ACE2 is an essential regulator of cardiac function, elevated ACE2 in HF has been considered as a compensatory mechanism against angiotensin II-induced cardioremodelling. Under the pro-inflammatory milieu in HF, through sirt1 activation, MLV could normalize ACE2 expression. Decline in ACE2 by MLV could be due to its cumulative role in inducing antiviral, anti-oxidant and anti-inflammatory effects; and optimizing the levels of NAD+, sirt1 and renin biosynthesis, besides correcting the renin–angiotensin–aldosterone system (RAAS). Importantly, normal sirt1 level is known to restore RAAS; hence the trigger for increased ACE2 (as a compensatory mechanism) gets neutralized by sirt1 activation. Thus, it appears that ACEi/ARBs can regulate only a section of the HF complexity. Taken together, through sirt1 activation, with ACE2 being the molecular target, viral entry and HF can be attenuated.

Given that sirt1 activation exhibits immunomodulatory, antiviral and cardioprotective effects, dual compound effect (metformin and vitamin-D, sirt1 activators) restores normal endothelial functions and leucine (sirt1 activator) prevents muscle loss, we suggest that a combination of the three sirt1 activators (MLV) could arm the cells sufficiently to alleviate heightened immune responses, prevent viral entry and lessen the progression of HF, through sirt1 activation (Figure 3).

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**APOBEC3B and ACE1 indel polymorphisms as prima facie candidates for protection from COVID-19**

Population-specific differences in mortality are becoming evident after several months of the COVID-19 pandemic. This is despite differences in the extent of disease prevalence – China reported a case fatality rate of ~5%, India ~2.5%, with parts of Europe witnessing much higher rates (~11–15%). Factors including demographics (elderly populations), containment responses, co-morbidities, quality of health care and other confounders could enhance differences in reported fatality rates. Within India, COVID-19 displays a skewed distribution with some states from the western and central region reporting much higher numbers. This trend has been consistent from March to July 2020 (Figure 1). An inverse relation of the overall number of cases infected with coronaviruses (i.e. MERS, SARS and COVID-19) and malaria across continental populations has been recently reported. A long history of exposure to malaria could have led to accumulation of genetic variants that confer protection to populations in disease-endemic regions. We highlight how signatures of selection in populations from malaria-endemic regions can help identify genetic variants that could modulate COVID-19 morbidity.

Multiple innate immune and immune regulatory pathways linked to host selection provide possible signals of adaptation to malaria. Several studies have noted that sirtuin expression rises in malaria-infected patients, which has implications for the role of sirtuin in the regulation of immune responses. Sirtuin 1 (sirt1) has been shown to have a role in the maintenance of the immune system, and could play a role in the protection of COVID-19 from SARS-CoV-2. A recent study has shown a relationship between the expression of sirt1 and the presence of COVID-19 in patients.
responses in infections such as malaria intersect with those in coronavirus infection. Cytidine deaminase APOBEC3B is one such innate immunity gene that harbours a 29.5 kb insertion/deletion (indel) polymorphism. The APOBEC3 locus has been implicated in widespread editing of viral genomes and its activity limits the replication and infectivity of not only hepatitis B and human immunodeficiency viruses, but also coronaviruses. A wide range of the APOBEC3B indel frequency is reported across global populations, including India, with fixation of the insertion allele in Africa. High frequency of the insertion allele was seen in malaria-endemic regions across India and the deletion allele was significantly associated with severity of disease caused by Plasmodium falciparum. Interestingly, geographic distribution of the protective allele in India (frequency range: 0.55–1.0) presents a striking overlay with low-incidence COVID-19 regions (Figure 1).

APOBEC3B, through its editing activity, also limits retro-transposition events in the human genome. A recent study indicates that one of the consequences of APOBEC3B deletion is the facilitation of Alu insertion in the ACE1 (angiotensin converting enzyme 1) gene across global populations. This widely studied Alu insertion allele results in lower expression and reduced plasma levels of ACE1. The deletion allele is a risk factor for essential hypertension, diabetic nephropathy and has also been reported in the progression of pneumonia in SARS patients with hypoxemia advancing to acute respiratory distress syndrome (ARDS). In addition, homozygous deletions have been associated with acute lung injury/ARDS mortality in Asian patients. A recent meta-analysis carried out on 48,758 healthy subjects from 30 different countries in over 116 studies also revealed that increase of the ins/del allele frequency ratio, was significantly correlated with recovery, with the insertion allele being more frequent in the Asian population compared to the European population. Researchers argue these might also explain the higher impact of the disease in Europe compared to China and Japan.

Counter-intuitively, the deletion polymorphism in ACE1 is associated with extreme longevity in centenarians from French and a few other European populations. Would the presence of this allele influence morbidity in elderly COVID-19 patients? Despite ethnic differences, the interplay between APOBEC3B and ACE polymorphisms could also influence recovery outcomes in COVID-19 (Table 1).

The ACE1 indel could also regulate levels of ACE2, the major receptor for cell invasion by SARS-CoV-2. ACE2 counterbalances the actions of ACE1, and there is evidence that increase in ACE1 expression leads to greater production of angiotensin II, which in turn serves as a negative regulator of ACE2 (ref. 11). SARS-CoV-2 infected individuals carrying the ACE1 deletion allele would not only experience down-regulation of ACE2 by SARS-CoV-2-mediated shedding/internalization, but might also see additional down-regulation of ACE2 by higher levels of ACE1. Such two-way suppression of ACE2 might contribute to increased morbidity.

In light of the above observations, we propose inclusion of APOBEC3B and ACE1 indel polymorphisms in genetic screening, triaging and prognosis of COVID-19.

Table 1. Possible influence of APOBEC3B and ACE1 indel polymorphisms on recovery outcomes in COVID-19

<table>
<thead>
<tr>
<th>APOBEC3B-insertion</th>
<th>ACE1 deletion</th>
<th>ACE1 insertion</th>
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<tr>
<td>Protection/Risk</td>
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<td>Protection/Protection</td>
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Figure 1. Spatial frequency plot of APOBEC3B insertion/deletion frequency overlaid with bar plots representing state-wise COVID-19 cases in India as on (a) 3 May 2020 and (b) 13 July 2020. The numbers below each bar represent the case fatality rate.
COVID-19 patients. Clinical studies for testing this hypothesis are the next step.


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Rehydration induces early and rapid bud break in drought stressed mulberry plants

Bud break is a natural phenomenon in trees to re-activate growth in response to favourable changes in the environment. Trees enter the growth arrest stage called dormancy, as an adaptive strategy to survive the unfavourable environmental conditions. In temperate trees, bud break is triggered after winter dormancy, whereas in tropical trees, these phenological events mostly depend on water availability. In plants, under unfavourable conditions like desiccation stress, one of the earliest responses is the accumulation of abscisic acid (ABA), an endogenous growth hormone. ABA is a long-distance signalling hormone which is generally transported from roots to shoots resulting in growth arrest. In addition to ABA, ethylene also has a key role in triggering the induction of bud dormancy and repressing bud activity, thereby delaying bud break, whereas gibberellin (GA) induces dormancy release. Therefore, it is likely that the buds from the plants grown under ideal conditions would exhibit early and rapid bud break compared to those from the drought-stressed plants. We tested this hypothesis in mulberry (Morus alba L.), a commercially important perennial system, where periodic pruning is required to regenerate vegetative growth. In India, most of the mulberry cultivation falls under arid or semi-arid conditions, where the plants are routinely exposed to intermittent drought that adversely affects foliage production. To examine the effect of drought stress on bud break, we created two different levels of soil water status (100% and 40% field capacity, FC) in potted mulberry plants by gravimetric approach, thereby simulating drought stress. The pots were maintained in open field and at ambient conditions, while being protected from rain with the help of rain out shelters. The stress effect on the plants was confirmed by measuring the relative water content (RWC) and quantifying total chlorophyll. As expected, the RWC was significantly lower (67%; P < 0.05) in the pots maintained at 40% FC, when compared to the pots maintained at 100% FC (85%). This reduction in water status resulted in a significant reduction in total chlorophyll content from 2.3 to 1.7 mg/g fresh weight (P < 0.05) in the control pots to stressed pots respectively. Drought induces chlorophyll degradation as reported in many other studies. These observations indicated that the plants were experiencing drought stress and the specific level of drought stress was maintained for a period of two weeks. At the end of the stress period, the plants were subjected to total defoliation followed by full rehydration to bring the soil FC to 100%. Artificial defoliation is used to induce bud break in perennial plants. We expected slow or delayed bud opening in stressed plants due to high levels of accumulation of inhibitors as reported in earlier studies. From this context, it was expected that the control plants (maintained at 100% FC) would exhibit early bud break when compared to the stressed ones. However, an early and rapid bud break was observed in drought-stressed plants compared to non-stressed plants (100% FC), (Figure 1). Though bud break was observed in 34% of the total buds in stressed plants, it was significantly lesser (P = 0.01) in control plants (11%) 10 days post defoliation and re-watering (Figure 2). Bud break increased to 32% and 51% in control and stressed plants respectively at 20 days post defoliation and re-watering. At 30 days post defoliation and re-watering, the stressed plants exhibited 54% bud break and the plants maintained at control conditions exhibited significantly lesser bud break (34%, P = 0.01) (Figure 2). The overall results showed an early and rapid bud break in stressed plants compared to the control plants, and such a phenomenon is not reported so far in mulberry. In India, mulberry cultivation is practised under

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