.8	–
Hispanic/Latino				
<i>n</i>	27	–	65	–
%	29.3	–	70.7	–
African Amer/Black				
<i>n</i>	52	2	32	2
%	59.1	2.3	36.4	2.3

Maori

N	11	-	6	-
%	65	-	35	-

Dunedin Longitudinal Study (2002) - tested for association between MAO-A and antisocial behaviour in 442 males. Evidence of association only when maltreatment accounted for - 'high' MAOA alleles were protective of antisocial behaviour. Gene x environment interaction.



ORIGINAL ARTICLE

MAOA, maltreatment, and gene–environment interaction predicting children’s mental health: new evidence and a meta-analysis

J Kim-Cohen^{1,2}, A Caspi^{2,3}, A Taylor², B Williams², R Newcombe², IW Craig² and TE Moffitt^{2,3}

¹Department of Psychology, Yale University, New Haven, CT, USA; ²Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King’s College London, London, UK and ³Department of Psychology, University of Wisconsin at Madison, Madison, WI, USA

Participants = members of the Environmental Risk Longitudinal Twin Study (1994 and 1995 birth cohorts, England and Wales). 975 boys.

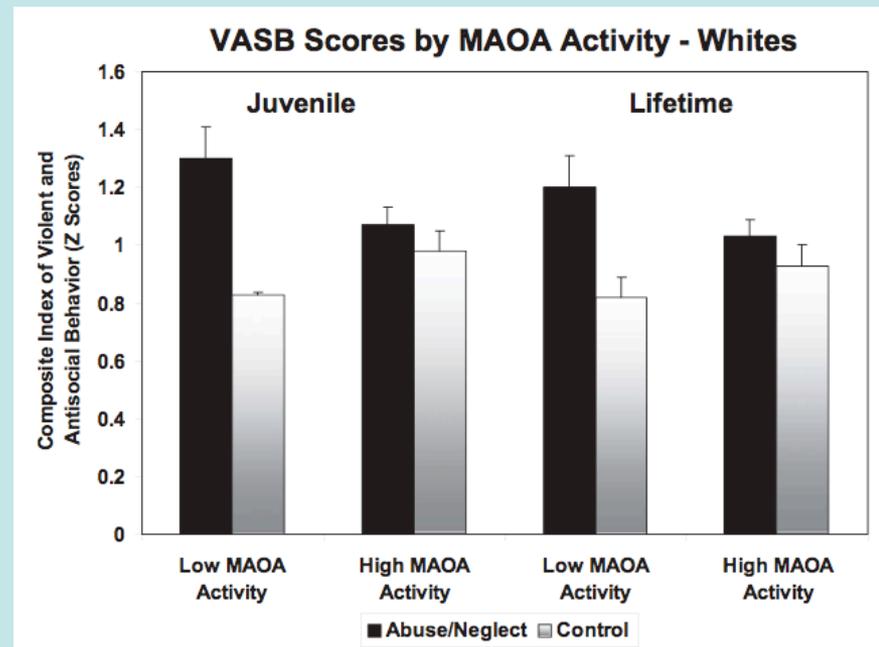
They found that boys with the high activity allele had a higher level of psychopathology. They replicated the gene x environment interaction observed in the Dunedin study:

“the effect of physical abuse exposure on development of psychopathology was significantly weaker among boys with high MAOA activity”

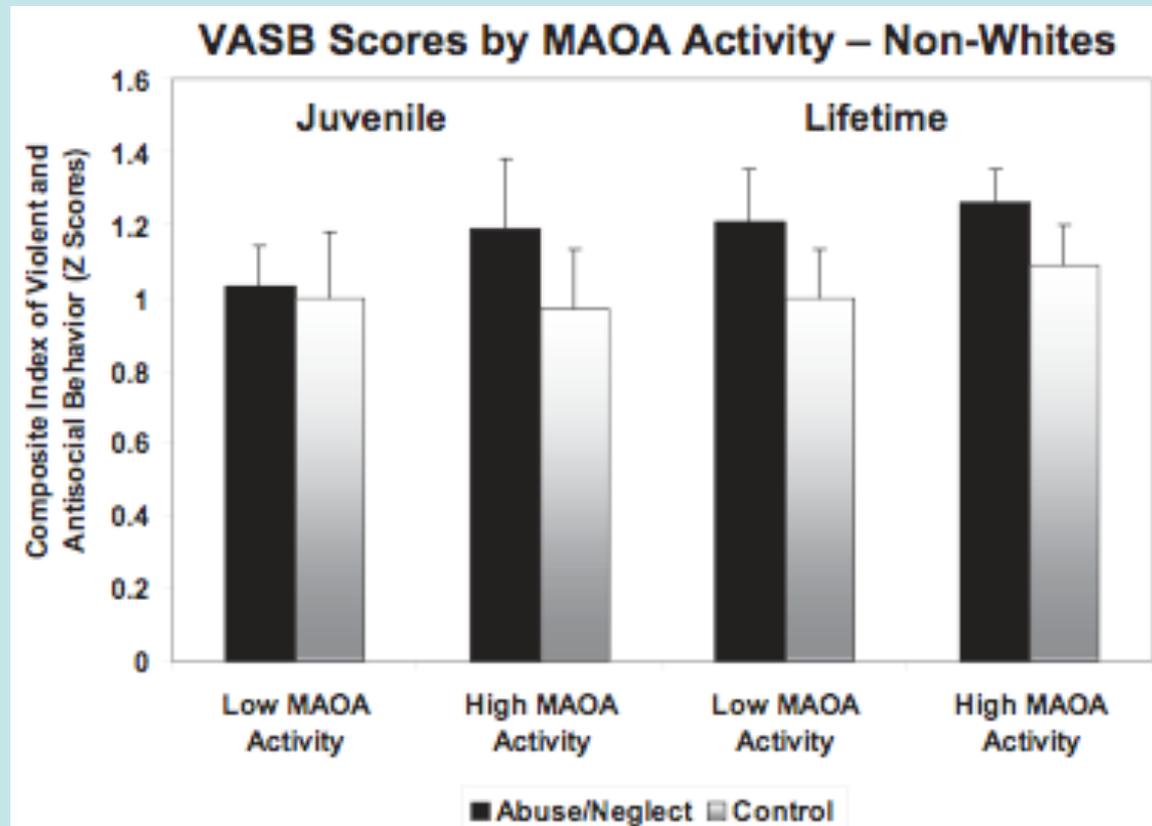
MAOA and the “Cycle of Violence:” Childhood Abuse and Neglect, MAOA Genotype, and Risk for Violent and Antisocial Behavior

Cathy Spatz Widom and Linda M. Brzustowicz

Participants = prospective cohort design study involving court-substantiated cases of child abuse and neglect and a matched comparison group. 802 ‘white’ males.



Notably Widom and Brzustowicz reported no evidence for a role of MAO-A in violent and antisocial behaviour in American ‘non-whites’



This illustrates a central tenet of complex phenotypes: Genetic associations are likely to vary between racial groups

PADI4

FCRL3

1: [Arthritis Rheum.](#) 2006 Jan;54(1):90-6.

A functional haplotype of the PADI4 gene associated with increased rheumatoid arthritis susceptibility in Koreans.

[Kang CP](#), [Lee HS](#), [Ju H](#), [Cho H](#), [Kang C](#), [Bae SC](#).

1: [Arthritis Rheum.](#) 2004 Apr;50(4):1117-21.

A functional haplotype of the PADI4 gene associated with rheumatoid arthritis in a Japanese population is not associated in a United Kingdom population.

[Barton A](#), [Bowes J](#), [Eyre S](#), [Spreckley K](#), [Hinks A](#), [John S](#), [Worthington J](#).

PADI4 polymorphisms are not associated with rheumatoid arthritis in the Spanish population

[A. Martinez](#), [A. Valdivia](#), [D. Pascual-Salcedo](#)², [J. Ramón Lamas](#)¹, [M. Fernández-Arquero](#), [A. Balsa](#)³, [B. Fernández-Gutiérrez](#)¹, [E. G. de la Concha](#) and [E. Urcelay](#)

A family based study shows no association between rheumatoid arthritis and the PADI4 gene in a white French population

[L Caponi](#)¹, [E Petit-Teixeira](#)², [M Sebbag](#)³, [F Bongiorno](#)⁴, [S Moscato](#)⁴, [F Pratesi](#)⁴, [C Pierlot](#)², [J Osorio](#)², [S Chapuy-Regaud](#)³, [M Guerrin](#)³, [F Cornelis](#)⁵, [G Serre](#)³ and [P Migliorini](#)⁴ for ECRAF*

ARTICLE

Nature Genetics **37**, 478 - 485 (2005)
Published online: 17 April 2005; | doi:10.1038/ng1540

There is an [Erratum](#) (June 2005) associated with this Article.

A functional variant in FCRL3, encoding Fc receptor-like 3, is associated with rheumatoid arthritis and several autoimmunities

[Yuta Kochi](#)^{1, 2}, [Ryo Yamada](#)¹, [Akari Suzuki](#)¹, [John B Harley](#)³, [Senji Shirasawa](#)⁴, [Tetsuji Sawada](#)², [Sang-Cheol Bae](#)⁵, [Shinya Tokuhiko](#)¹, [Xiaotian Chang](#)¹, [Akihiro Sekine](#)⁶, [Atsushi Takahashi](#)⁷, [Tatsuhiko Tsunoda](#)⁷, [Yoza Ohnishi](#)⁸, [Kenneth M Kaufman](#)³, [Changsoo Paul Kang](#)⁹, [Changwon Kang](#)⁹, [Shigeru Otsubo](#)¹⁰, [Wako Yumura](#)¹¹, [Akio Mimori](#)⁴, [Takao Kolke](#)¹², [Yusuke Nakamura](#)^{10, 13}, [Takehiko Sasazuki](#)⁴ & [Kazuhiko Yamamoto](#)^{1, 2}

Supportive evidence for a genetic association of the FCRL3 promoter polymorphism with rheumatoid arthritis

[K Ikari](#), [S Momohara](#), [T Nakamura](#), [M Hara](#), [H Yamanaka](#), [T Tomatsu](#) and [N Kamatani](#)

1: [Arthritis Rheum.](#) 2006 Mar;54(3):1022-5.

The functional -169T->C single-nucleotide polymorphism in FCRL3 is not associated with rheumatoid arthritis in white North Americans.

[Hu X](#), [Chang M](#), [Saiki RK](#), [Cargill MA](#), [Begovich AB](#), [Ardlie KG](#), [Criswell LA](#), [Seldin MF](#), [Amos CI](#), [Gregersen PK](#), [Kastner DL](#), [Remmers EF](#).

Research article

Association of the FCRL3 gene with rheumatoid arthritis: a further example of population specificity?

[Stephen Eyre](#) ✉, [John Bowes](#) ✉, [Catherine Potter](#) ✉, [Jane Worthington](#) ✉ and [Anne Barton](#) ✉
ARC-EU, University of Manchester, UK

Arthritis Research & Therapy 2006, **8**:R117 | doi:10.1186/ar2006

Open Access

1. Is the gene “strongly associated” with aggressive behaviour?

- Definitely not.
- The high-activity allele protects from aggressive behaviour in the context of a negative upbringing.
- In Caucasian, there is no evidence for a causative role of the low-activity (‘warrior’) allele in aggressive behaviour (rather protective of high-activity allele).
- A recent editorial in *The American Journal of Psychiatry*:

seems clear, but the effect of the high-risk MAO-A allele, alone or in interaction with an adverse environment, is either small or uncertain. Thus, on a community level, it would not yet make sense to use this particular allele as part of screening for high-risk children.

□

□

2. If the gene is associated with aggressive behaviour, is this the case in Maori men?

- We simply do not know. To find out would require large prospective studies similar to the NZ, UK and US ones
- To relate MAO-A to aggressive behaviour in Maori, either ancestral or modern, is pure speculation (given the difficulty of testing such a hypothesis).

3. Why is MAO-A called the
'warrior' gene ?

Evidence for gene x environment interaction in a small study of Rhesus macaque monkeys. Not consistent with human.

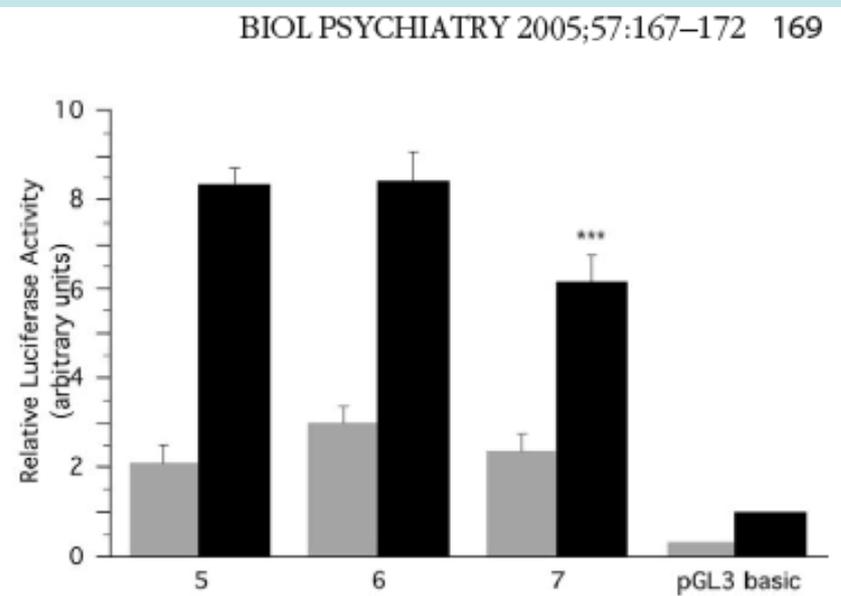
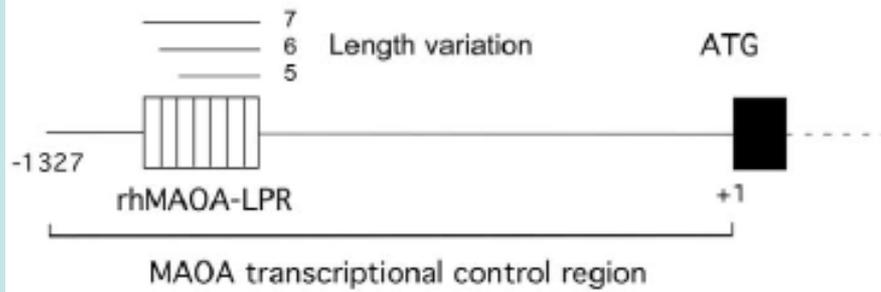
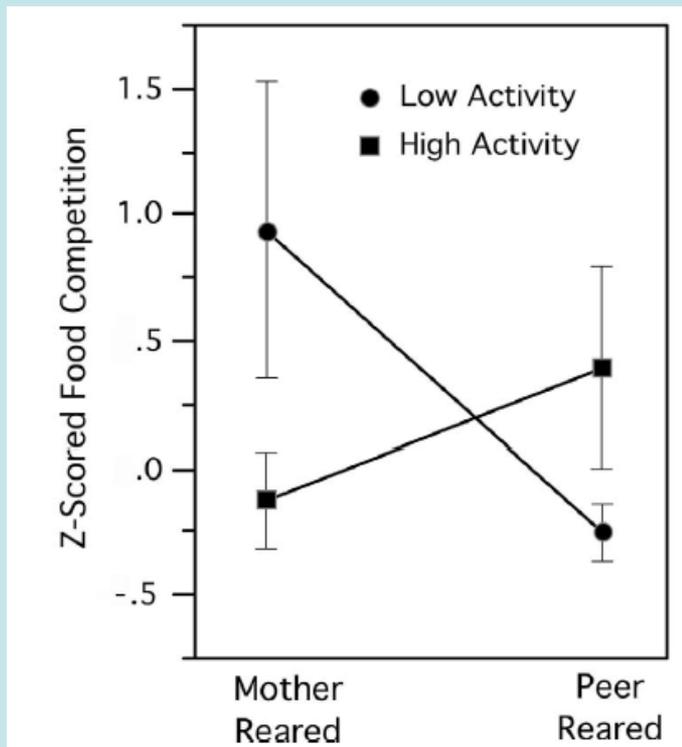


Figure 2. Transcriptional activity of the 5-, 6-, and 7-repeat rhMAOA-LPR variants in SH-SY5Y human neuroblastoma cells, which constitutively express MAOA (black bars) and in MAOA-negative cos 7 (gray bars). Results are



A scientific journalist (Gibbons) coined the term ‘warrior gene’ on the basis of the unreplicated macaque research.

Meeting American Association of Physical Anthropologists

Tracking the Evolutionary History of a “Warrior” Gene

TAMPA, FLORIDA—About 1200 researchers attended the 73rd Annual Meeting of the American Association of Physical Anthropologists here from 14 to 17 April to hear talks on primate genes, behavior, and fossils.



Mad macaque. A genetic variant linked to violence in men has counterparts in primates and can make macaques like this one more aggressive.

Summary comments

Dr Lea is the only researcher to use ‘warrior’ gene for MAO-A in the context of human studies.

He applies this term to Maori when the literature shows only a weak gene x envt effect on aggression in Caucasian with no data from Maori

He continues to use “warrior” gene and continues to speculate (NZMJ 2/3/07) that the MAO-A gene may have conferred some selective advantage during waka voyages and inter-tribal wars that occurred during the Polynesian migrations.

He does not, however, intend to test this hypothesis (ie relate MAO-A genotype to aggression and risk-taking in modern Maori).

It is important to characterise MAO-A genetic variation in Maori in the context of biomedical research into addiction, but the ‘warrior’ angle is not necessary for this research.

Lessons

- Science has to be robust, both in interpreting and applying the relevant literature and in design and execution of studies
- Appropriate and careful dissemination to the public is essential

Guidelines in dissemination of research findings

- The 1998 NZ Health Research ‘Guidelines for Researchers on Health Research Involving Maori’: ‘Permission to collect and analyse potentially sensitive information does not equate to permission to publish such information. Publication may be possible but the format needs to be negotiated with the Maori organisations involved.’
- The 2002 Council for International Organisation of Medical Sciences ‘International Ethical Guidelines for Biomedical Research Involving Human Subjects’ provides that among those items to be included in a research protocol are ‘Circumstances in which it might be considered inappropriate to publish findings of an epidemiological, sociological or genetics study that may present risks to the interests of a community or population or of a racially- or ethnically-defined group of people.’

Thanks

- Assoc Prof Vicky Cameron (Chch School of Medicine)
 - Prof Peter Crampton (Wn School of Medicine)
 - Prof Richie Poulton (Dunedin Multidisciplinary Study)
 - Dana Wensley (Law Foundation Human Genome Research Project, Otago University)
 - Prof Don Evans (Bioethics, Otago University)
-
- Refer to NZMJ 2 March issue