



Contents lists available at ScienceDirect

NeuroToxicology



Full Length Article

Genetic variation associated with the occurrence and progression of neurological disorders

Julian Little, Dr.^{a,*}, Caroline Barakat-Haddad^b, Rosemary Martino^{c,d,e},
Tamara Pringsheim^f, Helen Tremlett^g, Kyla A. McKay^g, Pascal van Lieshout^{c,e,h,i},
Stephanie J. Walsh^j, James Gomes^k, Daniel Krewski^{a,l,m}

^a School of Epidemiology, Public Health and Preventive Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Canada

^b Faculty of Health Sciences, University of Ontario Institute of Technology, Canada

^c Department of Speech-Language Pathology, University of Toronto, Canada

^d Health Care and Outcomes Research, Krembil Research Institute, University Health Network, Canada

^e Rehabilitation Sciences Institute, University of Toronto, Canada

^f University of Calgary and the Hotchkiss Brain Institute, Calgary, AB, Canada

^g Faculty of Medicine (Neurology), Djavad Mowafaghian Centre for Brain Health, Vancouver Coastal Health Research Institute, University of British Columbia, Canada

^h Department of Psychology, University of Toronto, Canada

ⁱ Toronto Rehabilitation Institute, University Health Network, Canada

^j Newfoundland and Labrador Centre for Health Information, 70 O'Leary Avenue, St. John's, NL, Canada

^k Interdisciplinary School of Health Sciences, University of Ottawa, Ottawa, ON, Canada

^l McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada

^m Risk Sciences International, Ottawa, Ontario, Canada

ARTICLE INFO

Article history:

Received 23 September 2016

Accepted 23 September 2016

Available online xxx

Keywords:

Neurological condition

Onset

Progression

Genetic variation

Familial association

Genome wide association

ABSTRACT

This paper presents an overview of genetic variation associated with the onset and progression of 14 neurological disorders, focusing primarily on association studies. The 14 disorders are heterogeneous in terms of their frequency, age of onset, etiology and progression. There is substantially less evidence on progression than onset. With regard to onset, the conditions are diverse in terms of their epidemiology and patterns of familial aggregation. While the muscular dystrophies and Huntington's disease are monogenic diseases, for the other 12 conditions only a small proportion of cases is associated with specific genetic syndromes or mutations. Excluding these, some familial aggregation remains for the majority of cases. There is considerable variation in the volume of evidence by condition, and by gene within condition. The volume of evidence is greatest for Alzheimer's disease, Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis. As for common complex chronic diseases, genome wide association studies have found that validated genomic regions account for a low proportion of heritability. Apart from multiple sclerosis, which shares several susceptibility loci with other immune-related disorders, variation at *HLA-DRB5* being associated both with Parkinson's disease and Alzheimer's disease, and the association of the *C9orf72* repeat expansion with ALS and frontotemporal degeneration, there was little evidence of gene loci being consistently associated with more than one neurological condition or with other conditions. With the exception of spina bifida, for which maternal *MTHFR* genotype is associated with risk in the offspring, and corroborates other evidence of the importance of folate in etiology, there was little evidence that the pathways influenced by genetic variation are related to known lifestyle or environmental exposures.

© 2016 Published by Elsevier B.V.

* Corresponding author.

E-mail address: jlittle@uottawa.ca (J. Little).

Key scientific facts

- Only a small proportion of cases of most neurological disorders is associated with specific genetic syndromes or mutations.
- However, genetics plays a more important role in monogenic diseases such as the muscular dystrophies and Huntington's disease.
- The volume of evidence on genetic associations is greatest for Alzheimer's disease, Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis.
- For most neurological diseases, there is substantially less evidence on genetic risk factors for progression than onset.
- Genome wide association studies have found that validated genomic regions account for a low proportion of heritability.
- There was little evidence of gene loci being consistently associated with more than one neurological condition.

1. Introduction

Neurological disorders are heterogeneous in terms of their frequency, age of onset, etiology and progression. These differences have generated a number of challenges for investigators, as is reflected in the volume and diversity in the nature of the evidence regarding risk factors for onset and progression. This paper is based on a set of systematic reviews of risk factors for onset and progression of 14 neurological disorders as described in companion papers (Donnan et al., 2016a, 2016b; Walsh et al., 2016; van Lieshout et al., 2016; Barakat-Haddad et al., 2016; Wang et al., 2016; Martino et al., 2016; Hersi et al., 2016a; McKay et al., 2016; Quach et al., 2016; Morrissey et al., 2016; Krewski et al., 2016), following a common methodological approach (Hersi et al., 2016b). We present an overview of genetic variation associated with recurrence and progression of each of these disorders, focusing primarily on association studies. We consider the extent to which the genetic variants associated with the conditions overlap across conditions, and whether they point to pathways which have been implicated in studies focused on environmental risk factors as identified in the systematic reviews.

We first consider four conditions – spina bifida, hydrocephalus, cerebral palsy and muscular dystrophy – in which all or a substantial proportion of cases are congenital. Second, we consider three disorders that occur in young people, although not exclusively so – Tourette's syndrome, epilepsy and dystonia. Third, we consider two rare disorders that have a poor prognosis, specifically Huntington's disease and amyotrophic lateral sclerosis. Last, we consider conditions that are fairly common, and which have been investigated in large numbers of genetic association studies focusing on common variants – Parkinson's disease, Alzheimer's disease, multiple sclerosis and brain tumours.

1.1. Spina bifida

Spina bifida is a neural tube defect. Much of the evidence about genetic and other risk factors derives from studies in which neural tube defects of all types were combined (Little, 1992). The risk of a neural tube defect occurring in a full sibling of an index case is around 4%, and most studies show a higher recurrence risk after two or more affected births than after one affected birth (Little,

1992). A small proportion of cases are associated with specific genetic syndromes, notably Meckel's syndrome, and there are isolated reports of families exhibiting an X-linked mode of inheritance for neural tube defects (Little and Nevin, 1992). Substantial geographical variation in prevalence of birth, secular trends, seasonal variation (which has become attenuated in areas where prevalence at birth has declined), migrant studies, investigations of variation by socio-economic status point to a major role of environmental factors in etiology. A major focus of research was on diet and vitamin intakes in particular, which cumulated in randomized control trials showing that periconceptional folic acid supplementation was associated with a reduced risk of recurrence (MRC Vitamin Study Research Group, 1991) and first occurrence (Czeizel and Dudas, 1992; Berry et al., 1999) and has in turn driven decisions to fortify grains with folic acid in Canada, the United States, parts of Latin America and parts of Australia (Berry et al., 2010).

Evidence of genetic factors being involved in the etiology of neural tube defects derives from twin studies, with concordance rates in monozygotic twins being greater than those in dizygotic twins (both direct evidence and indirect evidence from comparison of same sex and opposite sex twins) and from studies of risk to first, second and third-degree relatives (Little, 1992; Little and Nevin, 1992).

As documented in the companion paper by Donnan et al. (2016a), only one meta-analysis of genetic factors associated with spina bifida was identified. This related to two common alleles (C677T and A1298C) of the gene encoding the 5,10-methylenetetrahydrofolate reductase (MTHFR) enzyme, and included data on genotypes of 675 mothers of cases and 1559 mothers of controls from eight studies, 15 studies of the genotype of the index individual, and five studies of the genotype of the father (Botto and Yang, 2000). The analysis showed an increased risk of spina bifida for the offspring of mothers homozygous for the C677T allele, a somewhat lower magnitude of risk for index individuals who were homozygotes, and no effect apparent for the offspring of fathers who were homozygous for this allele. Davey Smith and Ebrahim (2003) have interpreted this pattern of associations as indicating that the intra-uterine environment, influenced by maternal TT genotype, rather than the genotype of offspring, influences the risk for spina bifida, which is consistent with the evidence from the RCTs. The magnitude of the maternal effect has remained apparent in a more recent meta-analysis of neural tube defects (Yan et al., 2012).

Less evidence was available for the A1298C allele and the studies that investigated this were very different in design, precluding pooling estimates of risk (Botto and Yang, 2000). The individual studies had mixed results, and overall the evidence was interpreted as suggesting that this variant does not appear to have an impact on the risk for spina bifida. A meta-analysis of the association between this variant and neural tube defects in 1761 mothers of cases and 2869 mothers of controls from 19 studies, genotypes of index cases and controls from 18 studies, and paternal genotypes from eight studies did not show any associations (Wang et al., 2012).

Primary studies identified from the HuGE Navigator also have focused on MTHFR variants and variants of other genes putatively affecting folate metabolism (Donnan et al., 2016a). These studies indicate unclear associations between MTHFR and spina bifida occulta (Relton et al., 2003; Eser et al., 2010). In single studies, there were positive associations between spina bifida in the offspring and maternal homozygosity for the 19 base pair deletion for the dihydrofolate reductase (DHFR) gene (Johnson et al., 2004) and the A80G variant of the RFC1 folate carrier gene (Relton et al., 2003).

Over a hundred candidate genes other than those involved in folate metabolism have been investigated for genetic association

متن کامل مقاله

دریافت فوری ←

ISIArticles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات