Genetic Architecture of Grey Matter - A Review

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Article History:
Received on: 23 Jul 2020
Revised on: 22 Aug 2020
Accepted on: 23 Aug 2020

Keywords:
Grey Matter, Genetic Influence, Genetic Factors, Cortical Thickness, Brain Mapping

ABSTRACT
Genetic architecture explains about characteristics of different types of genetic variants which affect the traits for heritable variability. The present review is to document the deeper understanding of the genetic architecture of grey matter obtained from reliable sources of information which are associated with grey matter density and volume, cortical thickness, surface area, genetic variants, genetic heritability and genetic effects including Alzheimer disease, Huntington disease and some various diseases. The literature search on genetic architecture was carried out for papers published by google scholar and PubMed with the intention of retrieving all original reports that were relevant to it. The quality assessment of selected studies was conducted for 77 collected articles. This review is an attempt to update recent advances and provide a deeper understanding of the genetic architecture of grey matter which benefits scientists and geneticists.

INTRODUCTION
Genetic architecture identifies heritable phenotypic variability which is responsible for the features of genetic variation depending on the type of genetic variants influencing their trait, extent of effects, environment and their interaction with each other (Mackay, 2001). Understanding genetic architecture is essential for many biological questions, includes speciation, the Evolution of sex and recombination, survival, inbreeding, understanding diseases and understanding the processes and genetics of adaptation and population differences (Hansen, 2006). Genetic factors that influence the surface region of cortex and its thickness, all related to various clinical symptoms, including attention deficit hyperactivity disorder (ADHD), schizophrenia, depression and autism (Ober, 2008). The complex structure of the human brain could be much affected by genetic effects. Genetic architecture concept is applicable to traits like Huntington's disease, which is caused by a rare deterministic variant (Timpson, 2018).

Studies have shown that genetic factors constitute about 60% of subcortical structural variation (Braber, 2013). Each individual genetic architecture composed of common rare variants which acting individually and in combinations, confer disease risk. The cell-specific and/or context-dependent functional implication of risk variants associated with brain disease may be solved (Schadt, 2008; Keerthana and Thenmozhi, 2016). As advancement in larger studies has explained more about their genetic architecture, the need to elaborate additional architecture has become evident. Even if we have full knowl-
edge about the genetic architecture of grey matter; (Pratha and Thenmozhi, 2016; Nandhini, 2018; Subashri and Thenmozhi, 2016) deep understanding is required for functional genomic architecture, and so results will act as a tool for scientists to help in addressing critical questions about the brain’s genetic factors and how they contribute to other conditions.

Over the past years, various research done by our team was on Osteology (Choudhari and Thenmozhi, 2016; Hafeez and Thenmozhi, 2016; Kannan and Thenmozhi, 2016), stature estimation, (Krishna, 2016), use and ill effects of electronic gadgets (Sriram, 2015; Thejeswar and Thenmozhi, 2015), animal studies (Seppan, 2018) and in few other fields (Menon and Thenmozhi, 2016; Samuel and Thenmozhi, 2015). There is a lack of much information on the current topic of the genetic architecture of grey matter. Hence, the aim of this review was to elaborate on the genetic architecture of grey matter which is associated with genetic variants, cortical thickness and surface area, genetic heritability, genetic factors, grey matter volume and density and genetic effects including several diseases.

MATERIALS AND METHODS

This article is a narrative review of primary research literature obtained from the following database: PubMed, Scopus and google scholar.

Included criteria Research articles, articles discussion about pros and cons

Excluded criteria Articles collected were placed on the time period between 1990 - 2020 and abstract of non - English were excluded. All international articles were searched for by relevance to the genetic architecture of grey matter determined by article title, abstract and complete article—the keywords of this study utilized to consult the database. Reference lists of relevant articles were used. A checklist was assessed for the quality of selected studies using a quality assessment tool and graded as strong, moderate and weak (Table 1)

RESULTS AND DISCUSSION

Grey matter density and volume

Grey matter density and volume link with higher standards of intelligent scores developed with age in healthy children for intelligent scores. More severe obstructive sleep apnea in children had a deficiency of grey matter density in prefrontal regions (Chan, 2014). Recently (Adrián-Ventura, 2020) stated that Spanish dyslexic children show less grey matter volume in the left occipitotemporal cortex revealed that the area which influences brain size and age were found to be frontal and temporal neocortical regions and also increases in grey matter density were found to be temporal (Brodmann’s area - 21,37,22,42), prefrontal (Brodmann’s area - 9,10,46) and parietal (Brodmann’s area - 43,3) in healthy adults.

Cortical surface area and thickness

Cortical surface area and thickness closely linked to grey matter concentration. Different longitudinal changes were associated with cortical surface area and its thickness on adult life span and found that accelerating changes increases with age in occipital and temporal cortices and decelerating changes in anterior and prefrontal cingulate cortices and results showed that it exists throughout a lifetime (Wierenga, 2014). Interactive effects of gender and sexual orientation on the surface area were found to be the region of the left rostral middle frontal lobe, inferior temporal lobe, left middle temporal lobe, lateral occipital lobe, caudal middle frontal lobe, pars opercularis and regarding grey matter volume, an interaction found in inferior frontal gyrus of left pars opercularis and thickness interactions were not found in any regions. Similarly, (Abé, 2018) study revealed that in medial occipital cortices found larger surface area bilaterally, which was compared with heterosexual women.

Genetic Variants

Human subcortical brain structure is influenced by common genetic variants but is seldom considered. ATXNT- ataxia causing gene influences grey matter volume causes polyglutamine expansion in rare brain disorder Heijden and Der (2013). Recently, genome-wide association study identified single nucleotide polymorphism (SNPs) and rs4746720 near the gene SIRT1 showed significant association with grey matter density in two brain cortical regions (i.e., orbital part of left inferior frontal gyrus and right inferior frontal gyrus with major depressive disorder (MDD) (Rao, 2020).

Genetic Heritability

A previous study suggested that some of the significantly heritable functional networks, making them appropriate targets for more specific genetic analysis (Feng, 2020). This study proposed an analysis of partitioned heritability for multidimensional traits, and it could enhance the statistical power of heritability analysis. (Foo, 2020) showed resting-state brain functional networks from low to moderate heritability in healthy adults. The first
| S No | Author                  | Year   | Type of Study                  | Key Points                                                                                                                                                                                                 | Quality of Study |
|------|-------------------------|--------|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| 1    | (Adrián-Ventura, 2020)  | 2020   | Randomised Controlled Study    | Spanish dyslexic children show less grey matter volume- left occipito-temporal cortex-area-influence brain size and age-frontal and temporal neocortical regions -increases in grey matter density were found to be temporal (Brodmann's area - 21, 37, 22, 42), pre-frontal (Brodmann's area - 9, 10, 46) and parietal (Brodmann's area - 43, 3) in healthy adults. | Moderate         |
| 2    | (Wierenga, 2014)        | 2014   | Randomized Control Study       | Accelerating changes increases with age in occipital and temporal cortices-decelerating changes in anterior and prefrontal cingulate cortices- results showed it exists throughout lifetime.                                                                                       | Strong           |
| 3    | (Abé, 2018)             | 2018   | Case-controlled study          | In medial occipital cortices found larger surface area bilaterally-compared with heterosexual women.                                                                                                                                                             | Moderate         |
| 4    | (Rao, 2020)             | 2020   | Systemic review                | Identified single nucleotide polymorphism (SNPs) and rs4746720 near the gene SIRT1 showed significant association with grey matter density in two brain cortical regions (i.e., orbital part of left inferior frontal gyrus and right inferior frontal gyrus.)                          | Moderate         |
| 5    | (Joshi, 2011)           | 2011   | Randomised controlled study    | Showed-medial frontal regions strong sulcal surface area & width heritability-confirms that temporal lobe, central sulcus, corpus callosum area shows high heritability in temporal and prefrontal lobes for cortical thickness and surface area.                                                        | Moderate         |

*Continued on next page*
| S No | Author       | Year | Type of Study          | Key Points                                                                                                                                                                                                 | Quality of Study |
|------|--------------|------|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| 6    | Vilgis, 2016 | 2016 | Randomised controlled study | Shows lower local grey matter volumes significantly-in right parietal, bilateral frontal and right temporal regions compared to typically developing children-results-right caudate nucleus age and volume are more strongly related more in ADHD when compared to TD. | Weak             |
| 7    | Jubault, 2011| 2020 | Case-controlled study   | Cortical thickness correlates with left temporal pole and duration of disease and prominently found in Broca's area, and bilateral occipital cortex shows PD related visual-spatial defect.                           | Weak             |
| 8    | Taylor, 2020 | 2020 | Systemic review        | Identified more than 300 genetic variants which may influence the cortical structure and also play a role in neurological and psychiatric conditions.                                                          | Weak             |
| 9    | Timpson, 2018| 2018 | Systemic review        | Shows variables in place and time-influenced phenotypic measurement theoretically contributed by genetic determinants-useful for identifying prognosis, etiology for most common disease.                      | Moderate         |
| 10   | Yu, 2020     | 2020 | Systemic review        | Found that tumours powered by this type of variants have divergent molecular properties-can manifest in the selective brain hyperexcitability initiation and synaptic constituency remodelling.           | Moderate         |
evidence of structural covariation heritability in grey matter revealed important sex and age-related differences among non-human primates across largely heritable source-based morphometry (SBM) components (Hopkins, 2019). Relevant studies showed that medial frontal regions strong sulcal surface area & width heritability and also confirms that temporal lobe, central sulcus, corpus callosum area shows high heritability in temporal and prefrontal lobes for cortical thickness and surface area (Joshi, 2011).

Genetic Factors
(Xia, 2017) showed the influence of global grey by genetic effects and volume of white matter intracranial in infants which shows an association between genetic risk for both ASD and schizophrenia and also found that global brain tissue volumes had no association. Emil F. Coccaro et al. reported modest in aggression; inverse association with grey matter volume in the lateral prefrontal cortex, medial prefrontal cortex and genetic factors for phenotypic corrections between aggression and lateral PFC was found to be 63.7% and between aggression and medial PFC was found to be 85.3% (Coccaro, 2018).

Genetic Effects

Attention Deficit Hypertensive Disorder (ADHD)
The ADHD group shows lower local grey matter volumes significantly within clusters in the right parietal, bilateral frontal and right temporal regions compared to typically developing children and also revealed that right caudate nucleus age and volume are more strongly related more in ADHD when compared to TD (Vilgis, 2016).

Huntington's Disease (HD)
Multidisciplinary rehabilitation can reduce the loss of hypothalamic volume and maintain peripheral brain-derived neurotrophic factor (BD NF) levels with preclinical Huntington's disease in individual person (Stahl and Feigin, 2020).

Alzheimer Disease (AD)
Severity and presence of regional grey matter reduction, which was seen in the region of posterior and temporal cingulate precuneus and gyrus mainly to the right associate with Alzheimer disease (Frisoni, 2002). (Jack, 1997) shows AD has more sensitive to reduction in medial temporal grey matter density even in very mild patients and also demonstrates grey matter density reduction found outside the medial temporal lobe confined to areas in the precuneus, temporal gyri, insular and a cingulate nucleus which was sensitive to temporoparietal atrophy associated with disease progression.

Parkinson Disease (PD)
Dementia with mild cognitive impairment was found to be lost in grey matter, and Parkinson disease correlated to global cognitive score shows far less extensive changes (Hall, 2016). In early Parkinson disease clearly predicted the pattern of cortical surface area and thickness and concluded that cortical thickness correlates with left temporal pole and duration of disease and prominently found in Broca's area and bilateral occipital cortex shows PD related visual-spatial defect (Jubault, 2011).

Advance Research
The first genetic map is shown in the cerebral cortex clearly identified more than 300 genetic variants which may influence the cortical structure and also play a role in neurological and psychiatric conditions (Taylor, 2020). Most recently, (Yu, 2020) illustrate about Glioblastoma which is known to be a universally lethal form of brain cancer; develop a high recorded study in vivo screening platform and discover several driver gene variants called PIK3CA. It also found that tumours powered by this type of variants have divergent molecular properties which can manifest in the selective brain hyperexcitability initiation and synaptic constituency remodelling.

Genetic architecture assessed by difference through genome-wide association studies in genetic variants and shows variables in place and time which influenced phenotypic measurement theoretically contributed by genetic determinants which can be useful for identifying prognosis, etiology for most common disease (Timpson, 2018). Pathway of particular genes changes in fundamental understanding which is unclear about disease pathophysiology because common variants show very small effects. Last recent study was unclear about many diseases and determined very few common variants increase 50% of inherited attributable to common alleles (Nicolas, 2016).

The limitations in this review were collected retracted articles which were used as references relevant to grey matter associated with genetic factors, genetic influence and disease related to it. Future study about this topic has to be reviewed for improved technology for large scale, which can be detected using less cost-effective sequencing approach, the goal of making complete sets of genes for research tool clinical applications.

CONCLUSIONS
This review is an attempt to update recent researches in various genetic effects and abnormalities associated with grey matter. This provides a
deeper knowledge of the genetic architecture of grey matter, and it would be a source for scientists to numerous conditions reflecting differences in exposures and genetic factors, so further research had to be done to know about the impact of genetic influence in grey matter.

**Funding Support**

The authors declare that they have no funding support for this study.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

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