nature publishing group

► **COVER:** 'Acid trip' by Patrick Morgan, inspired by the Review on p541.

LOUISA FLINTOFT

TANITA CASCI

PATRICK GOYMER

As complex traits go, psychiatric conditions are about as complicated as you get, characterized as they are by many distinct biological mechanisms, genetic, allelic and phenotypic heterogeneity, and environmental influences. The nature of this beast means that we must proceed with caution when applying genome-wide association (GWA) studies, which are the present 'answer' to complex traits.

Our current, still rather unclear, picture of the genetics of psychiatric conditions is the result of a string of failed or irreproducible attempts at identifying variants using linkage, candidate and association studies. But there are signs that the field has turned a corner — convincingly replicated findings have emerged by incorporating endophenotypes and environmental risk factors into analyses. We also have stricter standards for GWA studies — increasing sample sizes and sharpening phenotypic boundaries should iron out many of the current statistical limitations. Or will it?

As Burmeister and colleagues point out on page 527, the best strategy will be determined by the degree of heterogeneity. If variants are common and each makes only a marginal contribution to risk for any disorder, then GWA studies using vastly larger sample sizes might be fruitful, as was the case for type 2 diabetes. But recent publications highlight the importance of rare structural mutations in autism (see the Review by Abrahams and Geschwind in our May issue) and schizophrenia (Walsh, T. *et al. Science* **320**, 539–543 (2008); Xu, B. *et al. Nature Genet.* 30 May 2008 (doi:10.1038/ng.162)). If many risk alleles are rare then we need to throw efforts into high-throughput resequencing instead. And these are just the extreme scenarios.

Reproducible results will be hard won but hugely valuable — perhaps unusually for complex disorders, new biological information is expected to be incorporated quickly into clinical practice, primarily in diagnosis.

EDITORIAL OFFICES
LONDON NatureReviews@nature.com
The Macmillan Building,
4 Crinan Street,
London N1 9XW, UK
Tel: +44 (0)20 7843 3620;
Fax: +44 (0)20 7843 3629
CHIEF EDITOR: Louisa Flintoft
SENIOR EDITOR: Tanita Casci
ASSISTANT EDITOR: Patrick Goymer
COPY EDITOR: Elizabeth Neame
SENIOR ART EDITOR (NRG): Patrick Morgan
EDITORIAL SUPPORT MANAGER: Elinor Faulkner
ART CONTROLLER: Susanne Harris
SENIOR ART EDITOR: Vicky Askew
MANAGING PRODUCTION EDITOR: Judith Shadwell
DEPUTY PRODUCTION EDITOR: Simon Fenwick
PRODUCTION CONTROLLER: Natalie Smith
EDITORIAL ASSISTANTS: Laura Firman, Jacques Smit
WEB PRODUCTION MANAGER: Deborah Anthony
MARKETING MANAGERS: Tim Redding, Leah Rodriguez

MANAGEMENT OFFICES
LONDON nature@nature.com
The Macmillan Building,
4 Crinan Street,
London N1 9XW, UK
Tel: +44 (0)20 7833 4000;
Fax: +44 (0)20 7843 4596/7
OFFICE MANAGER: Sheryl Ocampo
ASSOCIATE PUBLISHER: Magdalena Skipper
MANAGING DIRECTOR: Steven Inchcoombe
EDITOR-IN-CHIEF, NATURE PUBLICATIONS: Philip Campbell
ASSOCIATE DIRECTORS: Jenny Henderson, Tony Rudland
EDITORIAL PRODUCTION DIRECTOR: James McQuat
PRODUCTION DIRECTOR: Yvonne Strong
DIRECTOR, WEB PUBLISHING: Timo Hannay
HEAD OF WEB PRODUCTION: Alexander Thurrell
NATUREJOBS PUBLISHER: Della Sar

NEW YORK nature@natureny.com
Nature Publishing Group,
75 Varick Street, 9th floor, New York,
NY 10013-1917, USA
Tel: +1 212 726 9200;
Fax: +1 212 696 9006
CHIEF TECHNOLOGY OFFICER: Howard Ratner
HEAD OF INTERNAL SYSTEMS DEVELOPMENT: Anthony Barrera
HEAD OF SOFTWARE SERVICES: Luigi Squillante
HEAD OF GLOBAL ADVERTISING, SALES AND SPONSORSHIP: Dean Sanderson
HEAD OF NATURE RESEARCH & REVIEWS MARKETING: Sara Girard
BUSINESS DEVELOPMENT EXECUTIVE: David Bagshaw

TOKYO nature@natureasia.com
Chiyoda Building 5F, 2-37-1 Ichigayatamachi,
Shinjuku-ku, Tokyo 162-0843, Japan
Tel: +81 3 3267 8751; Fax: +81 3 3267 8746
ASIA–PACIFIC PUBLISHER: Antoine E Bocquet
MANAGER: Koichi Nakamura
ASIA–PACIFIC SALES DIRECTOR: Kate Yoneyama
SENIOR MARKETING MANAGER: Peter Yoshihara
MARKETING/PRODUCTION MANAGER: Takesh Murakami

INDIA 5A/12 Ansari Road, Daryganj,
New Delhi 110 002, India
Tel/Fax: +91 11 2324 4186
SALES AND MARKETING MANAGER, INDIA: Harpal Singh Gill

Printed in Wales by Cambrian Printers on acid-free paper