Twin Research and Human Genetics (2020), **23**, 105–106
doi:10.1017/thg.2020.22

CAMBRIDGE UNIVERSITY PRESS

Article

Migraine, Human Genetics and a Passion for Science

Dale R. Nyholt

School of Biomedical Sciences, Faculty of Health, and Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia

Abstract

This note reflects on my collaborations with Nick Martin and the GenEpi group over the past 20 years. Over the past two decades, our work together has focused on gene mapping and understanding the genetic architecture of a wide range of traits with particular foci on migraine and common baldness. Our migraine research has included latent class and twin analyses cumulating in genome-wide association analyses which had identified 44 (34 new) risk variants for migraine. Leveraging these results through polygenic risk score analyses identified subgroups of patients likely to respond to triptans (an acute migraine drug), providing the first step toward precision medicine in migraine [Kogelman et al. (2019) Neurology Genetics, 5, e364].

Keywords: Gene mapping; migraine; baldness

(Received 18 February 2020; accepted 25 March 2020; First Published online 19 May 2020)

My first interactions with Professor Nicholas (Nick) G. Martin occurred at the end of my PhD during the inaugural Australasian Human Gene Mapping ('GeneMappers') Meeting held in Thredbo (NSW, Australia) in early February 1999 — a couple of weeks before I flew to New York to begin my first postdoc in Jurg Ott's Statistical Genetics Laboratory at Rockefeller University.

I vividly recall (okay, foggily recall [there may have been alcohol involved]) lively discussions on gene mapping and encouragement to contact him should I want to continue my research career upon returning to Australia. Less than two years later and I was sitting in Nick's office with a lovely view of the Brisbane skyline finalizing my NHMRC early career (Peter Doherty) fellowship application. From these early interactions, I learnt that Nick always spoke his mind (often with wild abandon), but he was always motivated by a desire to perform good science. It is this infectious passion for science that attracts and inspires those around him.

My fellowship application was successful, and a few months later, I began my journey as Nick's colleague and collaborator within his Genetic Epidemiology Laboratory.

Nick created and continues to maintain a world-class research environment that is rich in data, expertise and excellence. I will always be grateful for the opportunity to learn and benefit from this environment. Indeed, although I was initially attracted to Nick's lab to ask new and deep questions that extended my PhD research on migraine genetics, I was able to both lead and contribute to hundreds of genetic studies comprising dozens of traits — prominent examples include depression (Yang et al., 2018), endometriosis (Nyholt et al., 2009; Sapkota et al., 2017), leukocyte telomere length (Broer et al., 2013), male pattern baldness (Nyholt et al., 2003), obesity (Locke et al., 2015; Rahmioglu et al., 2015) and twinning (Mbarek et al., 2016).

Our collaborative research has produced important advances and paradigm changes. For example, one of our first publications rebuked the widely accepted opinion that common baldness was an autosomal dominant phenotype in men and an autosomal recessive phenotype in women. In this first large-scale study of 476 monozygotic (MZ) and 408 dizygotic (DZ) male twin pairs, we estimated a heritability of 0.81 (95% CI [0.77, 0.85]) and indicated that additive genetic effects play a major part in the progression of common male hair loss (Nyholt et al., 2003).

Similarly, our migraine research applied latent class and twin genetic analyses to identify subgroups of migraine sufferers and show the existence of a severity continuum, where migraine with aura (MA) is more severe, but not, as previously thought, etiologically distinct from migraine without aura (Nyholt et al., 2004). This research attracted international attention and led to high impact migraine collaborations that persist today. Indeed, this research, together with Nick's extensive network of international twin/genetic researchers, led to the cofounding of the International Headache Genetics Consortium (IHGC), which brought together headache geneticists and clinicians from around the globe to conduct numerous large-scale genetic studies on migraine (Anttila et al., 2006, 2008; Ligthart et al., 2006, 2008; Mulder et al., 2003; Nyholt et al., 2005; van den Maagdenberg et al., 2019).

With advancing genotyping technology, our migraine research was at the forefront of genetic association studies. Our 2008 IHGC publication showed that contrary to the leading hypothesis at the time, ion transport genes — implicated in familial hemiplegic migraine (FHM), a Mendelian subtype of MA associated with hemiparesis — did not play a major role in the common forms of migraine (Nyholt et al., 2008). Our research also showed that despite the female:male prevalence ratio of >2:1, female and male migraineurs are not genetically distinct (Mulder et al., 2003; Nyholt et al., 2004, 2015). These advances were crucial to the design and execution of subsequent well-powered genetic studies of migraine — all led by the IHGC.

Author for correspondence: Dale R. Nyholt, Email: d.nyholt@qut.edu.au

Cite this article: Nyholt DR. (2020) Migraine, Human Genetics and a Passion for Science. *Twin Research and Human Genetics* **23**: 105–106, https://doi.org/10.1017/thg.2020.22

In 2016, we published the largest ever genetic study of migraine (involving 59,674 migraine cases and 316,078 controls) and identified 44 (34 new) risk variants for migraine (Gormley et al., 2016). Most prominently, this research provided valuable insight into migraine pathophysiology, by indicating vascular dysfunction to be a primary mechanism underlying migraine. This is important because there is a long-running debate about whether migraine is a disease of vascular dysfunction or a result of neuronal dysfunction with secondary vascular changes. This paper's Altmetric attention score is in the top 0.02% of all research outputs ever tracked. Moreover, the results from this study allow polygenic risk score (PRS) analyses in migraine risk prediction to identify and quantify comorbidities, endophenotypes and drug responses and paves the way to develop relevant vascular cellular models of migraine that are required to understand the molecular mechanisms of migraine and develop new drugs. Indeed, our migraine PRS was able to identify subgroups of patients likely to respond to triptans (an acute migraine drug), providing the first step toward precision medicine in migraine (Kogelman et al., 2019).

The above highlights are but a few of the many that I have been fortunate to share with Nick over the past 20 years, and I hope to share many more. As we celebrate Nick's 70th birthday (besides from mentally noting his fitting Platinum Jubilee themed hair color), I fondly reflect on the countless discussions, opportunities and accomplishments we have shared and I marvel at the amazing legacy he continues to build for current and future generations. Cheers Nick, you are truly a unique and special individual.

References

Anttila, V., Kallela, M., Oswell, G., Kaunisto, M. A., Nyholt, D. R., Hamalainen, E., Palotie, A. (2006). Trait components provide tools to dissect the genetic susceptibility of migraine. *American Journal of Human Genetics*, *79*, 85–99.

Anttila, V., Nyholt, D. R., Kallela, M., Artto, V., Vepsalainen, S., Jakkula, E., Palotie, A. (2008). Consistently replicating locus linked to migraine on 10q22-q23. *American Journal of Human Genetics*, *82*, 1051–1063.

Broer, L., Codd, V., Nyholt, D. R., Deelen, J., Mangino, M., Willemsen, G., … **Boomsma, D. I.** (2013). Meta-analysis of telomere length in 19,713 subjects reveals high heritability, stronger maternal inheritance and a paternal age effect. *European Journal of Human Genetics*, *21*, 1163–1168.

Gormley, P., Anttila, V., Winsvold, B. S., Palta, P., Esko, T., Pers, T. H., … **Palotie, A.** (2016). Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. *Nature Genetics*, *48*, 856–866.

Kogelman, L. J. A., Esserlind, A.-L., Christensen, A. F., Awasthi, S., Ripke, S., Ingason, A., … **The International Headache Genetics Consortium**. (2019). Migraine polygenic risk score associates with efficacy of migraine-specific drugs. *Neurology Genetics*, *5*, e364.

Ligthart, L., Boomsma, D. I., Martin, N. G., Stubbe, J. H., & Nyholt, D. R. (2006). Migraine with aura and migraine without aura are not distinct entities: further evidence from a large Dutch population study. *Twin Research and Human Genetics*, *9*, 54–63.

Ligthart, L., Nyholt, D. R., Hottenga, J. J., Distel, M. A., Willemsen, G., & Boomsma, D. I. (2008). A genome-wide linkage scan provides evidence for both new and previously reported loci influencing common migraine. *American Journal of Medical Genetics, Part B, Neuropsychiatric Genetics*, *147B*, 1186–1195.

Locke, A. E., Kahali, B., Berndt, S. I., Justice, A. E., Pers, T. H., Day, F. R., … **Speliotes, E. K.** (2015). Genetic studies of body mass index yield new insights for obesity biology. *Nature*, *518*, 197–206.

Mbarek, H., Steinberg, S., Nyholt, D. R., Gordon, S. D., Miller, M. B., McRae, A. F., … **Boomsma, D. I.** (2016). Identification of common genetic variants influencing spontaneous dizygotic twinning and female fertility. *American Journal of Human Genetics*, *98*, 898–908.

Mulder, E. J., Van Baal, C., Gaist, D., Kallela, M., Kaprio, J., Svensson, D. A., … **Palotie, A.** (2003). Genetic and environmental influences on migraine: a twin study across six countries. *Twin Research*, *6*, 422–431.

Nyholt, D. R., Gillespie, N. A., Heath, A. C., & Martin, N. G. (2003). Genetic basis of male pattern baldness. *The Journal of Investigative Dermatology*, *121*, 1561–1564.

Nyholt, D. R., Gillespie, N. G., Heath, A. C., Merikangas, K. R., Duffy, D. L., & Martin, N. G. (2004). Latent class and genetic analysis does not support migraine with aura and migraine without aura as separate entities. *Genetic Epidemiology*, *26*, 231–244.

Nyholt, D. R., Gillespie, N. G., Merikangas, K. R., Treloar, S. A., Martin, N. G., & Montgomery, G. W. (2009). Common genetic influences underlie comorbidity of migraine and endometriosis. *Genetic Epidemiology*, *33*, 105–113.

Nyholt, D. R., International Headache Genetics Consortium**, Anttila, V., Winsvold, B. S., Kurth, T., Stefansson, H.,** … **Palotie, A.** (2015). Concordance of genetic risk across migraine subgroups: impact on current and future genetic association studies. *Cephalalgia*, *35*, 489–499.

Nyholt, D. R., LaForge, K. S., Kallela, M., Alakurtti, K., Anttila, V., Farkkila, M., … **Palotie, A.** (2008). A high-density association screen of 155 ion transport genes for involvement with common migraine. *Human Molecular Genetics*, *17*, 3318–3331.

Nyholt, D. R., Morley, K. I., Ferreira, M. A., Medland, S. E., Boomsma, D. I., Heath, A. C., … **Martin, N. G.** (2005). Genomewide significant linkage to migrainous headache on chromosome 5q21. *American Journal of Human Genetics*, *77*, 500–512.

Rahmioglu, N., Macgregor, S., Drong, A. W., Hedman, A. K., Harris, H. R., Randall, J. C., … **Zondervan, K. T.** (2015). Genome-wide enrichment analysis between endometriosis and obesity-related traits reveals novel susceptibility loci. *Human Molecular Genetics*, *24*, 1185–1199.

Sapkota, Y., Steinthorsdottir, V., Morris, A. P., Fassbender, A., Rahmioglu, N., De Vivo, I., … **Nyholt, D. R.** (2017). Meta-analysis identifies five novel loci associated with endometriosis highlighting key genes involved in hormone metabolism. *Nature Communications*, *8*, 15539.

van den Maagdenberg, A. M. J. M., Nyholt, D. R., & Anttila, V. (2019). Novel hypotheses emerging from GWAS in migraine? *Journal of Headache and Pain*, *20*, 5.

Yang, Y., Zhao, H., Boomsma, D. I., Ligthart, L., Belin, A. C., Smith, G. D., Nyholt, D. R. (2018). Molecular genetic overlap between migraine and major depressive disorder. *European Journal of Human Genetics*, *26*, 1202–1216.

https://doi.org/10.1017/thg.2020.22 Published online by Cambridge University Press