Genetic Indicators in Young-onset Morbid Obesity: Need for Further Research A BHARAT Group Initiative

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Obesity has attained epidemic status in many South Asian countries affecting about 20% of the Asian population, and is primarily a familial disorder[1,2]. Data from different twin studies – involving more than 25,000 twins, has revealed that the impact of the genetic component is much more than the environmental effect and that adiposity is now considered one of the most heritable traits[3,4]. Research has shown that genetics is responsible for about 45% to 75% of the inter-individual variations in body mass index[5]. These heritable factors are likely to operate through a range of potential pathophysiological pathways, and several candidate genes have been proposed to elicit the cause and predict management strategies based on the individual's genetic makeup[6-8].

The **BHARAT** (**B**arop**H**enotype **A**ssessment and **R**egional variations **A**mong people living with Obesi**T**y in India) group represents a consortium of 6 clinician scientists located in 4 different regions of the country interested in the field of obesity (Fig. 1). The BHARAT group recognizes the need for assessment of the genetic causes of obesity in the Indian setting.

Given that obesity is a widespread disorder in South Asian countries and has a significant genetic component, especially so in the morbidly obese, it would be helpful to study the genetic characteristics in the Indian and other Asian populations, which not only harbor a unique obese phenotype with high rates of consanguinity but currently has minimal published literature on this subject. This is concordant with the recent call by Saeed et al, which has suggested more genetic work in the field of obesity from consanguineous populations, with which we strongly agree and discern[9]. So far, understanding the genetic basis of obesity has been essentially through recognition of the monogenic causes of this disease, leading to identifying pathogenic pathways and possible therapeutic options. However, since this work is carried out at few locations involving a small number of patients, future collaborative work from such centers is likely to provide the foundational data required to design future diagnostic and therapeutic protocols[10].

The genetic factors are more pronounced in extreme forms of obesity, and studying the genetic makeup of morbidly obese individuals is more likely to improve the understanding of the genetic architecture of this disorder[11]. Previously published literature in another consanguineous population has demonstrated that genetic variants in only three genes could contribute towards nearly 30% of the causes of morbid obesity[12].

These included homozygous loss of function mutations in leptin (LEP), leptin receptor (LEPR), and melanocortin-4 receptor (MC4R) genes. Using a step-wise screening regimen, the genetic causality identified in a consanguineous population of unrelated morbidly obese children of Pakistani origin was about 30%. In contrast, only 3% to 5% of such cases published from other populations. Pathogenic mutations were diagnosed in only three genes; however, the lack of data on the incidence

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The BHARAT Group

Barop**H**enotype **A**ssessment and **R**egional variations **A**mong people living with Obesi**T**y in India

6 centers across all 4 zones of India



West Zone	
1.	Dr Shehla Shaikh, Prince Aly Khan Hospital, Mumbai
North Zone	
2	Dr Saptarshi Bhattacharya, Indraprastha Apollo Hospitals, New Delhi
3.	Dr Sanjay Kalra, Bharti Hospital, Karnal
East Zone	
4	Dr Sambit Das, Kalinga Institute of Medical Sciences, Bhubaneswar
5	Dr Sunil Kota, Diabetes & Endocare Clinic, Berhampur
South Zone	
6	Dr Nitin Kapoor, Christian Medical College, Vellore

of pathogenic variants in the remaining obesity-related genes warrants further need for an extensive panel/exome analysis in the future. These results underscore the need comprehensively screen obesity-associated genes in similar large consanguineous populations that offer distinctive genetic insights. These could lead to uncovering the underlying novel genes and mechanisms associated with weight gain and could be potential future targets for its treatment.

Individuals with an underlying genetic cause of obesity are likely to have early-onset obesity and, thereby, many affected years. In our multidisciplinary bariatric clinic located in a tertiary care hospital located in southern India, we have found that a large number of patients, who have young-onset obesity, are more likely to have associated psychiatric disorders underscoring the clinical implications and need for prioritization in this field[13].

Recent advances in genetic sequencing technology have made tremendous progress in identifying the underlying genetic etiology of several disorders. The next-generation sequencing (NGS) has shown to be robust, especially when there is more than one gene to be tested, and has revealed the ability to yield a higher chance of finding a causative mutation. The NGS-based parallel multigene testing has also shown to be a cost-effective and scalable strategy and is currently being utilized in clinical settings as an efficient research and diagnostic tool for clinically and genetically heterogeneous disorders[14,15].

Therefore, studies and future research investigations in this area will not only increase the understanding of this disease but also has a significant future potential of utility in clinical practice, including patient-specific etiological analysis, planning on management strategies, and conceivably individualized prognostic opinions.

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