

Association of hypomelanotic skin disorders with autism: links to possible etiologic role of vitamin-D levels in autism?

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Vitamin D is crucial for several key physiological processes, including brain development, DNA repair, and regulation of many genes. Much evidence indicates prenatal and early postnatal vitamin-D deficiency increases autism risk, probably through multiple effects, including impaired brain development and increased de novo mutations. High autism rates in several genetically based hypomelanotic skin disorders are puzzling, because ultraviolet-B radiation (UVB) in sunlight acting on skin is a key source of vitamin-D, and lighter skin protects against vitamin-D deficiency, especially at high latitudes. We consider two hypotheses to help explain autism's co-morbidity with hypomelanosis. 1) Because genetic and epigenetic variants that produce hypomelanosis help protect against vitamin-D deficiency, they increase reproductive fitness of individuals who also have other autism risk factors. 2) Hypomelanotic children have increased autism risk because photosensitivity and skin-cancer concerns lead families to excessively reduce children's sun exposure. Hypothesis testing could involve studies comparing genomes, epigenetic markers, skin pigmentation, and vitamin-D levels in autistic individuals with and without hypomelanosis, their relatives and controls. Conducting such studies in samples from regions that differ widely in UVB availability would provide particularly valuable data. Support for either hypothesis would elucidate vitamin-D's role in autism and suggest vitamin-D enhancement may aid treatment and prevention of autism.

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Introduction: Human skin color and vitamin-D

HUMAN SKIN COLOR VARIES GREATLY among different geographical regions of the world, with people whose ancestral origin is in the tropics and sub-tropics having darker skin pigmentation than people with origins in middle and higher latitudes (1). Production of vitamin-D and the quantity of UVB radiation available in a particular region also influence diversity and distribution of human skin coloration (2). Yuen and Jablonski (3) review evidence that lighter skin color evolved through natural selection at higher latitudes of genes that facilitate vitamin-D production under conditions of low UVB radiation, thereby reducing morbidity and mortality associated with vitamin-D deficiency. Vitamin-D deficiency has been associated with a number of health problems, including rickets, osteomalacia, osteoporosis, certain cancers, and viral and bacterial infections (3). Recent studies have also linked vitamin-D deficiency to increased risk of autism (4, 5), leading Eyles (6) to ask whether skin color may modify the risk for autism.

Vitamin-D, brain development and embryonic survival

Recent studies suggest that vitamin-D availability and metabolism may have notable effects on mental health (7, 8). The mechanisms through which these effects could occur is not fully understood as yet, but animal studies have shown that low prenatal vitamin-D 3

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in utero can produce abnormal brain development characterized by increased brain size, enlarged ventricles, reduced brain content of nerve growth factor, and distortion in brain shape (9, 10, 11). It has also been reported that presence of adequate vitamin-D in follicular fluid plays a significant role in human embryonic survival in vitro and also aids with implantation (12, 13).

Genetics of autism and neuro-imaging findings

Autism is a syndrome consisting of a set of developmental and behavioral features that include impairment in areas of social interaction and communication, as well as restricted, repetitive and stereotyped patterns of behavior and interests. Evidence for the importance of genetic factors in the etiology of autism comes from many sources, including twin and family studies (14). Autism is, e.g., 50 to 200 times more prevalent in the siblings of autistic probands than in the general population. Among probands' relatives who do not have frank autism, there is also an increased prevalence of milder forms of developmental difficulties related to communication and social skills (15). Concordance rates for autism range from 36% to 96% in monozygotic twins but only 0% to 27% in dizygotic twins (15).

Although the heritability of autism has been estimated to be as high as 90% (16), the genetic factors are heterogeneous, complex,

and for the most part poorly understood. Epigenetic and environmental factors are also etiologically significant in autism. The precise mechanisms of genetic inheritance of autism are being explored through methods of whole-genome screening, cytogenetic studies, and evaluation of candidate genes (14). In studies of candidate genes, there are replicated findings of increased risk for autism associated with variants in single genes on chromosomes 2, 3, 4, 6, 7, 10, 15, 17 and 22 (17).

Cytogenetic studies have implicated abnormalities at the 15q 11-q 13 locus in individuals with autism (14, 18), and chromosome-15 abnormalities have also been documented in several hypomelanotic skin disorders associated with autism (18). It has been suggested that this association may be due either to tight linkage between genes underlying autism and those underlying the hypomelanotic skin disorders, or to shared brain pathophysiology (18).

Genome-wide association studies have implicated slight effects on autism risk with genetic variants at the 5p14.1 and 5p15 loci (19, 20). Also, replicated copy number variations, found in genome-wide association studies to be more common in individuals with autism than in controls, are located on chromosome regions 1q21, 2p16.3, 3p25-26, 7q36.2, 15q11-13, 16p11.2 and 22q11.2 (17).

Future directions for genetic research in autism lie in identifying specific gene-environment interactions that produce symptoms of autism. Research on genetic factors in autism must overcome challenges of elucidating the roles of genetic heterogeneity, epigenetic mechanisms, and environmental modifiers.

Neuro-imaging findings in autism, though not diagnostic, have consistently revealed enlargement in cerebral volume that affects both gray and white matter, as well as enlarged ventricles (21, 22, 23). Neuro-imaging findings in autism also include abnormalities in brain chemistry, serotonin synthesis, and brain electrophysiology (21, 22, 23); these structural and functional abnormalities resemble those found in animals with prenatal exposure to vitamin-D deficiency (9, 10, 11).

Vitamin-D etiological hypothesis and autism

Environmental as well as genetic factors are important in the etiology of autism (24). Cannell (25) and others (4, 5) have presented evidence that vitamin-D deficiency in utero and in early childhood is associated with an increased risk for autism. A number of studies have reported that different environmental factors contributing to vitamin-D deficiency are also associated with increased risk of autism (26, 27, 28, 29, 30).

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Human skin color is largely genetically determined, but environmental influences, particularly levels of exposure to UVB radiation, are also important (2, 31). Autism, like human skin color variation, may thus be influenced by an inter-play of genetic and environmental factors that affect human vitamin-D production (2). In addition, genes for melanin production and brain development may be tightly linked, and this linkage may further explain the association between autism and hypomelanotic skin disorders (18).

Evidence for an etiologic role of vitamin-D deficiency in autism includes, e.g., a higher prevalence of autism in populations born at higher latitudes, urban areas, or regions with intense air pollution and high precipitation – all environments where vitamin-D deficiency is likely to be more common because of

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reduced levels of UVB radiation essential for endogenous vitamin-D production (4, 32, 33). Moreover, autism is much more prevalent in dark-skinned individuals born at higher latitudes than in light-skinned indigenous inhabitants (32, 34, 35). In addition, children

with Williams Syndrome, who often have greatly elevated vitamin-D levels, usually show several behavioral phenotypes that are the opposite of those in autism (32). Estrogen and testosterone show different effects on metabolism of the active form of vitamin-D, a fact that may help explain the much higher prevalence of autism in males than females (32).

Complementary lines of evidence suggest that vitamin-D deficiency may also causally contribute to autism by increasing the frequency of de novo genetic mutations in the germ-cell lines of the parents of children who develop autism (33). A number of de novo mutations are associated with increased risk for autism, and vitamin-D deficiency is likely to contribute to de novo mutations because vitamin-D helps protect against oxidative stress, which is a key cause of DNA damage, and vitamin-D also aids in repair of DNA damage once it occurs (33, 36).

Physiological role of vitamin-D in autism

Activated vitamin-D is a steroid hormone that is present in a wide variety of human tissues, including the kidney (36). It exerts its influence on numerous tissues through autocrine and presumed paracrine functions (37). Activated vitamin-D acts as a molecular switch, like most steroid hormones, activating more than 200 target genes, thereby regulating gene expression through multiple mechanisms (38). Vitamin-D therefore may play a

major role in the etiology of autism by influencing expression of genes related to autism. An example of a gene that is implicated in autism and may have its expression influenced by vitamin-D is *Slc25a12* (39, 40).

Cannell and Hollis (36) have urged investigation of the clinical usefulness of vitamin-D in ameliorating symptoms of various disease conditions, based on its physiological role of regulating gene expression in many different body tissues. They (36) suggest that vitamin-D deficiency may contribute to increasing rates of a number of diseases in recent decades, in part because of medical advice to avoid sun exposure in order to reduce risk of skin cancer.

Hypomelanotic skin disorders and autism

A number of hypomelanotic skin disorders have been reported to occur co-morbidly with autism, and susceptibility genes for several of these hypomelanotic skin disorders have chromosomal loci that lie near the loci for several major susceptibility genes for autism. The hypomelanotic skin disorders that have been reported to occur co-morbidly with autism include oculocutaneous albinism (41, 42, 43), hypomelanosis of Ito (44, 45), tuberous sclerosis (14, 46, 47), Angelman syndrome (48, 49, 50, 51) and Prader-Willi syndrome (51, 52, 53).

Inconsistent findings on chromosomal abnormalities in hypomelanosis of Ito, together

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significant etiologic factors. Grafodatskaya et al (59) review evidence that several genetic syndromes that are co-morbid with autism show dysregulation of epigenetic marks that help regulate gene expression. The authors note that both genetic and environmental fac-

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tors can modify epigenetic marks, and they can do so in germ-line as well as somatic tissues. Moreover, because the epigenome can be influenced by mitotic cell divisions, it is more vulnerable to environmental factors than the genome. In Angelman and Prader-Willi syndromes, there are disruptions of normal genetic imprinting mechanisms, with a resultant lack of the normal patterns of expression of respectively, maternal or paternal, sets of genes on chromosome region 15q11-13.

Presentation of the hypotheses

We consider two hypotheses that may help account for autism's association with hypomelanotic disorders.

Hypothesis 1). Because genetic and epigenetic variants that produce hypomelanotic conditions may help protect against vitamin-D deficiency, especially at higher latitudes, these variants may tend to decrease mortality – and increase the fertility – of individuals who also carry genetic or epigenetic factors that increase vulnerability to autism.

As was noted earlier, there is evidence that vitamin-D plays very important roles in regulating hundreds of genes, and that vitamin-D also has significant roles in modulating inflammatory processes, in promoting normal brain development, in combating infection – even in aiding embryonic survival and successful implantation (12, 13). Thus, if individuals carry etiologic factors that increase their vulnerability to autism, then the added presence of genetic variants associated with hypomelanosis that prevent vitamin-D deficiency may tend to put these individuals on a healthier developmental path with reduced risk of embryonic, fetal, and childhood mortality, as well as with milder symptoms that lead to increased reproductive success as adults. This could create natural selection processes that result in genetic and epigenetic etiologic factors for both autism and

hypomelanotic disorders occurring together in the population at above-chance levels.

Hypothesis 2). An alternative hypothesis that might explain the co-morbidity of autism with hypomelanoses is that children with hypomelanotic conditions will actually be more likely to develop autistic disorders, because, paradoxically, they will be more likely to be deficient in vitamin-D. This could result if the children and their parents tend to reduce the degree of children's exposure to bright sunlight, for reasons such as the children's photosensitivity and/or parental efforts to protect their children from sunburn and skin cancer. Those individuals with hypopigmentation may in fact tend to have abnormally low levels of vitamin-D as indicated by the study of Goswani et al (60). That study found that individuals from New Delhi with albinism or vitiligo universalis were much more likely than individuals without hypopigmentation to seek lower levels of sun exposure, with a resultant mean level of vitamin-D that was so low in the winter that it was outside the range considered to be adequate/healthy.

If low sun exposure in children with hypomelanoses does produce low levels of vitamin-D in these children, then vitamin-D deficiency could combine synergistically with other genetic and environmental contributors to promote development of autism, through several pathogenic mechanisms noted earlier. These

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mechanisms could include, for example, a) further dysregulation of various target autism-related genes important for brain development, because deficiency of vitamin-D impairs its ability to play its normal role in regulating genes, b) disruptive epigenetic effects on chromosomal regions that include multiple genes important for brain development, and c) impairment of vitamin-D's role in regulating inflammatory processes, thereby exacerbating neuro-inflammatory processes implicated in the pathogenesis of autism (61).

Testing the hypothesis

A key approach to testing these hypotheses would compare genomes, epigenetic marks, skin color, and serum and brain levels of the active form of vitamin-D in a) carefully diagnosed autistic individuals with and without comorbid hypomelanoses, as well as in b) their respective relatives and demographically matched controls. Data that included assessments of prenatal and early childhood levels of vitamin-D as part of longitudinal studies of large cohorts would be particularly informative. Studies of these variables in samples from different geographic regions would be a valuable complementary approach for testing the hypotheses. If either hypothesis is true, it would be expected that the frequency of co-morbid hypomelanotic skin disorders and autism would be higher in populations at higher latitudes, where the level of available UVB radiation is usually reduced compared to

middle and lower latitudes. It would therefore be important to include samples from tropical or sub-tropical regions, such as sub-Saharan African countries, with their abundant availability of UVB radiation that is so important for vitamin-D production, particularly in individuals who lack adequate vitamin-D from dietary sources or vitamin supplements. Hence, more epidemiological and genetic studies of autism in tropical regions such as sub-Saharan Africa are warranted.

Implications of the hypotheses

If results of the proposed tests support either hypothesis, they will provide important evidence for an etiologic role of vitamin-D deficiency in autism, and will elucidate how this deficiency interacts with other genetic and epigenetic factors that contribute to autism. These results would also support clinical investigations of whether vitamin-D supplements may aid treatment and prevention of autism.**H**

Competing interests

Authors declare no competing interest.

Authors' contributions

All authors contributed to the conception of the study. MOB wrote the initial draft of the Manuscript. MOB, KMM, DKK revised the manuscript. All authors read and approved the final draft of the manuscript.

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