Methylation and the Physical Exam:
Applying Physical Phenotypes to Clinical Practice

ABSTRACT:
An approach is presented for clinicians to address methylation defects through recognition of specific physical phenotypes found on the physical exam. Current research evidence is reviewed in support of the close relationship between methyl donor status, inherited genetic polymorphisms, and tissue shape and symmetry. A functional model of methylation-related genetic diseases and their corresponding physical phenotypes is presented. Important physical exam findings are discussed.

Keywords:
Methylation, Epicanthal Folds, Congenital Birth Defects, Single Nucleotide Polymorphisms, Scoliosis

INTRODUCTION:
We are carbon-based organisms and methylation is one of the most important processes in the human body. This process of one-carbon metabolism is ubiquitous, and when disturbed, creates widespread biochemical imbalance. Methylation defects range from minor biochemical changes to major physical, chemical, and mental disturbances. Due to the fact that methyl reactions are central to our biochemistry, it follows that abnormalities in such an important pathway would show up on the physical exam. This paper intends to highlight specific physical exam findings that have a strong relationship to methylation cycle imbalances. By reviewing the etiology of common methylation problems, a comprehensive list of methylation phenotypes is provided as a screening tool for identification on the physical exam.

Overview of the Methylation Phenotype
Dr. Robert Rakowski, DC, correctly points out that “if there is something wrong on the outside, then there is something wrong on the inside.” Methylation issues fit this concept well as we shall see. Essentially all inherited methylation issues result either from a single nucleotide polymorphism (SNP), such as MTHFR, MTR, PEMT, etc., or from a gamete or zygote that has an extra chromosome. Since the basis for methylation weakness is genetic, it is from our parents that these methyl issues are passed down. Targeted nutritional supplementation can saturate pathways and create a healthy biochemical environment that overcomes these genetic weaknesses.

The aim of this paper is to illustrate that all mid-line congenital defects such as congenital heart malformation, spina bifida, cleft palate, scoliosis, arachnodactyly, hemivertebra, hypertelorism, epicanthal folds, etc. are fundamentally methylation issues. In fact, this author suggests that all congenital limb length discrepancies, malformed organs, and basically all congenital defects which produce a deviation from typical human symmetry are due to methylation issues. As tissues grow and cells divide, if there is a deficit of methyl donors, some tissues may grow faster than others creating a deviation from the original “human blue print”. A recent paper from Bio Med Central illustrates this point clearly:

\[ \text{Folate metabolism can influence the final form of any growing tissue due not only to its participation in nucleic acid synthesis, but also to its known function in regulating DNA and protein methylation.} \]
If methyl donors are not functionally adequate during intensive cell division, then there is a high likelihood that tissue formation will be incomplete and asymmetrical. This phenomenon may occur during sex cell division, gestation, childhood, and/or puberty. During gestation these functional deficiencies may result in life-threatening congenital defects or chromosomal aneuploidy leading to a host of serious genetic diseases. However, if these functional deficiencies arise later during childhood and puberty, the defects may be more physically subtle but still have a profound effect on all aspects of the triad of health.

Gestation and Fetal Development
The most serious and rare methylation problems occur when a sex cell gamete ends up with an extra chromosome leading to lifelong genetic disease. Failure to properly methylate at this early stage can have disastrous consequences on the outcome of the pregnancy, and often results in miscarriage. If the gamete fails to divide correctly, whatever errors occur will be passed on to each of the roughly 100 trillion cells that follow. As women age their ability to methylate declines which increases the risk of birth defects such as spina bifida, Down’s syndrome and other genetic diseases. Also the risk of miscarriage increases with maternal age, further highlighting this relationship between maternal age, methylation status, and healthy pregnancy.

The most common scenario is a lack of methyl donors in the mother’s diet, often in combination with genetic SNPs from one or both parents, which causes any number of congenital abnormalities to form in utero. A lack of methyl molecules in the cellular environment may cause faulty division of somites or slow cell division of germ cells leaving certain tissues incomplete upon birth. The presence of MTHFR and other SNPs in the mother correlate with rates of Autism, Down’s, Marfan’s, and Klinefelter’s syndrome - with each condition expressing a unique physical phenotype. Additionally, children born with cleft palates, malformed organs, and neural tube defects occur at higher rates in women with methylation SNPs. In fact the most common birth defect is spina bifida, which is widely known to be prevented by adequate intake of the primary methyl donor folic acid.

This link to methylation during gestation is further confirmed by research which indicates that women with the highest intake of methyl donors give birth to the least amount of congenitally defected children. In addition, mother’s who consume high levels of methyl donors before and during pregnancy significantly reduce their risk of having a child with Down’s syndrome, Autism and neural tube defects. The fact is that methylation is critical to normal development and health in utero. The question is whether or not the mother can provide enough methyl donors through her challenged pathways to ensure proper cell division and thus health of her child. The phenotype of the child ultimately rests on assuring adequate methyl donors in the womb to overcome any genetic weaknesses in the methylation cycle.

Childhood, Puberty and Beyond
A child born to parents with genetic methyl weakness may not be born with any visible signs of malformation. Only after tissues begin to mature and grow during childhood and puberty might the methylation problem manifest itself on the physical exam. Methyl groups are needed in higher amounts during periods of rapid growth and functional deficiencies might arise during this time. If a pathway is slow genetically and intake is not adequate, then there is a risk for asymmetrical cell development which can alter the final form of tissues. Methylation pathways are also critical for glutathione production as well as heavy metal and xenobiotic excretion. Individuals with a genetic tendency towards imbalanced methylation will be more sensitive to environmental toxins and will suffer more oxidative tissue damage. Exposure to toxins causes loss of methyl donors making a depleted state even worse. Since our modern environment is saturated with xenobiotics, metals, and other toxins, it is a virtual guarantee that individuals with slow pathways will manifest some form of tissue abnormality on the physical exam.
Many children present for chiropractic care with limb length inequality, scoliosis, spina bifida occulta, hemi-vertebrae, transitional segments, etc. which are discovered upon routine x-ray analysis. Each of these common abnormalities are simply outward manifestations of methylation defects during gestation, childhood, or puberty. As a child grows into an adult and the skeleton grows to full size it becomes easier to clinically identify methylation markers. For example, scoliosis and/or hemivertebrae may not be clinically evident or relevant until a child approaches adult size. This structural distortion may be asymptomatic at age five but when that child grows into a teenager, it may manifest as pain or postural imbalance. Also, limb length discrepancies may not show themselves until limbs reach adult length. By taking note of these common variants and asymmetries on the physical exam, clinicians can learn to quickly identify which patients are in need of targeted methylation support.

The Physical Exam
Clinical outcomes can be improved by focusing attention upon specific and distinct physical exam findings which are clear indications of methylation cycle abnormalities. Table 1 summarizes the relationship between genetic disease, methylation deficiency, and distinct physical phenotypes. The diagnostic physical exam findings are key clinical phenotypes for identifying which patients need to be screened for methylation support nutrients.

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<tr>
<th>Genetic Disease or Deficiency</th>
<th>Diagnostic Physical Exam Findings</th>
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<tr>
<td>Down’s syndrome</td>
<td>congenital heart disease, epicanthal folds, simian crease</td>
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<tr>
<td>Marfan’s syndrome</td>
<td>scoliosis, pectus excavatum, and arachnodactyly</td>
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<tr>
<td>Klinefelter’s syndrome</td>
<td>gynecomastia and female body shape</td>
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<tr>
<td>Fetal Alcohol syndrome</td>
<td>hypertelorism and low set ears</td>
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<tr>
<td>Autism Spectrum</td>
<td>wide upper face, mouth, orbits diminished height of maxilla and philtrum flat nasal bridge</td>
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<tr>
<td>Neural Tube Defects</td>
<td>spina bifida, arnold-chiari malformations, cleft palate</td>
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<tr>
<td>General Methyl Donor Deficiency</td>
<td>hemivertebrae, transitional segments, limb-length discrepancies, posterior ponticles</td>
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The key here is to maintain a functional perspective when screening patients. While most patients will not have a diagnosed genetic disease or condition listed above, many will share the same genetic polymorphisms and physical exam findings as those with more serious disease. For example, a patient may not have Marfan’s disease, but they may have a Marfanoid phenotype with pectus excavatum and very long, slender fingers creating a functional arachnodactyly. Carrying such a phenotype should alert the clinician that the same methyl disturbance that causes genetic disease is present, albeit at a lesser degree. This is a signal for the clinician to provide methyl donor nutrients - namely 5-MTHF, B12, trimethylglycine, SAMe, taurine and choline - in order to reduce the relative risks associated with the phenotype.

The most useful physical marker is the epicanthal fold which can be seen with the naked eye. In many cases however, a functional epicanthal fold exists, which can only be detected through a specific tissue challenge.
Dr. Jeff Brist, DC, shared with this author an excellent challenge technique for screening all patients for a functional epicanthal fold. Figure 1A shows a typical epicanthal area of the right eye without a fold. At first glance this patient would be assumed to not have an epicanthal fold and thus not be at a higher risk for methylation-related problems. Figure 1B demonstrates the epicanthal challenge which provokes the epicanthal tissue and uncovers the hidden, functional epicanthal fold (black arrow). As research has consistently shown, if there are methylation markers on the outside of the body, then there are biochemical parallels inside the body. The epicanthal challenge fits this paradigm well and should be considered a routine screening tool for every patient since methylation issues affect all sides of the triad of health.

**Epicanthal Challenge**

This challenge is performed by a digital contact over the skin of the medial orbit just inferior to the lacrimal bone (Figure 1B). The doctor pulls the skin in a caudal and slightly lateral direction to effectively tighten the skin of the epicanthal area. This skin tension will reveal functional, occult epicanthal folds on many individuals, indicating a need for methyl donor support.

By recognizing the physical phenotypes above clinicians are able to identify which patients are at a higher risk of methylation-related conditions such as depression, heart disease, stroke, and cancer. The presence of any of the diagnostic physical exam findings from Table 1 should alert the clinician to investigate further the methyl status of the patient using applied kinesiology techniques and health history questionnaires.

**CONCLUSION:**
Methylation cycle abnormalities may cause a person to carry a unique physical phenotype related to methylation genes. These physical variations are routinely seen in the chiropractic office and in clinical practice in general. The presence of any one of these methylation phenotypes should alert the clinician for a need to address methyl donor nutrients in that patient. Clinicians will be able to provide a higher level of care and reduce the risk profiles of their patients by addressing these weak pathways. Applying these methyl phenotype strategies to the physical exam improves clinical outcomes and can reduce the need for expensive and time consuming lab testing.

**ACKNOWLEDGEMENTS:**
I would like to thank Dr. Jeff Brist, DC, for sharing with me the technique for screening patients for an epicanthal fold. I would like to also thank Dr. Robert Rakowski, DC, for his relentless pursuit of clinical knowledge and for educating students, doctors, and patients everywhere.
REFERENCES:
Methylation and the Physical Exam:
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