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The barrier, airway particle clearance, placental and detoxification functions of autism susceptibility genes

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ABSTRACT

Even taking problems of diagnosis into account, a five-fold increase in the incidence of autism in recent decades, in the absence of any known changes in the human gene pool suggests a strong environmental influence. Numerous pollutants have been implicated in epidemiological studies, including pesticides, heavy metals, industrial solvents, air pollutants, particulate matter, bisphenol A, phthalates and flame retardants. Many genes have been implicated in autism, some of which are directly related to detoxification processes. Many are also expressed prenatally in the frontal cortex when the effects of such toxins on neurodevelopment are most relevant. To gain access to the foetal brain, toxins must pass placental and blood/brain barriers and access to maternal or children's blood necessitates passage across skin, airway and intestinal barriers. Literature survey of a subset of 206 genes, defined as prime autism susceptibility candidates from an Autworks/Genotator analysis, revealed that most could be related to barrier function at blood/brain, skin, intestinal, placental or other interfaces. These genes were highly enriched in proteome datasets from blood/brain and placental trophoblast barriers and many localised to skin, intestinal, lung, umbilical and placental compartments. Many were also components of the exosomal/transcytosis pathway that is involved in the transfer of compounds across cells themselves, rather than between them. Several are involved in the control of respiratory cilia that sweep mucus and noxious particles from the airways. A key role of autism susceptibility genes may thus relate to their ability to modulate the access of numerous toxins to children, and adults and, during gestation, to the developing foetal brain.

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1. Introduction

The incidence of autism spectrum disorders in the UK increased 5 fold in the 1990's, reaching a plateau in the 2000's up to 2010 (Taylor et al., 2013). In the USA, this increase has persisted with an incidence rising 2.2 fold from 2000 to 2010 (Wingate et al., 2014). These figures may in part be confounded by over- or misdiagnosis (Blumberg et al., 2015; Polyak et al., 2015) but the underlying increase, in the absence of any known changes in the human gene pool, suggest a strong environmental influence. Recent reviews have highlighted the dangers of environmental neurodevelopmental toxicants (pesticides, phthalates, polychlorinated biphenyl, solvents, toxic waste sites, air pollutants and heavy metals) in relation to autism and related disorders (Grandjean and Landrigan, 2014; Rossignol et al., 2014). Many such compounds are endocrine disruptors capable of modifying foetal and childhood neurodevelopmental pathways (de Cock et al., 2012; Gore et al., 2014; Kajta and Wojtowicz, 2010; Kalkbrenner et al., 2014). Endocrine disruptors have been associated with autism, IQ loss and associated intellectual disability, attention-deficit hyperactivity disorder, childhood obesity, adult obesity and diabetes, cryptorchidism, and male infertility. It has been estimated that the burden of health and economic costs attributable to endocrine disruptor exposure in the European Union amounts to 163 billion euros (Trasande et al., 2015, 2016).

Many genes have been implicated in autism and in a twin study susceptibility to autism spectrum disorders was suggested to have moderate genetic heritability and a substantial shared twin environmental component (Hallmayer et al., 2011). Autism is a neurodevelopmental disorder and the symptoms and pathology clearly neurally related. Autism related genes are preferentially expressed prenatally in the frontal cortex suggesting that an inherent genetic susceptibility may be confined to this period (Birnbaum et al., 2014) The high component of chemical pollutant risk is also concentrated in the prenatal period (Matelski and Van de, 2016).

Many studies, not unnaturally, have focussed on the neurobiological roles of autism susceptibility genes (Berbel et al., 2014; Chiocchetti et al., 2014; Kazdoba et al., 2016; Kleijer et al., 2014). Pathway analyses of autism genes have identified disruption of many functions including protein synthesis, transcriptional/epigenetic regulation, neurodevelopment and synaptic and immune signalling (Estes and McAllister, 2015; Sahin and Sur, 2015; Voineagu and Eapen, 2013). Certain autism susceptibility genes including paraoxonase (PON1), glutathione transferases (GSTM1 and GSTP1), δ-aminolevulinic acid dehydratase (ALAD), the iron transporter SLC11A3 and the metal regulatory transcription factor 1 modify (MTF1) can be directly related to detoxification pathways (Rossignol et al., 2014).

To gain access to the developing brain, chemicals have to traverse several barrier systems including the placental and blood brain barriers, while the passage of such compounds on the maternal side or in childhood depends on other barriers including skin, airway and intestinal interfaces. Intestinal barrier function is compromised in autistic subjects and their first degree relatives (de Magistris et al., 2010). Compromised placental function has also been associated with autism as evidenced by a high incidence of pre-eclampsia and of trophoblast inclusions in the mothers of autistic children (Anderson et al., 2007; Walker et al., 2013, 2015). Modified transport of amino acids (alanine, tyrosine) has also been observed in skin fibroblasts from autistic patients (Fernell et al., 2007). Comorbidity between autism and atopic dermatitis has also been observed, with the latter characterized by epidermal permeability defects (Billeci et al., 2015). Psoriasis is also common in autistic subjects (Wu et al., 2015; Zerbo et al., 2015) and this condition also affects skin permeability (Stawczyk-Macieja et al., 2015).

The importance of barrier function in relation to multiple environmental pollutants and autism, particularly during critical developmental periods when barrier components are still being formed has also been noted by others (Julio-Pieper et al., 2014; Liu et al., 2005; Ratajczak, 2011; Viggiano et al., 2015; Wong et al., 2015).

This article focuses on the barrier function of a subset of 206 autism susceptibility genes defined as prime autism susceptibility candidates based on an Autworks study of the Genotator association database (Nelson et al., 2012). The results suggest that a common feature of these candidates relates to diverse barriers in the human body.

2. Methods

Genes associated with autism are catalogued at the Autworks database using a ranking system derived from analysis of the Genotator association database (Nelson et al., 2012; Wall et al., 2010) http://tools.autworks.hms.harvard.edu/gene_sets/580/genes. This provided a list of 206 autism susceptibility genes regarded as prime susceptibility candidates. The genes and their definitions are listed in supplementary data. HUGO Gene Nomenclature Committee gene symbols are used, and those belonging to this list are highlighted in bold throughout the text.

The tissue and cellular distribution of the 206 Autism genes were analysed using the functional enrichment analysis tool (FUNRICH) (Pathan et al., 2015). http://funrich.org/index.html. This tool derives proteomic and genomic distribution data from >1.5 million annotations. It provides the total number of genes in datasets from each region sampled and returns the significance of any enrichment for members of the uploaded 206 autism genes, using the hypergeometric probability test.

Autism gene enrichment was also analysed in two published blood brain barrier proteome datasets of mouse cerebral arteries (6620 proteins) (Badhwar et al., 2014) and mouse brain microvessel membranes and basal lamina components (4054 proteins) (Chun et al., 2011), as well as in a proteome dataset of the placental syncytial trophoblast (Vandre et al., 2012). Ciliary proteomic datasets from the choroid plexus (Narita et al., 2012) and the membrane proteome of respiratory cilia were also analysed (Kuhlmann et al., 2014).

The presence of the autism genes in exosomes (a means of transit across rather than between cells (Haqqani et al., 2013; Mathivanan et al., 2010; Sun et al., 2013)) was assessed using ExoCarta (http://www.exocarta.org) a manually curated database of exosomal proteins, RNA and lipids (Simpson et al., 2012).