**List of 10 best papers of DG R Chandak highlighting the important contributions in them briefly**

1. C S Yajnik**, G R Chandak#\***, C Joglekar, P Katre, D S Bhat, S N Singh, C S Janipalli, H Refsum, G Krishnaveni, S Veena, C Osmond, CHD Fall. Maternal homocysteine in pregnancy and offspring birthweight: Epidemiological associations and Mendelian randomization analysis. International J Epidemiology 2014 Oct;43(5):1487-97. doi: 10.1093/ije/dyu132. Epub 2014 Jul 22. PMID: 25052622 **(First author/Equal contribution; Corresponding Author; Impact Factor – 7.176; Citations - 80)**

***[Accompanied by Editorial Commentary, Sarah J Lewis (2014). “One-carbon metabolism has major implications for fetal growth and development beyond neural tube defects” Int. J. of Epidemiol., 1–2 doi: 10.1093/ije/dyu132].***

*We have earlier showed that high maternal levels of homocysteine driven by low vitamin B12 and normal/high folate (leading to an imbalance in folate/B12 ratio and disturbed one-carbon metabolism) programs the baby to be born low birthweight and insulin resistant. However, these associations are subject to reverse causality since the B12 and folate levels are influence by many confounding factors. Using the approach of mendelian randomization, this paper provides first evidence of causal relationship of maternal one-carbon metabolism with fetal programming of obesity and insulin resistance, which are two strong intermediate traits that predict the risk of cardiometabolic syndrome. In the background of another study where we have showed reduction of homocysteine levels by vitamin B12 supplementation, these observations have large implications in public health perspective since improving the B12 status may be one of the strategies to prevent the epidemic of diabetes in India.*

1. Nongmaithem SS, Joglekar CV, Krishnaveni GV, Sahariah SA, Ahmad M, Ramachandran S, Gandhi M, Chopra H, Pandit A, Potdar RD, Hd Fall C, Yajnik CS, **Chandak GR\***. GWAS Identifies Population Specific New Regulatory Variants in FUT6 Associated with Plasma B12 Concentrations in Indians. Hum Molecular Genetics 2017 Jul 1;26(13):2551-2564. doi: 10.1093/hmg/ddx071. PMID: 28334792 **(Corresponding Author; Impact Factor – 5.10; Citations - 33)**

*A large proportion of Indians are deficient (40-70%) in vitamin B12 and this is strongly predictive of raised homocysteine levels, which is an established risk factor for neural tube defects, cardiovascular disease. We had earlier demonstrated elevated maternal homocysteine levels leading to fetal programming of risk of cardiometabolic disorders, hence understanding the genetic contribution to vitamin B12 was important to identify individuals who can be at risk of any disorder as mentioned above. Through this genome-wide association study combining multiple Indian cohorts (including both Indi-European and Dravidian ethnicities), we identified novel variants predicting risk of vitamin B12 levels and further established the molecular mechanism through which the genetic variants (especially FUT6 variants) predict the risk. Further, through the development of a genetic risk score combining all the genetic variants, we showed that only a small portion of heritability of B12 levels is predicted. Thus, our study is the first GWAS study that has not only identified novel variants related to vitamin B12 levels but also illustrated the molecular mechanism of its effects.*

1. Dilip K Yadav, Smeeta Shrestha, Karen A Lillycrop, Charu V Joglekar, Hong Pan, Joanna D Holbrook, Caroline HD Fall, C S Yajnik, **Giriraj R Chandak**\*. Vitamin B12 Supplementation Influences Methylation of Genes Associated with Type 2 Diabetes and its Intermediate Traits. Epigenomics. 2018 Jan;10(1):71-90. doi: 10.2217/epi-2017-0102. PMID: 29135286. **(Corresponding Author; Impact Factor – 4.112; Citations - 25)**

*Indians are centrally obese and develop diabetes at a younger age and at normal levels of obesity. We have earlier shown that Indians have more fat and less muscle mass (Thin-Fat Indian Phenotype) than in Europeans and that is present right at birth. We further showed a causal relationship between raised plasma homocysteine levels in mothers (a surrogate of one-carbon metabolism) and future risk of cardiometabolic disorders in their children and that vitamin B12 supplementation can reduce the homocysteine levels at any age. Through this study, we demonstrated that vitamin B12 supplementation through differential methylation of a micro RNA, miRNA21 regulates the methylation status of two strongest candidate genes like FTO and TCF7L2. This substantiated our earlier hypothesis that FTO may be regulated differently and influence the risk of obesity and type 2 diabetes. Thus, we demonstrated that some of the missing heritability of type 2 diabetes can be explained by epigenetic regulation of type 2 diabetes candidate genes and thus opened the path for future studies.*

1. Ayden Saffari, Smeeta Shrestha, Prachand Issarapu, Sara Sajjadi, Modupeh Betts, Sirazul Ameen Sahariah, Ashutosh Singh Tomar, Philip James, Akshay Dedaniya, Dilip K. Yadav, Kalyanaraman Kumaran, Andrew M. Prentice, Karen A. Lillycrop, Caroline H.D. Fall, **Giriraj R. Chandak\***, Matt J. Silver, and the EMPHASIS Study Group. Effect of maternal preconceptional and pregnancy micronutrient interventions on children’s DNA methylation: findings from the EMPHASIS study. American Journal of Clinical Nutrition 2020 Oct1;112(4):1099-1113. doi: 10.1093/ajcn/ nqaa193. PMID: 32889533 **(First author/Equal contribution; Corresponding Author; Impact Factor – 5.02; Citations -3)**

*As a central research theme in our lab, we have contributed to the observations that maternal nutrition in pregnancy is linked to offspring health in early and later life and changes to DNA methylation could be an important mediating mechanism. We have earlier shown that a micronutrient rich food-based supplementation increased the birthweight especially in mothers with high body mass index. In this study we investigated intervention-associated DNA methylation changes in children of mothers who had participated in two randomized trials of micronutrient intervention in India and Sub-Saharan Africa. We found several differentially methylated positions and regions harbouring important candidate genes likely associated with specific risk phenotypes. Further many of these were enriched in metastable epialleles indicating their role in early life programming. Overall, we demonstrated that maternal pre- and peri-conceptional micronutrient supplementation can alter the DNA methylation in children and these changes could be ethnicity, nature, duration and dose of the intervention.*

1. C S Yajnik, C S Janipalli, S Bhaskar, S R Kulkarni, R M Freathy, S Prakash, K R Mani, M N Weedon, S D Kale, J Deshpande, G V Krishnaveni, S R Veena, C H D Fall, M I McCarthy, T M Frayling, A T Hattersley, **G R Chandak\*** (2009). FTO gene variants are strongly associated with type 2 diabetes in South Asian Indians. Diabetologia; 2009 Feb;52(2):247-52. Doi: 10.1007/s00125-008-1186-6. Epub 2008 Nov 13. PMID: 19005641 **(Corresponding Author; Impact Factor – 7.518; Citations - 210)**

*India is known as the diabetes capital of the world. In contrast to Europeans, Indians develop type 2 diabetes, at least a decade earlier and even with a normal body mass index. In addition, Indians are known to be more insulin resistant and centrally obese with a higher abdominal obesity than in Europeans, the two are the most important intermediate risk traits for developing diabetes. Overall this suggest that there could be different genetic susceptibility to diabetes in Indians. This paper provided the first evidence of variable genetic basis of obesity in Indians and subsequent risk of type 2 diabetes in Indians. Further, it went on to show that FTO gene influences both obesity and risk of type 2 diabetes independent of each other which was different from Europeans, where it was shown that FTO gene variants predict risk of diabetes through obesity. Thus, the study suggested that the link between obesity and type 2 diabetes in Indians as observed in Europeans is not similar and different regulatory mechanism may be responsible for this difference.*

1. Harrison JW, Tallapragada DSP, Baptist A, Sharp SA, Bhaskar S, Jog KS, Patel KA, Weedon MN,**Chandak GR\***, Yajnik CS, Oram RA. Type 1 diabetes genetic risk score is discriminative of diabetes in non-Europeans: evidence from a study in India. Sci Rep. 2020 Jun 11;10(1):9450. doi: 10.1038/s41598-020-65317-1. PMID: 32528078 **(Co-corresponding Author; Impact Factor – 4.379; Citations - 5)**

*Diabetes can be of many subtype types and diagnosing them accurately has implications in disease management. The major issue is with differentiating between type 1 and type 2 diabetes and it is important since insulin is the preferred mode of treatment for the former while oral hypoglycaemic agents are the drug of choice for type 2 diabetes. Since diabetes occurs at an early age in Indians, this possibility is even higher. Through this study, we have demonstrated that a genetic risk score combining 9 genetic variants can discriminate between type 1 and 2 with great sensitivity and specificity. While this largely similar to Europeans, start differences were noted for the HLA genetic variants indicating the possibility of specific pathways driving the onset and course of type 1 and type 2 diabetes. This 9- single nucleotide polymorphisms-based genetic risk score can be used as a routine test to differentiate between the two subtypes of diabetes and thus prevent unnecessary use of insulin for any such misdiagnosed cases.*

1. **G R Chandak#\***, M Mohd Idris, D Nageshwar Reddy, S Bhaskar, PVJ Sriram and L Singh (2002). Mutations in Pancreatic Secretory Trypsin Inhibitor (PSTI/SPINK1) rather than Cationic Trypsinogen Gene (PRSS1) are Significantly Associated with Tropical Calcific Pancreatitis. J Medical Genetics; 2002 May;39(5):347-51. doi: 10.1136/jmg.39.5.347. PMID: 12011155 **(First author and Corresponding Author; Impact Factor – 4.943; Citations - 193)**

***[Based on this paper, Tropical Calcific Pancreatitis has been recognized as a genetic disease and given a number sign (#) in the Online Mendelian Inheritance in Man (OMIM) and has been assigned a number #608189]***

*Tropical calcific pancreatitis is an early onset severe chronic pancreatitis and its aetiology was not established. However, its phenotype of early age of onset, high calcification with large number of pancreatic stones and severe course with development of diabetes is extremely different from what is represented for idiopathic pancreatitis in Europeans. Mutations in the cationic trypsinogen gene were identified as the major cause of the disease in Europeans. Through this study, we demonstrated complete absence of cationic trypsinogen gene mutations and identified novel mutations in the SPINK1 gene as the cause of tropical calcific pancreatitis in Indians. This has changed the algorithm of genetic testing for risk of chronic pancreatitis. Thus, we established the genetic basis of Tropical Calcific Pancreatitis leading to its inclusion in the Online Mendelian Inheritance in Man (OMIM) as a genetic disease and showed it to be different than what is reported in Europeans.*

1. S Mahurkar, S Bhaskar, D N Reddy, G V Rao, S P Singh, V Thomas, G R Chandak (2009). The G191R variant in *PRSS2* gene does not play a role in protection against tropical calcific pancreatitis. Gut; 2009 Jun; 58(6):881-2. doi:10.1136/gut.2008. 170753. PMID 19433599 **(Corresponding Author; Impact Factor – 19.819; Citations - 13)**

***[Accompanied by an Editorial Commentary, Weiss FU and Sahin-Toth M (2009). “Variations in trypsinogen expression may influence the protective effect of the p.G191R PRSS2 variant in chronic pancreatitis” Gut 58:748-50].***

*In this study, we identified another novel gene Cathepsin B which was associated with the risk of both tropical calcific pancreatitis and idiopathic chronic pancreatitis. This was in addition to earlier identification of SPINK1 mutations rather than PRSS1 mutations to be responsible for the disease. We also showed that a combination of SPINK1 and Cathepsin B mutations lead to a relatively severe phenotype of chronic pancreatitis. This further established that chronic pancreatitis is a complex genetic disease where many genes will be involved and also the fact that Indians have a different type of chronic pancreatitis susceptible by different genes and mutations therein. Identification of the novel gene Cathepsin B and its association with chronic pancreatitis was included in the online mendelian inheritance in man as the second gene responsible for association with chronic pancreatitis. Again, this has implications for genetic testing of chronic pancreatitis in Indians.*

1. Paliwal S, Bhaskar S, Mani KR, Reddy DN, Rao GV, Singh SP, Thomas V, **Chandak GR#**. (2012). Comprehensive Screening of Chymotrypsin C (CTRC) Gene in Tropical Calcific Pancreatitis Identifies Novel Variants. Gut 2013 Nov;62(11):1602-6. doi: 10.1136/gutjnl-2012-302448. Epub 2012 May 12. PMID: 22580415. **(Corresponding Author; Impact Factor – 19.819; Citations - 59)**

*Continuing from the observations made in our earlier studies that identified novel genes associated with Chronic Pancreatitis in Indians. This study identified novel genetic variants in Chymotrypsin C gene. The study failed to identify any of the variants reported in Europeans and Americans. The variants are functionally identified to be loss of function mutations establishing their causal role.  Hence, observations from this study further stress on mutational heterogeneity in the genetic risk of Chronic Pancreatitis in Indians and a guide towards screening for genetic risk.*

1. Heiko Witt, Sebastian Beer, Jonas Rosendahl, Jian-Min Chen, **G R Chandak#**, et al. Variants in CPA1 are strongly associated with early onset chronic pancreatitis. Nat Genet. 2013 Oct;45(10):1216-20. doi: 10.1038/ng.2730. Epub 2013 Aug 18. PMID: 23955596 **(First author/Equal contribution; Impact Factor – 27.603; Citations - 246)**

***[Covered in Research Highlights N J Wood “Global role for CPA1 variants in the pathogenesis of chronic pancreatitis” in Nature Reviews Gastroenterology & Hepatology, ;doi:10.1038/nrgastro .2013.172].***

*We have earlier proved genetic heterogeneity (different genes) in Indian chronic pancreatitis patients compared to European patients through identification of novel genes like SPINK1 and Cathepsin B (both recognized in OMIM as the genes related to chronic pancreatitis). We also provided evidence of mutational heterogeneity (different mutations in the same genes) by identifying different mutations in genes like chymotrypsin C, etc. In this study, we have established the phenomenon of mutational heterogeneity as one of the possible mechanisms of the phenotypic heterogeneity as we identified different mutations in another gene, carboxypeptidase1 gene. This has implications in genetic testing for the risk of chronic pancreatitis, both at gene and at specific mutation level.*

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# First author/Equal contribution