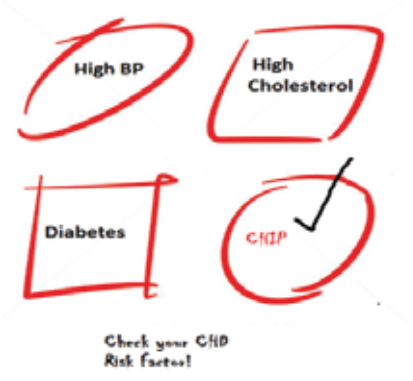
EDITORIAL

CHIP: A NEWFANGLED PERIL FOR CORONARY HEART DISEASE IN PAKISTAN

Zil-e-Rubab
MBBS, M-Phil
Cancer Biologist (CBT Programme)
Harvard Medical School.MA-Boston
Professor, Biochemistry Department, ZiauddinUniversity, Karachi. Pakistan

Certain somatic mutations are capable to confer a selective benefit to blood stem cells become much more common with aging[1]. This state was entitled "clonal hematopoiesis of indeterminate potential," (CHIP), and found that it upsurges the risk of developing a blood cancer more than 10-fold and it seemed to escalate mortality from heart attacks or stroke. But looking at the current understanding of Coronary heart disease CHD is that CHD in the world is the solitary empire where death rules,dictated by tobacco smoking and metabolic syndrome. Worldwide the anticipated rise in CHD is twice in the next 20 years in South Asia compared to any where else.[2,3]



There is scarcity of undeviating evidence about the contributing factors of CHD in South Asia and especially in country like Pakistan. Cardio metaboli cailments are considered main culprit but unswerving causality is not established[4,5].The possible distinct risk profile of South Asian populations, seemingly earlier inception of MIand greater familial clustering of CHD[6], highlight the requirement of genetic studies in this region[2,3].Pakistan is fortunate that a research titled Pakistan Risk of Myocardial Infarction Study (PROMIS:5,000 confirmed MI cases and 5,000 controls in urban Pakistan), a genome wide association study (GWAS) in 2009 was conducted. PROMIS was a large resource of epidemiological pool for Coronary heart disease in South Asia which laid the basis to ascertain and assess inherent and other risk factors of MI in South Asia along with discovery of new pathways[6].

Scientists at the Broad Institute of MIT and Harvard University[7]explored whole-exome sequencing data from two retrospective case–control studies[6,8], the Atherosclerosis, Thrombosis, and Vascular Biology Italian Study Group) (ATVB) and the Pakistan Risk of Myocardial Infarction Study (PROMIS). These studies (PROMIS) evaluatedearly-onset of MI in subjects age less than 50 years(40-50) comparing them with controls from the same medical centers who did not have cardiovascular disease. However ATVB participants were 45 years of age or younger, and with controls were age matched.

A set of genetic mutations was observed in blood cells that are usually seen during aging. These mutation may be a main new risk factor for coronary heart diseases. Contrary to genetic tendencies and outmoded lifestyle risk factors like tobacco smoking and unhealthy dietary habits, the fresh mutations are "somatic mutations" that instigate in stem cells in the bone marrow as age advances.Because the mutations are comparatively communal in elderly people (over 10% of people over the age of 70 encompass at least one of these mutations).The presence of these mutations[6] in CHD opens the wider canvas illustrating the patho genesis in coronary heart disease by supporting the hypothesis that inflammation, in addition to raised cholesterol levels, contributes animperative part in CHD and possibly other diseases of aging as well.

A crucial outcome from NEJM study[7]is that somatic mutations are truly modulating risk for CHD, some what, which haven't been perceived other than cancer." Previous research[1] already ascertained that these somatic mutations are due to clonal hematopoiesis of indeterminate potential," (CHIP), and found its relation with cancer and cardiovascular diseases. In the new study, the researchers evaluated data from four case-control studies including PROMIS and ATVB on more than 8,000 people and found that having one of the CHIP-related mutations nearly doubled the threat for CHD, with the mutations conferring an even greater risk in people who have previously had a heart attack before age 50.In both ATVB and PROMIS, MI patients had enrichment of CHIP, compared to controls. A combined fixed-effects meta-analysis of these two cohorts showed that CHIP was associated with anodds ratio of 4.0 (95% CI, 2.4 to 6.7; P<0.001) forearly-onset MI and this is the thump point for Pakistan that CHD have crabbed the adult population and alarmed to secure preventive as well as curative grounds.

As the human genetic data disclosed a resilient association between CHIP and coronary heart disease, further experiments were done on a mouse model prone to atherosclerosis to disclose the underlying mechanisms. It was observed that loss of one of the CHIP-mutated genes, *Tet2*, in bone marrow cells leads to development of atherosclerotic plaques in blood vessels, indicating the role of mutation in acceleration of atherosclerosis in mice. Atherosclerosis is supposed to be a disease of chronic inflammation that can developdue to excess cholesterol in the vessel wall. Further experiments revealed the presence of an immune cell in atherosclerotic plaques that can develop from CHIP stem cells and carry the same mutations. Mutations in *TET2, JAK2*, and *ASXL1 Tet2* are CHIP-related mutations also named as "epigenetic regulators" that can alter the activity of other genes.Gene expression levels in the *Tet2*-mutated macrophages from mice seem to be "hyper-inflammatory" with increased expression of inflammatory molecules that contribute to atherosclerosis. In support of this finding, humans with *TET2* mutations also had higher levels of one of these molecules, IL-8, in their blood.Significant enrichment mutation in *TET2, JAK2*, and *ASXL1* was also found among participants with early-onset MI. the studies identified *TET2* mutations in 12 of 13 participants, *ASXL1* mutationsin all 8 participants, and *JAK2* mutations in all 16 participants. *JAK2* accounted for 19% of the total mutationsamong patients with myocardial infarction inATVB and PROMIS.By combining genetic analysis on large cohorts with disease model and gene expression studies, CHIP's surprising role in cardiovascular disease is opening new avenues for a new genetic mechanism for atherosclerosis — mutations in blood stem cells that arise with aging.

Future research grounds can be built by finding role of other mutated genes in CHIP in increased inflammation. Interventional trials for possibility of cholesterol lowering therapy or anti-inflammatory drugs in people with CHIP can also be the focus of researchers. A noteworthy clinical impact can be achieved through prospective screening for the mutations in blood cells which would categorize persons at increased risk for coronary heart disease and diminish risk in those individuals through lifestyle modifications or therapeutic mediations.

REFERENCES

1. Siddhartha Jaiswal, Pierre Fontanillas, Jason Flannick .Age-Related Clonal HematopoiesisAssociated with Adverse Outcomes.NEngl J Med 2014;371:2488-98.DOI: 10.1056/NEJMoa1408617.
2. Abegunde DO, Mathers CD, Adam T, Ortegon M, Strong K. The burden and costs of chronicdiseases in low-income and middle-income countries. Lancet. 2007; 370(9603):1929–38. doi:10.1016/S0140-6736(07)61696-1. [PubMed: 18063029]
3. Ghaffar A, Reddy KS, Singhi M. Burden of non-communicable diseases in South Asia. BMJ. 2004;328(7443):807–10. doi: 10.1136/bmj.328.7443.807. [PubMed: 15070638]
4. Gupta M, Brister S. Is South Asian ethnicity an independent cardiovascular risk factor? Can JCardiol. 2006; 22(3):193–7. [PubMed: 16520847]
5. Ismail J, Jafar TH, Jafary FH, White F, Faruqui AM, Chaturvedi N. Risk factors for non-fatalmyocardial infarction in young South Asian adults. Heart. 2004; 90(3):259–63. doi:10.1136/hrt.2003.013631. [PubMed: 14966040]
6. Saleheen D, Zaidi M, Rasheed A, et al. The Pakistan Risk of Myocardial Infarction Study: a resource for the study of genetic, lifestyle and other determinants of myocardial infarction in South Asia. Eur J Epidemiol 2009;24:329-38.
7. Jaiswal S, Natarajan P, Silver AJ, Gibson CJ, Bick AG, Shvartz E. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease.NEngl J Med. 2017 Jul 13;377(2):111-121. doi: 10.1056/NEJMoa1701719. Epub 2017 Jun 21.
8. Atherosclerosis, Thrombosis, andVascular Biology Italian Study Group. Noevidence of association between prothromboticgene polymorphisms and thedevelopment of acute myocardial infarction at a young age. Circulation 2003; 107:1117-22.