

Developmental origins of adult metabolic disease: The Indian scenario, driving toward a unified hypothesis

Senthil K. Vasan^{1,2}, Nihal Thomas²

¹Rolf Luft Center for Diabetes and Endocrinology, Karolinska Institutet, Stockholm, Sweden, ²Department of Endocrinology, Diabetes and Metabolism, Christian Medical College and Hospital, Vellore, India

In 1961, Neel *et al.* proposed that an individual's adaptation to the environment is dependent on genes selected over a long period of time ("thrifty-genotype"), i.e., those genes that once favored survival in the presence of adverse environmental conditions, evolved into a status of being detrimental in circumstances of sustained energy surplus.^[1] This theory was subsequently challenged by Hales and Barker, who proposed that suboptimal fetal nutrition at critical points of time in intrauterine development may cause permanent alterations in fetal structure, function, and metabolism due to skewed programming ("thrifty phenotype"/"fetal origins").^[2] These theories are not mutually exclusive, but may complement one another, since the consequences of both theories are similar: adults are well adapted to an environment that is nutritionally limited, but are more likely to become unhealthy in a nutritionally rich environment. The fetal insulin hypothesis (FIH) proposed by Hattersley and Tooke states that genetic variants associated with insulin resistance may lead to impaired insulin-mediated growth prenatally, leading to low birth weight and adverse metabolic outcomes in adulthood.^[3] Epidemiological studies have provided sufficient evidence in favor of the fetal origins of adult disease, and in almost all studies, "low birth weight" is used as a surrogate marker of fetal nutritional status.

DO THESE THEORIES APPLY TO INDIANS?

It becomes increasingly interesting to explore the possibility as to whether these theories could provide sufficient explanation for the increasing prevalence of chronic noncommunicable diseases (NCDs) in India, for three exclusive reasons. Firstly, Indian babies weigh the least in the world. An average Indian baby weighs about 800 g less, and is leaner, compared to a European new born.^[4] Secondly, maternal malnutrition is a perennial problem, despite several efforts to improve maternal health, particularly in rural India. Thirdly, the Indian "thin-fat" phenotype is typically characterized by lower lean body mass and a higher quantum of subcutaneous fat, and is associated with an increased risk for cardio-metabolic disease at any given body mass index (BMI), compared to Caucasians.^[5]

GENES AND BIRTH WEIGHT

The most obvious phenotypic expression of the "thrifty genotype" is its association with adult onset obesity, glucose intolerance and essential hypertension. According to the "thrifty genotype" the emerging epidemic of type 2 diabetes and obesity are phenotypic consequences of genetic variants that have undergone positive selection during periods of famine/food inadequacy. Earliest evidence of this was from the Dutch famine study where an increased risk of obesity was observed in low birth weight babies born to mothers exposed to the famine.^[6] Subsequent studies have supported the concept of an evolutionary enrichment of thrifty genes, independent of the role of programming by maternal nutrition. Several genes have already been identified as candidates for the thrifty genotype, and include variants associated with insulin signaling and leptin-related pathways, as well as

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Corresponding Author: Dr. Nihal Thomas, Department of Endocrinology, Diabetes and Metabolism, Christian Medical College and Hospital, Vellore - 632004, India. E-mail: nihal_thomas@yahoo.com

intermediary fat metabolism, but the evidence for these in humans are scanty.

If the thrifty genotype hypothesis cannot be refuted, theoretically the genes that helped survival of a low birth weight baby exposed to an unfavorable *in utero* environment should be associated adult-onset disease. Recent genome-wide association studies have explored the genetic variants that modulate birth weight and have identified variants in the *ADCY5* and *CCNL1* locus to be robustly associated with low birth weight in Europeans.^[7] The GWAS also showed that the association with ponderal index was particularly strong for the near *CCNL1* variants (0.094 SD [95%CI: 0.074–0.113] per risk allele), suggesting a greater association of these variants with fat mass than with skeletal growth at birth, while no association was found with adult BMI or other obesity related traits in adulthood. We were unable to replicate this genetic association with birth weight and adult obesity traits in a longitudinal cohort of South Indians followed from birth until 30 years of age.^[8] Although lower statistical power could be one possible reason for non-replication of genetic association, we strongly argue that this could also be attributed to strong environmental influences that predominate over genetic effects. Interestingly, the birth weight-lowering variants in both Europeans (*ADCY5*, *CDKALI*) and Indians (*ADCY5*) have displayed significant associations with impaired glucose-insulin homeostasis in adulthood, reinforcing the genetic link between *in utero* growth, birth weight, and adult type 2 diabetes mellitus (T2DM). Evidence from genetic association studies, evaluating cardiovascular disease (CVD) risk and birth weight is another example. Contrary to the Spanish AVENA study, where variants in the *APOE*, *APOC3*, and *PPAR-γ* offsprings that are characterized loci were shown to influence weight at birth and elevated lipids during adulthood,^[9] the New Delhi birth cohort, failed to demonstrate any interaction between the *PPAR-γ* and *APOA5* variants and birth weight or longitudinal anthropometry, although they were associated with altered lipids in adulthood.^[10] Reasons for replication failure should be acknowledged. Both the above studies among Indians raise an important question: Why do genetic variants fail to influence both ends of the spectrum - the birth weight and adult metabolic phenotype especially in Indians, unlike the Western population? We may speculate that there could be other genetic variants that possibly influence birth weight in Indians, and that upstream or downstream exons and mutations may be responsible for this “negating” effect. It is also possible that alterations in the metabolic capacity in adulthood may be due to epigenetic effects in fetal life and early infancy having life-long impact on DNA expression. The current genetic epidemiological research has provided some evidence in favor of the “thrifty genotype” hypothesis, but a highly heterogeneous nature of genetic susceptibility to complex diseases makes it difficult to speculate the true

effect of the thrifty genes. However, it is quite evident that the metabolically thrifty genes (that cause insulin resistance and obesity in adulthood) adapted to powerful selective pressure and once provided survival advantage in the early periods have now become detrimental when exposed to an obesogenic environment.

THE “THRIFTY PHENOTYPE” IN INDIANS

Fetal undernutrition as a consequence of poor maternal nutrition results in permanent endocrine and metabolic adaptations that increase cardio-metabolic disease risk in adulthood. Animal models of maternal food restriction give birth to off-springs that are characterized by β -cell dysfunction and insulin resistance.^[11] Epidemiological studies by Barker *et al.* have shown an inverse relationship between birth weight and adult CVD and T2DM in a UK population.^[12] Amongst Indians birth weight is shown to be associated with adult T2DM phenotype (characterized by abnormal fat distribution, hyperinsulinemia, and insulin resistance). The Pune Maternal nutrition study,^[13] the Mysore study^[14] and results from the Vellore birth cohort,^[15] have provided a wealth of information favoring this association. Studies have also shown an association between maternal nutrition, body composition at pregnancy, and later disease in offspring independent of birth weight. Joglekar *et al.*^[16] was able to replicate similar inverse association between birth weight and cardio-metabolic risk factors such as unfavorable body fat distribution, insulin resistance, impaired glucose tolerance, and elevated blood pressure in young rural Indians similar to Europeans. These findings were further strengthened by Thomas *et al.* who showed using hyperinsulinemic euglycaemic “clamps,” assessment of bone composition with Dual energy absorptiometry and energy expenditure with indirect calorimetry that this effect was tempered when the environmental influences are less (i.e., is in fact more rural).^[17] In this situation, it was found that low birth weight was associated with an elevated diastolic blood pressure, increased body fat content and low bone mineral content at the age of 20 years but was not associated with a decline in insulin sensitivity. A similar association with adult disease risk was also observed in urban Indians.^[18] These studies provide robust clues to the existence of the “thrifty phenotype” in Indians. But, what is additionally interesting is if this provides sufficient explanation to the current diabetes/obesity epidemic in India. If the “thrifty phenotype” proves to be the case, the prevalence of NCDs should be higher in rural populations where low birth weight and maternal malnutrition appears to be a common phenomenon, and urban India should face relatively lower prevalence rates. However this appears not to be so. Quite explicably, the ICMR-INDIAB study reports that the prevalence of diabetes is higher in urban compared to rural India at any age interval.^[19] Yajnik *et al.*

provides a valid argument that besides *in utero* and maternal undernutrition, postnatal environmental cues play a significant role in the fetal origins of adult disease, and interactions between all of these factors could be more detrimental than the effect of either alone. This appears logical, since individuals born in urban communities are postnatally exposed to an obesogenic environment wherein accessibility to food is straightforward and physical activity is limited. It is now clear that the maternal phenotype influence fetal weight at birth, and in an environment where food availability is in excess, a predisposition to variability in the metabolic load exists which accounts for adverse health outcomes in adulthood.

Our understanding of the fetal origins theory among Indians has improved substantially. We conclude that both the thrifty genotype and phenotype do exist among Indians, and appear to play overlapping roles in the development of complex adult disease. The postnatal environmental is also an important factor that influences adult disease. The underlying mechanisms of this complex interaction still remain elusive. It is tempting to speculate that relatively stable epigenetic changes might explain some of these effects. However, to date, such changes, which may very well be tissue specific, have not been identified, and so remains a challenge. The current initiative that is considered toward building a consortium of the existing birth cohorts from India is promising, and optimistically may offer more opportunities to validate the fetal origins hypothesis in Indians and particularly with respect to potential gene-environment interactions and epigenetic mechanisms.

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