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Review

Human Genetic Susceptibility to Chagas Disease Phenotypes

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Abstract: This short review covers our current knowledge of human genetic susceptibility to Chagas disease and phenotypes associated with Chagas disease, such as chronic cardiomyopathy. Recent candidate gene studies, in some instances, are providing further information on genetic associations with particular variants, and sufficient data for meta-analyses. Increasing numbers of patients across populations, collaborative studies and improved technology are facilitating genome wide association studies, where the relative importance of genetic contributions may be considered. To date, there are no biomarkers of disease progression for clinical use, although genetic associations provide clear avenues for future research.

Keywords: genetic susceptibility; Chagas disease; chronic cardiomyopathy.

1. Introduction

The study of human genetic susceptibility to phenotypes associated with Chagas Disease (CD) developed after that of other infectious diseases such as malaria, mycobacterial disease and HIV. This is perhaps because of the more restricted geographic distribution of CD, rather than the numbers of individuals affected or the resulting economic burden. Like malaria, CD is a complex vector borne protozoal disease, and the greater level of complexity can pose challenges and lack of tractability. The early reports were predominantly case control candidate gene studies [1,2] with candidate loci selected based on our understanding of host immunity, including autoimmunity, host-parasite interactions, or more broadly on genetic variants in loci showing association with other infectious diseases. There have been surprisingly few additional candidate gene studies over the last decade.

2. The Immune Response

Current knowledge of immunological responses to *Trypanosoma cruzi*, causing CD, has been reviewed [3,4]. Clinical stages are associated with differing immune responses, from the early acute, symptomatic or asymptomatic stage, most progressing to the intermediate asymptomatic phase, with immunosuppression and parasite reactivation, finally resulting in some individuals progressing to the later chronic phase with organ specific pathology. In addition to the changes in immunity seen with the different clinical stages, there are differences between patients showing mild and severe disease [5]. Involvement of a wide variety of cells and tissues is associated with a variety of pathologies caused directly by the parasite or by the immune response itself [6]. Both early innate and adaptive immunity are established during the acute phase of disease, and the indeterminate form can be diagnosed by positive serology. Many of the published studies focus on innate immunity and inflammatory profile with macrophages producing the cytokines IL-1, IL-12, TNF-α and IL-10, and natural killer cells producing IFN-g. There is a paucity of longitudinal studies, which could be beneficial in view of the complex immunology, determined not only by stage of disease but also by parasite strain and host genetics.

3. Phenotypes Used for Genetic Studies

CD phenotypes used for human genetic studies have included susceptibility to disease per se, sometimes defined by seropositivity, and phenotypes marking disease progression whether chronic cardiomyopathic (CCC) or digestive forms. Seropositivity is taken as a guarantee of exposure, rather than using 'healthy controls' taken from endemic areas. Further descriptions of disease progression e.g., stage of cardiomyopathy or LVSD/left ventricular systolic dysfunction [7] or LVEF/left ventricular ejection fraction [8,9] have been included in some reports. Longitudinal studies and studies of quantitative traits remain rare, although these would be beneficial if traits such as parasitaemia are to be incorporated into analyses [10]. Covariates such as age and HIV status will impact on such measurements.

Some studies have assessed levels of immunological markers in serum alongside genotyping of polymorphisms in candidate loci. In some instances, genotype and protein levels are compared directly e.g., for CR1 [11] and CCL2 and CCL5 [12], whereas in other instances a range of related proteins are assayed e.g., complement proteins alongside *MASP1* genotyping [13] and cytokine levels in MBL deficiency [14], or a protein such as TNF assayed simply as an inflammatory marker in a study of *ACE* and *AGTR1* [9]. Of course, protein measurements made at a single timepoint are not necessarily reliable indicators of status.

4. Population Heterogeneity

Although population uniformity is often assumed, due consideration can be given to population admixture, a particular problem with respect to the study of CD in South American populations. As studies increase in size, several populations may be analysed both individually and when combined. Candidate gene studies may use an admixed population per se [15] or control for population stratification [16]. Lima-Costa et al. used full Single Nucleotide Polymorphisms (SNP) arrays to test 1341people for African, European and Native American ancestry and correlated ancestry with CD outcomes [17]. Baseline infection was higher in African and Native American groups, an association not extending to cardiomyopathy, although these groups were also noted to be associated with poor socioeconomics.

5. Sample Sizes

To date, sample sizes in candidate gene studies are highly variable; some are too small to provide sufficient power, particularly when combined with uninformative markers. Markers themselves are often in Linkage Disequilibrium (LD) with contributory variants, meaning that the marker itself is not causal. Whilst any positive association is taken as a contribution to disease susceptibility, the Relative Risk (RR) conferred by carriage of any allele is likely a small contribution to overall disease heritability. And since heritability is population, time and place dependent, such factors may confound development of diagnostic tools. The heritability of seropositivity is estimated as ~50%, acknowledging that it is difficult to control for shared environment, and heritability estimates of disease progression e.g., CCC may be more useful for overall assessment of the magnitude of genetic contributions [1]. The choice of SNPs, whether based on functionality or previous studies is improving concomitant with improvements in technology allowing better gene coverage [18].

6. Candidate Genes and Regions

There have been remarkably few recent studies of complex regions such as the MHC loci, including *TNF* and *LTA*, and KIR genes, to build on the earlier studies [1]. Ayo et al. looked at MICA and KIR haplotypes, as well as testing HLA by Sequence Specific Oligonucleotide methodology, with cardiac LVSD and digestive forms as phenotypes, although < 200 patients provided low power for analysis of complex haplotypes [19]. In the context of drug responsiveness, Bosch-Nicolau et al. tested for HLA-B alleles, based on drug reactions seen with HIV, and found association between *HLA B*35* and cutaneous reactions after treatment of chronic CD with benznidazole [20].

A little further work extends, confirms or refutes earlier suggestive associations with genes coding for chemokines and their receptors, with *CCR2* and *CCR5* studied in an admixed Argentinian population [15]. The focus remains on the CCC phenotype. *CCL2*, *CCL5*, *CCR1* and *CCR5* were studied in Brazil, with a reported association with a SNP in *CCL5* [12]. Similarly, there are few papers extending previous work on genes coding for cytokines and their receptors [1]. Nevertheless, these illustrate the diversity of literature, with Gomes dos Santos et al. genotyping *IL1B*, *IL6*, *IL17A* and *IL18* in relation to parasitaemia, as measured by RT-PCR, and suggesting an association with *IL6* [10]. Also, by considering cardiomyopathy and HIV status, these authors suggested involvement, including that of variation in *IL17A*, supporting earlier work of Reis et al. [7] on CCC, *IL17A* and *IL17F* [10]. Many such publications are limited in terms of genotyping, although a tag SNP approach

was usefully employed for *IL12B*, *IL4*, *IL10* and *IFNG* by Farage Frade-Barros et al. [18]. There has been a second study of *TGFB1*, albeit with a small sample size but 5 SNPs, suggesting association with susceptibility to CD per se [21,22], and a study of *TYK2*, a gene involved in cytokine regulation, with good sample size but poorly informative markers [23].

Over the last decade, there have been a handful of further papers with genotyping of other loci proposed to be relevant to the immune response to *T. cruzi*. These include loci involved in the complement cascade, innate immunity and the inflammasome: *MBL* [14], *CR1* [11], *C3* [8], *MASP1* [13], *COLEC11* [24]), *FCN3* [25], *TLR4* [26], and *CASP1* [16,27]. Some reports have focussed on disease progression such as that on Human Platelet Antigen polymorphisms, considered to be associated with cardiovascular disease, and tested against CCC [28], or the loci determining the carbohydrate antigens ABO/Secretor/Lewis against the digestive form [29].

7. Meta-Analysis of Candidate Gene Studies

Many of these candidate gene studies add to previous work [1], but remain compromised by population heterogeneity, sample size and information content of markers, and where there are positive associations reported it is difficult to draw robust conclusions on the RR to disease phenotypes and overall contribution to heritability. Hence there is insufficient information to assess the potential usefulness of markers in a clinical context. However, we are now able to meta-analyse data for a more balanced assessment of a handful of loci and look at population heterogeneity within greatly increased sample sizes. The populations included in these analyses are drawn together in a single publication or derived from the literature i.e., previously published studies. Published meta-analyses are summarised in Table 1, where 'association' indicates $p < 0.05$ when analysed under at least one mode of inheritance. Often authors will meta-analyse data considering multiple modes of inheritance, with significant findings occurring under one or more, but with no clear meaning to the observations at this stage. Many of the polymorphisms studied are in promoter regions where, directly or indirectly through LD, they may influence protein production. Hence interpretation of any particular allelic association i.e., directionality of association is complex. Associations seen in individual populations often fail to be replicated in further populations and in meta-analyses e.g., *IL18* associations seen comparing seropositive and seronegative individuals, or comparing CCC and asymptomatic patients, in Colombia are not replicated in other Latin American populations [30]. The low information content of some of the polymorphisms tested in several papers still compromises these meta-analyses and subsequent haplotype analyses, and therefore meta-analysis is an ongoing process. The output of meta-analyses will inform further studies rather than provide useful diagnostic markers.

Table 1. Meta-analyses of Candidate Gene Studies for Chagas Disease.

Gene	Variant	Populations (n)	n Patients + n Controls	Findings *	Reference
IL6	rs1800795	Colombia (2), Argentina (1), Bolivia (1), Peru (1)	1963 seropositive + 1124 seronegative	no signif. difference	[31]
		Colombia (2), Argentina (1), Bolivia (1), Peru (1)	900 CCC + 1063 asymptomatic	no signif. difference	
IL10	rs18008969	Brazil (3), Argentina (1), Colombia (1)	851 CCC + 443 asymptomatic	no signif. difference	[32]
	rs1800871	Brazil (2), Argentina (1), Colombia (1)	754 CCC + 385 asymptomatic	association	
IL17A	rs4711998	Argentina (1), Brazil (1), Colombia (1)	1469 seropositive + 868 seronegative	no signif. difference	[33]
		Argentina (1), Brazil (1), Bolivia (1), Colombia (1)	1070 CCC + 1029 asymptomatic	no signif. difference	
		Argentina (1), Brazil (1), Colombia (1)	970 CCC + 868 seronegative	no signif. difference	
	rs8193036	Argentina (1), Brazil (1), Colombia (1)	1469 seropositive + 868 seronegative	no signif. difference	
		Argentina (1), Brazi (1), Bolivia (1), Colombia (1)	1070 CCC + 1029 asymptomatic	no signif. difference	
		Argentina (1), Brazil (1), Colombia (1)	970 CCC + 868 seronegative	no signif. difference	
	rs2275913	Argentina (1), Brazil (1), Colombia (1)	1469 seropositive + 868 seronegative	association	
		Argentina (1), Brazil (1), Bolivia (1), Colombia (1)	1070 CCC + 1029 asymptomatic	no signif. difference	
		Argentina (1), Brazil (1), Colombia (1)	970 CCC + 868 seronegative	association	
IL18	rs2043055	Argentina (1), Colombia (1)	1209 seropositive + 718 seronegative	no signif. difference	[30]
		Argentina (1), Bolivia (1), Brazil (1), Colombia (1)	1807 CCC + 1183 asymptomatic	no signif. difference	
	rs1946518	Argentina (1), Colombia (1)	1209 seropositive + 718 seronegative	no signif. difference	

Table 1. *Cont.*

Gene	Variant	Populations (n)	n Patients + n Controls	Findings *	Reference
		Argentina (1), Bolivia (1), Brazil (1), Colombia (1)	1807 CCC + 1183 asymptomatic	no signif. difference	
	rs360719	Argentina (1), Colombia (1)	1209 seropositive + 718 seronegative	association	
		Argentina (1), Bolivia (1), Brazil (1), Colombia (1)	1807 CCC + 1183 asymptomatic	no signif. difference	
CCR5	rs2856758	Argentina (1), Colombia (2)	654 CCC + 601 asymptomatic	association	[34]
	rs2734648	Brazil (1), Colombia (2)	712 CCC + 635 asymptomatic	association	
	rs1799987	Argentina (1), Brazil (3), Colombia (2), Peru (1), Venezuela (1)	1093 CCC + 840 asymptomatic	no signif. difference	
		Argentina (1), Colombia (2), Peru (1), Venezuela (1)	716 CCC + 688 asymptomatic	association	
	rs1799988	Argentina (1), Brazil (1), Colombia (2)	782 CCC +725 asymptomatic	association	
	rs41469351	Brazil (1), Colombia (2)	712 CCC + 635 asymptomatic	no signif. difference	
	rs1800023	Argentina (1), Colombia (2)	615 CCC + 601 asymptomatic	association	
	rs1800024	Argentina (1), Colombia (2)	713 CCC + 633 asymptomatic	association	
	rs333[D32]	Brazil (1), Colombia (1), Peru (1), Venezuela (1)	366 CCC + 217 asymptomatic	no signif. difference	

***** refers to allelic association $p < 0.05$ found under at least one mode of inheritance tested, versus no significant difference in allele frequency between patients and controls.

8. Family Studies

Family studies are rare for CD phenotypes and candidate gene markers, and results at best are consistent with, not providing evidence against, genetic influence [35]. Nevertheless, a family-based approach may be appropriate e.g., for investigation of congenital CD [1]. Next generation sequencing and array technologies are making step changes in our abilities to take broader genome wide approaches to disease susceptibility. Such studies can incorporate family members, an appropriate approach used to good effect by Ouarhache et al. [36]. Whereas focus is usually on common variants associated with susceptibility to CD phenotypes across broad populations, this study is on rare variants in exome data shared by all family members with CCC compared to asymptomatic individuals (siblings or controls). This is an approach previously used for rare variants influencing susceptibility to mycobacterial disease. Only 6 nuclear families were employed, but 22 rare pathogenic variants were reported in the heterozygous state, 20 in genes that were mitochondrial, or inflammation (most proinflammatory) related. These rare variants highlight loci worthy of further study, and that 'causative' loci may not be the same in all patients.

9. Genome-Wide Association Studies (GWAS)

The first reported GWAS for CD, specifically for cardiomyopathy in *T. cruzi* seropositive subjects, included 600 Brazilian admixed samples, with 675,718 genotyped SNPs, and a further 5 million SNPs imputed for 580 samples [1,37]. Seven phenotypes were analysed, including anti-*T. cruzi* antibody levels, cardiomyopathy and parameters from ECG. Two SNPs were highlighted in *SLCO1B1*, coding for a solute carrier with a role in drug metabolism and previously implicated in myopathy. Although 46 SNPs in novel genes were described as associated with 7 traits, none of the SNPs reached accepted genome wide significance levels, likely due to lack of power. Hence this Brazilian data was meta-analysed along with GWAS data for the Colombian, Argentinian and Bolivian populations, as previously described by Strauss et al. [33], with a total of 3413 Chagas disease patients in this second GWAS conducted by Casares-Marfil et al. [38]. For CCC, after imputation, a total of 8,218,190 SNPs were meta-analysed across the 4 populations. A novel genome-wide statistically significant association for CCC development with rs2458298 (OR = 0.90, 95%CI = 0.87–0.94, *p*-value = 3.27×10^{-8}), nearby *SAC3D1* was reported. SAC3D1, also known as SHD1, has been identified as a transcriptional regulator of *STAT5*, associated with cardio protection in humans, and with T cell STAT-5 signalling, via IL-2, IL-7, and IL-15 receptors, affected in CCC [38]. In silico analyses suggested functional relationships between rs2458298 and *SNX15*, *BAFT2*, and *FERMT3* [38]. A further study looked to support the functional relevance of the single associated region in this second GWAS, by looking at further SNPs and DNA methylation levels in the region of *SAC3D1*, in 37 CCC patients and 20 asymptomatic individuals, with six cis methylation quantitative trait loci (cis-mQTL) potentially modulating *SAC3D1* expression. Further, cis-mQTLs showed differential methylation between CCC and asymptomatic individuals within *POLA2*, *PLAAT3* and *CCDC88B*, all supporting the functional relevance of this particular region [39].

10. In Conclusions—The Future

In summary, there are a number of candidate gene studies for CD phenotypes which have not provided robust associations. But we are now reaching a stage where there is sufficient data for a handful of variants for meta-analysis. So far, we might speculate that remarkably little of the heritability of CD phenotypes has been accounted for, and there are no obvious biomarkers e.g., for disease progression. Hopefully the future will include some longitudinal studies. Informed by our greater understanding of disease biology and from genome wide approaches we might expect to see more in-depth studies of novel single genes. However, these new genes will likely differ from the previously selected candidate loci, which were picked through *a priori* hypotheses.

There is increased recognition of the role of markers of oxidative stress [36,40], which can be followed up with genetic studies, with SOD-Mn and CCC a published example [41]. The focus will change to include study areas where 2 diseases are prevalent e.g., HIV [20]. The recent COVID epidemic, and the use of ACE inhibitors to treat CCC, have prompted a plethora of studies on the interaction between CD and COVID, and genetic studies examining the *ACE* I/D polymorphism and *AGTR1* [9,42]. Pharmacogenetic studies in relation to benznidazole treatment, or other such treatments, with greater consideration of the drugs' pharmacological properties, could have real practical benefit [9,20]. As more genes are identified as contributors to the heritability of CD and its phenotypes, gene interactions may be explored using programmes such as ORVAL [43].

To date, there have been hardly any functional studies to directly compliment genetic findings, for example using mouse models. With the increase in genome wide sequence technologies and meta- analyses of findings to establish broad relevance across populations, hopefully theses to underpin functional studies will rapidly appear in the literature. Genome wide approaches in particular often require large sample sizes and major funding, and study of CD across the varied South American populations will necessitate extensive collaboration. Genes providing markers for disease progression and responsiveness to treatments will likely provide the fastest and most useful practical benefits.

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Conflicts of Interest

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