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Article

The Genetics of Endometriosis

Grant W. Montgomery

Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, Australia

Abstract

Mapping genetic risk factors for endometriosis continues from early studies on women's health initiated by Nick Martin and Susan Treloar. Their initial recruitment of endometriosis cases and family members received a major boost and became a flagship project within the Cooperative Research Centre (CRC) for the Discovery of Common Human Disease. We extended the study through a formal collaboration with Professor Stephen Kennedy and his group in Oxford. Our first joint scientific meeting was held in Brisbane and was sadly memorable as the day the planes were flown into the Twin Towers in New York. Our initial collaboration expanded into the International Endometriosis Genetics Consortium (IEGC). The IEGC now has 15 groups around the world, and the most recent meta-analysis will be published this year.

Keywords: Endometriosis; gene mapping; Nick Martin

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The genesis of the endometriosis mapping project was results from a survey on women's health in twins conducted by Susan Treloar and Nick Martin. One rather surprising result from analyses of these data was the relatively high heritability for hysterectomy. Of course, the reason for this is the relatively high heritability for endometriosis and uterine fibroids, two of the main risk factors for hysterectomy. Sue and Nick were considering follow-up studies on the two main genetic risk factors. Not for the first time, a chance dinner party tipped the balance on which project to start with. A collaboration with local gynecologist Dr Dan O'Connor was started; and with his support, the project on genetic risk factors for endometriosis began. The project was helped in the initial stages by a generous donation from a family with a history of the disease. Not long afterward, a successful application to the Commonwealth Government provided funding for the Cooperative Research Centre (CRC) for the Discovery of Common Human Disease and the endometriosis project became a flagship project for the Disease CRC. This major injection of funding enabled recruitment of a large cohort of women with surgically confirmed disease and genetic marker analysis for linkage mapping. The sample and data set recruited by Sue and Nick remain one of the largest samples in the world with surgically confirmed disease, and a cornerstone of the continuing efforts to map genetic risk factors for endometriosis.

The project had started before I arrived in Brisbane. At the time, I was working in the Biochemistry Department at the University of Otago in New Zealand and running an animal gene-mapping program. We had spent the previous 10 years mapping and cloning genes for dizygotic twinning. The fact this project could now be done in a matter of months using next generation sequencing is one measure of progress. I had been corresponding with Nick about the twinning projects and visited Brisbane for the first time on my way home from a conference in Darwin. Nick's program was expanding and I was looking for new challenges, so I packed up and moved to Brisbane to join Nick's group.

Sue and her team were working hard at identifying women with endometriosis, obtaining individual surgical reports to confirm surgical diagnosis, and arranging for collection of blood samples. I took over the laboratory component, receiving and processing the blood samples, extracting DNA, and preparing sets of samples to send away for genotyping. Over the course of the project, we collected blood samples from over 9000 women with endometriosis and their families. This coincided with several large National Institutes of Health (NIH) grants to collect blood and DNA samples in other projects including the twins. I had run some big studies in my animal genomics program but not on this scale or with the same level of detail. It was a hectic few years developing systems while handling the increasing volume of incoming samples as recruitment ramped up in multiple studies.

At the peak, we were recruiting and processing samples from 8000 participants each year. There were some funny incidents along the way, like the day early on when we saw a delegation of senior institute staff going into Nick's office. It appeared they were not aware that Nick had a laboratory. Ordering laboratory supplies had triggered a delegation to ensure we had regulatory approvals (we had) and were paying our share of laboratory costs (perhaps not so much). There were also the days of the long rolls of brown paper used to map out the needs, database developments, and timelines for the laboratory, so we could meet the increasing demands. In the end, the formidable team Nick assembled for both recruitment and laboratory processing was highly successful. The scale and quality of data and sample processing achieved were second to none and provided the platform for the many successes to follow in projects including our studies in endometriosis.

Following the major recruitment drive in the endometriosis project, samples were prepared and sent to the Australian

Author for correspondence: Grant W. Montgomery, Email: g.montgomery1@uq.edu.au
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Genome Research Facility (AGRF) in Melbourne for microsatellite genotyping funded by the CRC. This was the largest genotyping project undertaken by the AGRF. At the time, of course, it was emerging that early hope for linkage studies was optimistic and larger samples were likely needed for success. In parallel with our studies, the group in Oxford led by Stephen Kennedy was also conducting linkage studies. We began discussing collaboration though the CRC and the respective commercial partners for both Australia and Oxford. The terms of collaboration were agreed and the deal was signed in Singapore, perhaps in the bar of Raffles Hotel but that could be apocryphal.

The next step was the great unveiling of results by the two sides. That took place at a meeting in Queensland Institute of Medical Research (QIMR) when a delegation from Oxford flew out to Australia. It was a memorable day because it was the day the planes flew into the Twin Towers in New York. I was woken early by a phone call from family in New Zealand, telling me to turn on the television and like so many others watched events unfold in real-time. By the time, we arrived at QIMR for the great unveiling, we were all shocked, not least because our colleagues were due to fly out from Australia in a few days and the immediate future of air travel looked very uncertain.

Nevertheless, we addressed the business at hand and the two sides presented fascinating results with both groups showing evidence of linkage on chromosome 9 near *CDKN2A*, a region we were very familiar with from our melanoma studies. The genotyping was still to be completed by each group; and when the final results were analyzed, the evidence for linkage to this region had faded away. The marginal evidence was at its best for linkage on a region of chromosome 10. These results were published in the *American Journal of Human Genetics* in 2005 (Treloar et al., 2005). We obtained an NIH grant to conduct follow-up genotyping across this region. However, a curious fact is that the fine mapping and subsequent genome-wide association study (GWAS) results have not provided evidence of association on chromosome 10 (Painter, Nyholt et al., 2011), but there is association in the region of the original linkage evidence on chromosome 9 (Nyholt et al., 2012).

New approaches were needed and this corresponded with the development of high-throughput genotyping chips and GWAS. We were successful with National Health and Medical Research Council and Wellcome Trust Funding for single nucleotide polymorphism genotyping of samples from Brisbane and Oxford. At QIMR, we conducted replication genotyping in a sample from the Nurses' Health Study from Boston. We published the first GWAS study for European women in 2011 (Painter, Anderson et al., 2011). We identified one novel region on chromosome 7 and replicated a result published by a Japanese group the year before of association on chromosome 1 (Painter, Anderson et al., 2011). We contacted the Japanese group and the next year completed a meta-analysis of data from the two groups, replicating both earlier results and discovery of novel associations for a further five genomic regions (Nyholt et al., 2012). The studies continue with the International Endometriosis Genetics Consortium that has greatly expanded from the early days with just Brisbane and Oxford. In 2017, we published a meta-analysis reporting a total of 14 'hits', and this has expanded to 44 hits with analysis of 60,000 cases likely to be published this year. The research continues to expand in other ways, and this is but one example of how the foundations were firmly laid by Nick's drive and enthusiasm for the project.

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