Genetic Epidemiology of Arterial Blood Pressure: A Review

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INTRODUCTION

Hypertension affects approximately one billion individuals worldwide (JNC7, 2003), almost 20% of the adult population (Lifton, 1996). Hypertension is a complex trait found to be determined by the interaction of genetic and environmental factors. Identification of environmental and genetic factors that influence blood pressure (BP) are important because high BP / hypertension is associated with several forms of cardiovascular diseases and risk factors which eventually alter the mortality and morbidity rates in a population. Essential hypertension is undoubtedly a heterogeneous group of disease with a common end result of elevated BP. Therefore, determination of the relative roles of genes and environment in the etiology of high BP is very important. Epidemiologic interest in the genetic determinations of high BP received a major stimulus in 1950s and 1960s prompted by the Platt-Pickering controversy (Tyroler, 1977). This controversy concerning the nature of the inheritance of hypertension is of basic importance. There has been considerable controversy in the past as to the relative influence of genes and environment to the expression of BP. Numerous studies have been conducted in favor of mostly environmental etiology. In contrast to these studies, several other studies have reported evidence of genetic influence for familial aggregation of BP.

Factors affecting BP are diverse and complex. Many researchers tried to elucidate factors contributing to variation in BP levels within and between populations. Several personal, social, and environmental factors contribute towards this variation. Environmental factors play a significant role in the observed variations in the distribution of BP among different population groups (Borhani et al., 1969). Socio-cultural differences rather than genetic heritability are found to be responsible for the majority of the differences in BP levels between populations (Ward, 1983). Age and sex differences are well known. Other factors are body composition, as it relates to overall mass and fatness; physiological variables involving sympathetic and parasy-mpathetic nervous systems; biochemical variables such as rennin, aldosterone, lipids and lipoproteins, etc; environmental variables such as sodium intake, heavy metals, climate and noise; psychological variables involving personality type, and mental stress. Many of these factors are reviewed in Feinleib and Garrison (1979), Altschul and Grommet (1980), Verma et al. (1980), Siegel and Leitch (1981), Siervogel (1983), Nirmala (1987), Gerber and Stern (1999), Stevenson (1999), Hanna 1999, Dressler (1999) and in edited books by Stammler et al. (1967), Paul (1975), and Rao et al. (1984). A number of socio-cultural variables are also causal elements for BP elevation. For example, marital status, number of children, church attendance, etc., may also contribute to BP variation (Scotch, 1963).

Studies conducted on populations with very diverse geographical and cultural environments reported familial aggregation of BP (Tyroler, 1977). Genetic differences among individuals are ascertained with estimates of the fraction of phenotypic variation in BP (Borhani et al., 1979; Krieger et al., 1980; Morton et al., 1980). In all these studies the genetic variability associated with either diastolic or systolic BP variation was significant. In contrast to these studies, Harburg et al. (1977) from their study on blacks and whites living in Detroit, Michigan, did not find any significant BP variation associated with genetic variability. They concluded that unspecified environmental factors are the main determinants of BP. Both genetic and environmental influences in the variation of BP have been thoroughly studied by many investigators (Lowe, 1964; Langford et al., 1968; Havlik et al., 1979; Canessa et al., 1980). Some other researchers used path analysis to separate the genetic and environmental influences in BP variation (Weinberg et al., 1979; Krieger et al., 1980; Morton et al., 1980; Perusse et al., 1989; Rice et al., 1989, 1992). Some investigators have concentrated on delineating environmental factors which influence BP. The usual method for dealing with environmental correlates is to use them for covariance adjustment of the phenotype. The most common findings suggest significant effect of body weight, pulse rate, and cholesterol (Kannel and Sorlie, 1975), psychic stress, excessive salt intake,

prostaglandin deficiency and a variety of other environmental factors (Kannel and Dawber, 1973; Remington, 1976), obesity (Feinleib et al., 1977; Pan et al., 1986), nutrition especially alcohol, calcium and phosphorous intake (Fortmann et al., 1983; Harlan et al., 1984; Jackson et al., 1985), smoking (Morton et al., 1980), oral contraceptive usage (Feinleib et al., 197), and stress (Matthews et al., 1987). Physical activity has also been related to BP (Laporte et al., 1984). With the advent of DNA technology in general and particularly after the development of rapid screening methods in the 90s the focus has shifted to identify/isolate genes responsible/linked to hypertension or BP regulation. In the mean time, with the plethora molecular genetics studies aiming at understanding the mechanisms leading to hypertension and cardiovascular diseases a large body of literature has accumulated. In this review we try to provide an overview of the pre-molecular and molecular genetics studies in order to project the status of present understanding of the etiology of high BP.

Ethnic, Cultural and Age-Sex Variation in Blood Pressure

There is considerable variation in BP distribution between different ethnic groups especially between traditional and nontraditional societies (Dressler 1999). Donnison (1929) and Vint (1937) indicated extremely rare cases of hypertension in the black population of Africa in contrast to the white population. They thought that the genetic differences between blacks and whites might be the main cause for this. But Keith et al. (1939) observed the prevalence of hypertension among U.S. blacks nearly double that observed in U.S. whites. This variation of BP may be due to sociocultural factors rather than genetic background (Ward, 1983).

In contrast to many westernized societies, majority of traditional societies have low mean values of BP and are characterized by an insignificant increase of BP with age (Epstein and Eckoff, 1967). The etiologic factors affecting the distribution of BP in traditional societies are different from those in urbanized societies (Siervogel, 1983; Ward, 1983). The factors identified as the significant determinants of BP distributions even among traditional societies are not the same (Ward, 1983). Hypertension is also rare in traditional societies with some exceptions (Neilson and Williams, 1978; Marmot, 1979). Population studies from many parts of the world show the rise of BP with age and substantial prevalence of hypertension (Hamilton et al., 1954a; Epstein and Eckoff, 1967; Akinkugbe and Ojo, 1969; Kahn et al., 1972; Kimura, 1973; Miall and Chinn, 1973). Non-Caucasians, especially the American blacks, show steeper age gradients and substantially higher prevalence of hypertension than whites (Comstock, 1967; Heyden et al., 1969; Boyle, 1970).

In United States the death rates for hypertension and hypertensive heart disease are higher in males than in females in white population and in contrast to this in the blacks the rates are consistently greater for females than for males (Lennard and Glock, 1957; Stammler et al., 1960). Aderounmu (1981) reported that organ pattern and drug responses also differ between races. MacLean et al. (1974) reported significant positive relationship between DBP and percent of African genes.

GENETICS OF BLOOD PRESSURE

Familial Nature

Most health relevant characteristics are determined by family factors. The joint effect of genetic and cultural transmission mechanism and also shared physical and social environments are responsible to maximize similarities of individuals within families. There is ample evidence that high BP tends to cluster in families. Such clustering may be due to shared genetic factors or shared environment or an interaction of both. Familial aggregation in BP may vary in different populations with basic difference in genetic characteristics, cultures, and life styles. A large number of investigations indicated that in spite of large environmental effects on BP 20-40 % of this variability within a population is due to polygenic factors (Feinleib et al., 1980). The overall relationship between BP of first degree relatives and their propositi strongly supports the hypothesis that BP levels in the general population are determined multifactorially and that a family factor is involved (Miall et al., 1967). The familial nature and the inheritance of BP have been under investigation for several decades. Hamilton et al. (1954) indicated that records of single families, family history studies, twin studies and measurement of BP in relatives of patients with

essential hypertension were four kinds of evidences in the study of inheritance of BP. These evidences have been utilized by many researchers to study the genetics of BP (MacLean et al., 1974; Tyroler, 1977; Lee, 1978; Havlik et al., 1979; Rose et al., 1979; Kreiger et al., 1980; Morton et al., 1980; Perusse et al., 1989; Rice et al., 1989; 1992; Nirmala et al., 1992). Hybrid analysis also provided a unique evidence for analyzing the biological consequences of admixture (Hutchinson and Crawford, 1981).

Family History Studies

Heredity is the most important factor in the development of arterial hypertension. The nature of the hereditary component of BP may be estimated by examining the phenotypic similarity between relatives. According to Thomas and Cohen (1955) cerebral hemorrhage occurring in a father and three sons was described by Morgagni as early as 1769 as hereditary, because of the frequent occurrence of cerebral hemorrhage in certain families. Two hundred years later the occurrence of elevated BP in families was reported by Broadbent and Broadbent (1898) and Allbutt (1915). Janeway (1916) obtained familial history of cardiovascular disease form 50 % of a group of patients with hypertension.

Weitz (1923) observed elevated blood pressures among the brothers and sisters of their hypertensive patients when compared to the similar relatives of subjects with normal BP. O'Hare et al. (1924) from their study of 300 hypertensive persons reported 68 to 76 % of family history for the prevalence of vascular disease and concluded that heredity plays an important role in causing hypertension. Frost (1925) obtained a positive family history of vascular disease from 28 % of 400 young adults who had elevated BP. Popper (1932) by studying 1031 cases of hypertensives concluded that heredity factor was the most important in the inheritance of BP. Ayman (1934) by studying the BP of 1524 members of 277 families found that only 3 % of children showed the incidence of elevated BP values in the families in which both parents had normal blood pressures. If one parent was hypertensive the incidence increased to 28 % and it was 45 % if both parents had essential hypertension. Hines (1937) and Thakker (1940) reported a positive family history of hypertensive cardiovascular disease in approximately 87% of patients with essential hypertension and only 30% of persons with normal BP. Sobye (1984) found a statistically significant higher prevalence of hypertension among the relatives of 186 patents with essential hypertension and nephrosclerosis than in the control group.

Thomas (1959) reported that the greatest proportion of offspring were affected when two parents are hypertensive, whereas the smallest proportion of affected persons were found among the offsprings of two unaffected parents. This finding was consistent and it can be explained that hypertension at least in part is a hereditary disorder. Stammler et al. (1979) from nation wide screening program of BP measurements, family (parental) histories for more than a half million people reported positive family history. More than 40 % of the persons screened reported the presence of hypertension in one or both of their parents. Positive family history was associated with prevalence of hypertension that is approximately double to those with negative family history. Heller et al. (1980) also observed significant difference in BP levels between the relatives of hypertensives and controls.

In contrast to these studies Palmer (1931) by studying the inheritance of familial vascular disease in 100 unselected hypertensive patients and 100 controls did not find any statistically significant difference between the two groups. Feldt and Wenstrand (1943) from their study of the family histories of 4376 insurance applicants (2188 with normal and 2188 with high BP) found only a slight difference between the two groups and concluded that heredity is probably not a primary important factor in the etiology of hypertension.

Certain degree of sex specific differences in the transmission of hypertension was also observed by Thomas (1959). When both parents were hypertensive the occurrence of hypertension among the female offspring was 20.7 %; when one parent was hypertensive 13.0 % and where neither parent was hypertensive the prevalence of hypertension among the female offspring was only 4.5 %. The incidence of hypertension among the male offspring in these three categories are much more alike (11.1; 10.0 and 7.9 %, respectively). By comparing the incidence of hypertension in male and female siblings of hypertensive mothers and fathers, Thomas and Cohen (1955) reported that when the probands were women their female siblings had twice as much

hypertension as their male siblings. Whereas when the probands were men their male siblings has nearly twice as much hypertension as their female siblings. Allen and Spuhler (1957) reported good correlations between systolic blood pressure (SBP) when sisters were compared with sisters and brothers with brothers; but almost none when they compared siblings without regard to sex. In two generation comparisons (parents v/s offspring) they found the highest correlations in father-son and mother-daughter categories. From these results they postulated that the pattern of inheritance for BP is 'sex specific'. Hurwich et al. (1982) also reported sex-specific trend in parent-child correlations.

Twin Studies

Stocks (1924) presented evidence of some genetic involvement in BP from his study on monozygotic and dizygotic twins. Verschuer and Zipperlen (1929), Stocks (1930) and Kahler and Weber (1940) observed close resemblance in BP of monozygotic twins than in the dizygotic twins suggesting the involvement of genetic component. Feinleib (1972) also reported the excess concordance of BP levels in monozygotic when compared to dizygotic twins suggesting that the BP differences are genetically determined. Rose et al. (1979) from their analysis of SBP within the families of identical twins revealed that socio-cultural similarities, environmental effects, and aggregation of body size influence familial aggregation of BP. But substantial genetic additive effects were also evident and genetic variance remained even after the removal of influence of body size. Levine et al. (1982) by studying 166 pairs of new born twins from 2 days after birth to one year through 14 days, one month, 3 months and 6 months intervals, found significant genetic variance in both systolic and diastolic blood pressures. Hunt et al. (1989) from their study of Utah pedigrees and twins concluded in favor of a greater genetic influence of BP than that of shared environment. Osborne et al. (1963) and Downie et al. (1969) did not find any significant genetic component in the determination of BP. Wang et al. (1990) implied higher association of body size indices with BP suggesting the increase in body size among children was responsible for the change of BP with age.

Family Studies

Familial aggregation of BP and its magnitude among the different relatives has been estimated by many researchers from different parts of the world (Table 1 and 2). Miall and Oldham (1963) reported excessive heterogeneity in the amount of resemblance between different classes of first degree relatives. Chazan and Winkelstein (1964) reported household aggregation of systolic and diastolic blood pressures in all members regardless whether they are genetically related or not. Significant correlations between non-related household members were also reported by Wikelstein et al. (1966), Hayes et al. (1971), and Byard et al. (1989).

Johnson et al. (1965) reported significant parent-child correlations from their study of the entire community of Tecumseh, Michigan. Similar findings were also reported by Biron et al. (1976) Annest et al. (1979a, b), Hutchinson and Crawford (1989). Slight decrease in the familial correlations after adjusting the BP for body size was observed by Havlik et al. (1979). Zinner et al. (1971) from a study of 190 families with mothers and 721 children of 2 to 14 years of age range reported a familial influence on BP in childhood. They suggested that the familial tendency to elevated BP establishes early in life and common environmental factors are responsible for this tendency. Hennekens et al. (1976) reported significant sib-sib aggregation by the age of one month for diastolic blood pressure (DBP). Kass et al. (1977) have shown that sibling to sibling aggregation of DBP probably begins during the first few months of life, whereas mother-child correlations seems to be present from the first days life (Biron et al. 1977). De Swiet et al. (1976) reported that an infant's BP at 4 to 6 days correlates significantly with its pressure at seven weeks. Mother-child resemblance for arterial BP may be as high at 72 hours after birth as it is at 18 years (Zinner et al., 1971). In the new borns the mother-infants relation for BP was reduced by half when the mother-infant aggregation for body weight was taken into account (Biron and Mongeau 1978). Clarke et al. (1986) from their Muscatine study of families of children with labile high SBP reported higher correlations than those for the families of children with middle and low SBP.

Gerson and Foder (1975) reported higher correlation coefficients for mother-offspring than

Table 1: Familial correlations for systolic pressure

Study		*FM*	*FS*	*FC*	*FD*	*PC*	*MS*	*MC*	*MD*	*BB*	*SS/CC*	*BS*	*DZ*	*MZ*
Havlik	No Adj	.13	.18		.13		.17		.25	.17	.23	.18		
et al., 1979b	Adj Age		.17		.10		.14		.17	.14	.21	.19		
	Adj Wt Age									.17	.16	.19		
	Adj Env Wt Age	.03	17		.08		.17		.15	.12	.08	.20		
Havlik et al., 1982		.03	.17		.10		.14		.17	.14	.21	.19		
Annest	Biol.			.24				.27			.38			
et al., 1979a,b	Adop.			.09				.08			.17			
Havlik	Black												.31	.54
et al., 1979a	White												.49	.54
(7Y/0)	All												.49	.54
Krieger et al., 1980		.12		.13				.16			.24			
Morton et al., 1980		.05		.16				.17			.27			
Hurwich														
et al.,1982	Age			.15				.08			.20			
	Wt Age			.20				.08			.21			
Iselius et al.,	Ranges from	.02				.14					.22			
1983*-meta	-to	.15				.26					.38			
(17 studies frp, 17 studies from the 1960s and 1970s)														
Claarke Adj	BP low			.07				-.06			.06			
et al., Age	Med			-.01				.21			.13			
1986	Hi			.20				.33			.31			
Adj	BP low			.07				-.33			.22			
Age	Med			-.01				.21			.11			
Bs	Hi			.25				.32			.25			
Perusse et. al.,1989		.21		.20				.25			.38			
Rice	Biol.	.21		.21				.25		.25	.55	.38	.59	.71
et al.,1989	Adop.			.16				.17			.40			
Byard et al.,1989		.16				.27					.29			
Rice et al., 1992		.18		.15				.20			.38			

*The 17 studies referenced by Iselius et al., 1983 are (Johnson et al., 1965; Langford et al., 1968: Wolanski, 1969; Hayes et al., 1971; Zinner et al., 1971; Beaglehole et al. 1975; Feinleib et al. 1975; Holland and Beresford 1975; Klein et al. 1975; Borhani et al. 1976; Hennekens et al., 1976; Miall et al., 1967; Chakraborty et al., 1977; Tyroler, 1977; Annet et al.,1979; Bengtsson et al., 1979; Feinleib and Garrison, 1979).

FM=father-mother, FS=father-son, FD=father-daughter, MS=mother-son, MD=mother-daughter, BB=brother-brother, SS=sister-sister, BS=brother-sister, FC=father-child, MC=mother-child, CC=child-child, DZ/MZ=Di/Mono-zygotic twins, PC=parent-child, Adj.=Adjusted , Biol.= Biological, Adop.=Adopted, Wt.=Weight, Env. Environment, BS=Biceps Skinfold

for father-offspring. Bengtsson et al. (1979) by studying 373 families reported significant correlations between mother and children. However such findings imply possibly maternal genetic or environmental effects on offspring BP. Maternal effects possibly mediated through dietary habits are responsible for small but significant fraction of cultural inheritance (Morton et al. 1980). In contrast Rose et al. (1979), Kreiger et al. (1980), Perusse et al. (1989) and Rice et al. (1992) reported no evidence of maternal effects. However, Morton et al. (1980) and Iselius et al (1983) reported small maternal effects. Longini et al. (1984) implied that in addition to the genetic influence there might be some maternal influence on determination BP.

Small positive aggregation of BP was observed among adoptees living together (Beaglehole et al. 1975; Biron et al. 1975). But this aggregation was not related to the age at adoption and was linked to the duration of adoption and to the co-resemblance in body weight. Biron et al. (1976),

Table 2: Familial correlations for diastolic blood pressure

Study		*FM*	*FS*	*FC*	*FD*	*PC*	*MS*	*MC*	*MD*	*BB*	*SS/CC*	*BS*	*DZ*	*MZ*
Havilik	No Adj	.10	.18		.17		.21		.22	.19	.24	.20		
et al., 1979b	Adj Age		.16		.15		.13		.15	.15	.22	.18		
	Adj Wt Age									.18	.21	.19		
	Adj Env Wt Age	.02	.15		.13		.13		.15	.16	.15	.20		
Havlik			.16		.15		.13		.15	.12	.08	.20		
et al., 1982														
Annest	Biol.			.21				.26			.53			
et al., 1979a,b	Adop			.13				.10			.29			
Havlik	Black												.18	.44
et al., 1979a	White												.34	.54
(7Y/0)	All												.27	.54
Krieger		.16		.19				.14			.20			
et al., 1980														
Morton		-.04		.14				.08			.18			
et al., 1980														
Hurwich	Age			.12				.06			.26			
et al., 1982	Wt Age			.18				.09			.23			
Iselius														
et al., 1983*	Ranges from			-.01				.11			.18			
-meta	– to			.18				.23			.53			
17 studies from the														
1960s and 1970s)*														
Claarke Adj	BP low			.18				.09			.10			
et al., Age	Med			-.01				.09			.10			
1986	Hi			.23				.31			.31			
Adj	BP low			.08				.07			.13			
Age	Med			-.08				.15			.12			
BS	Hi			.35				.22			.17			
Perusse		.28		.31				.27			.57			
et. al.,1989														
Rice	Biol.	.29		.31				.29		.58	.58	.58	.59	.68
et al.,1989	Adop.			.10				.10			.19			
Byard		.28				.23					.22			
et al.,1989														
Rice		.04		.14				.13			.34			
et al., 1992														

*Please refer to table 1, for sources of the 17 studies

Annest et al. (1979a; 1979b), Rice et al. (1989) did not find any significant aggregation between parents and adopted children. From this it may be suggested that the sharing of the same household environment may not be a significant contributing factor for the familial aggregation of BP.

The degree of familial aggregation of BP appears to vary depending upon the type of familial relationship examined. Miall et al. (1962) in Jamica and Johnson et al. (1965) in Tecumseh, Michigan, Perusse et al. (1989) in French Canadian population, Rice et al. (1992) in Andhra population found higher sib-sib correlations than parent-offspring correlations which imply an involvement of a strong heritable component of BP in sibs. In contrast to this higher parent-offspring than sib-sib correlations were reported by Benglehole et al. (1975), Biron et al. (1975) and Feinleib et al. (1975) from their studies of Montreal, Toklauan and Framingham, respectively. Rao et al. (1975) and Tyroler (1977) reported that parent-offspring and sib-sib correlations change with the ages of children. Johnson et al. (1965) and Deutscher et al. (1966) did not find any consistent trend for the correlations to change with age. Deutscher et al. (1966) observed variation in the degree of aggregation of BP between siblings of different ages. But Bebgtsson et al. (1979) did not observe any age effect in the degree of resemblance between siblings. However, an interaction of genetic and environmental effects at a given age may be responsible for individual's BP. These effects may change in course of time as genes turn 'on' and 'off' or due to changes in individual's habits. The impacts of these habits

in determining BP may be different at different ages. In the course of development, familial factors dominate sometimes, while non-familial and independent factors may be prominent at other stages (Province et al., 1989).

Both heredity and environment together are responsible for the similarities between blood relatives. The finding of a similar aggregation of BP between the spouses (individuals who do not have similar genetic background but share similar environmental factors) questions the genetic hypothesis of BP clustering within families (Speers et al., 1986). The relationship of BP between spouses has been examined by numerous investigators and the conflicting results have been reported for spouse similarity. Gearing et al. (1962) from their New York study of spouses of normotensives and hypertensives; Miall and Oldham (1963) from their study of random population samples in South Wales; Schull et al. (1977) from their Detroit project did not find any spouse aggregation. Johnson et al. (1965) from their Techumseh study found statistically significant spouse correlations in only one age group of wives i.e., 50-59. Without taking duration of marriage into account Borhani et al. (1969) from their Alameda county study did not report spouse correlation for SBP but reported for DBP. In contrast to this, Rice et al. (1992) found significant marital correlation for SBP from their study in Andhra population, India. Byard et al. (1989) also reported significant spouse correlation for DBP. Morton et al. (1980) did not find significant positive correlation between spouses for both SBP and DBP.

Many researchers reported significant spouse correlation (Chazan and Winkelstein, 1964; Winkelstein et al., 1966; Tseng 1967; Hayes 1971; Sackett 1975; Annest et al., 1979a; 1979b; Rose et al., 1979; Kreiger et al., 1980; Haynes et al., 1983; Suarez et al, 1983; Speers et al. 1986). Sackett et al. (1975) from their Framingham study reported concordance of BP between spouses and it did not increase over a twelve year observation period suggesting that it might be due to the marriage of similar people rather than the sharing of common marital environment. Speers et al. (1986) reported that the spouse resemblance for BP remains even when several indices of household environment such as education, activity levels, and dietary intakes are controlled. Suarez et al. (1983) from their study of 1702 spouse pairs, including 403 pairs married 40 or more years, found that the reported duration of marriage did not show any effect on spouse concordance/correlations, but are found to be influenced by age of wife. They further inferred that the differences in spouse similarities by wife's age may be due to different degrees of shared behavior between couples at different ages. The increase of spouse concordance in direct proportion to the duration of marriage was reported by Winkelstein et al. (1966). Borhani et al. (1969) suggested a cumulative effect of common marital environment. However, the estimates differ among studies probably because the populations studied were different with different study designs and statistical methods. In most of these studies the aggregation seems to be more due to genetic similarity rather than shared environment.

ENVIROMNENTAL INFLUENCE OF BLOOD PRESSURE

Aggregation of a variable within a family does not necessarily imply that the variable is under genetic control, shared environment can also lead to familial aggregation. Borhani (1976) observed that though the resemblance between the relatives in their levels of BP can be explained as due to the 'sharing of genes', the environmental factors is also important. Feinleib et al. (1975) suggested that 82 % of SBP and 64 % of DBP differences were genetically determined. Whereas Miall and Oldham (1963) believed that only 30 % of the SBP variation was genetic and 70 % may be due to environmental factors. Pickering (1968) expressed that while the environmental factors contribute 36 to 67 % to the variation of BP, the contribution of genetic factors would be between one third to two thirds of the total variation. On the basis of the extensive data collected on first degree relatives by Miall and Oldham (1963), Cavalli-Sforza and Bodmer (1971) have concluded that at least 70-80 % of the variation in BP may be genetically determined. They also suggested that only about 14 and 30 % of the total variation in systolic and diastolic blood pressures respectively, can be attributed to the environmental factors.

The results of the study on 500 families of French-Canadian descent by Biron and others indicate that about half of the total phenotypic variation in BP is due to familial factors, whereas the remaining one half is due to the shared genes and the other half due to shared environment

(Biron et al., 1976, 1977; Brion and Mongeau, 1978; Annest et at., 1979a, b; Mongeau and Biron, 1981). Longinin et al. (1984) reported that for SBP approximately 70 % of the total variance is explained. Of this variance, shared polygenes account for 25 % variance and 5 % is by shared familial environment mostly within generation. For the DBP, approximately 55 % of the total variance is explained by shared polygenes, with about 22 % by shared familial environment of which about 6 % is within a generation. Measurement error and environmental factors specific to individuals contribute to the remaining unexplained variance (i.e., 30 and 45 % respectively for SBP and DBP).

Examining the role of 18 biological and environmental variables in BP variation among a variety of Israeli groups, Sive et al. (1971) reported 16.6 to 29.0 % of variation in SBP as due to these variables and about 80 % due to age, pulse rate, and weight/height. Jorgenson et al. (1972) in a study of culturally similar but genetically isolated Lancaster and old order Somerset-Garrett, Amish, concluded that environmental factors have a strong influence on BP. Dawber et al. (1964) studied the incidence of hypertension and the distribution of BP levels in relation to a number of environmental factors including physical activity, smoking, nutrient intake, alcohol consumption, salt intake, and educational status and did not find any evidence on the effect of environment in the Framingham population. However, they found significant correlation between BP and body weight.

Using another method called path analysis, environmental variables were used conjointly with the phenotype to ascertain the relative effects of heredity and common environment on the phenotype (Rao et al., 1979), as opposed to the covariance adjustment of the phenotype for the effects of the environmental variables. This approach summarizes all available environmental variables into a single continuous index of common or familial environment as was done by Morton et al. (1980), Kreiger et al. (1980), Perusse et al. (1989), and Rice et al. (1989, 1992). The genetic and cultural heritabilities reported for these studies are not different from those reported using the covariance adjustment methodology. Both genetic and cultural heritability estimates for systolic and diastolic blood pressures using twins, adoptees, and family data were reported from different parts of the world by many investigators from 1976 to 1992 (Table 3). Using extensive environmental indices, Perusse et al. (1989) found a substantial proportion of the variability in BP in the French-Canadian population to be due to familial environment. Rice et al. (1989) using twins and adoptees in addition to the above data found higher proportion of variance due to genetic factors in offsprings (about 50 %) than in parents (about 10 %). These estimates were generally higher than the results previously reported using family data and lower than the reported values for adult twin data (Feinleib and Garrison, 1979).

They attributed these findings to the use of extensive environmental indices, which were based on a set of 103 environmental variables known to be related to BP. Rice et al. (1992) reported higher cultural heritability estimated for SBP (about 40 %) than for DBP (15 %). They also reported that path analysis of BP suggested inbreeding effects with genetic variance for SBP being lower in the sample that included inbred families. Genetic heritability for DBP did not vary in the inbred and non-inbred samples and also no sample difference in cultural heritability detected either for systolic or diastolic blood pressure.

Mode of Inheritance

While there is little doubt that genetic factors play an important role in BP, specific genetic mechanism remains largely unidentified. The genetic contribution to the arterial BP was identified as early as 1930. However, whether BP is influenced by a major gene effect modified by environmental factors (Platt, 1967) and/or whether multi-factorial inheritance predominated (Pickering, 1968) still remained unresolved at this stage. To differentiate single gene from polygenic inheritance, the distribution of a characteristic in the first degree relatives of index cases can be used (Galton, 1889). Hamilton et al. (1954b) studied the distribution in a population sample, in relatives of hypertensive and in relatives of controls. They found elevated BP values with increase of age in all the three samples, but in the second group the readings were skewed toward high pressures than in the other groups in that they were roughly at the same level. They concluded that BP was multi-factorially determined and at least partly inherited. Pickering (1955) suggested that arterial BP is a continuously distributed variable without any sharp boundary

Table 3: Heritability estimates based on twin, family and adoptee studies

Study		*SBP*		*DBP*	
		h^2	c^2	h^2	c^2
Twin Studies					
Borhani et al., 1976-US male twins (aged 42-56) (ANOVA approach)		.82		.64	
Feinleib et al., 1977-Nhlbi twin study (aged 42-56)		.82		.64	
Havlik et al., 1979(a) - 7 year old twins	Black	.46		.52	
	White	.10		.70	
	Combined	.28		.27	
Levine et al., 1982-infant twins	Adj sex:0-1 Y	.22		0	
	Adj Sex wt:0-1 Y	.21		0	
	Adj sex: 6-12m	.33		.24	
	Adj Sex wt: 6-12m	.27		.17	
Hunt et al., 1989-Utah male twins(2(r-r))	Adj age	.54		.60	
	Adj age Env	.62		.65	
Wang et al., 1990-7-12 Y/O twins(2r-r)), Holzinger and within pair methods	Un Adj	.32-.41		.32-.51	
	Adj Ht BMI in SBP	.11-.28		.32-.41	
	Adj Ht SFT in DBP				
Adoption Studies					
Annest et al., 1979b-Montreal Adoption Survey (Candadian)	P	.34	.11	.30	.20
	O	.34	.11	.30	.31
Family Studies					
Iselilus et al., 1983* -meta (17 studies from the 1960s and 1970s)	Ranges from	.19	.04	.15	.01
	- to	.36	.18	.35	.31
Ewell et al., 1978 – families of female MZ twins		.47		.33	
Weinberg et al., 1979 – Bogalusa Heart Study	White	.48	-.01	.08	.13
	Black	.49	.02	.24	.04
Honis et al., 1983-Muscatine family Study (Iowa)		.15			
Longini et al., 1984 – Tecumesh		.42	.1	.30	.1
Krieger et al., 1980-Ne Brazil Fams (Triracial) (usual index)	P	.14	.04	.34	.01
	O	.41	.04	.34	.01
Morton et al., 1980-Honolulu Hear Study and Lipoprotein Family Study (Japanese-American)	P	.24	.17	.19	.20
	O	.24	.17	.19	.09
Ward et al., 1979-Tokelau Islands (Polynesian, migratory)		.28		.25	
Moill et al., 1983-Detroit Family Project (Family sets design)	White MLE	.32	.13	.23	.21
	Family sets	.43		.38	
Moll er al., 1983-Detroit Family Project (Family sets design)	Black MLE	.13	0	.29	0
	Family sets	.35		.53	
Province & Rao, 1985-HHS&LFS (age trends in c, not h, with 1gr Cultureal effect in middle ages)	From Birth	.30	.1		
	At age 36	.30	-.3		
	At age 49	.30	-.1		
Perusse et al., 1989-Quebec Family study (French-Canadian, Extensive Index)	P	.18	.31	.08	.42
	O	.49	.31	.52	.42
Rice et al., 1989-Quebec Family Study (including twins, Adoptees and extensive environmental index)	Pheno only	.16	.53	.33	.37
	P	.15	.31	.11	.42
	O	.45	.31	.52	.21
Rice et al., 1992 – Families from Andhra Pradesh		.23	.35	.28	.21

between normal and abnormal values. A review by Tyroler (1977) reported that all epidemiological studies based on large number of samples have confirmed the existence of uni-model, continuous distribution of BP in populations.

Thomas (1973) failed to find clear support for either single gene or polygenic inheritance in his study on the inheritance patterns in three generations of 262 American families. But he confirmed a strong genetic influence of both hypertension and coronary heart disease. Many researchers agreed to a multi-factorial mode of inheritance for BP (Mckusick, 1975; Longinin et al., 1984; Williams et al., 1984; Province and Rao, 1985).

Murphy et al. (1967) found a bimodal distribution of BP but the results were consistent with major gene and multi-factorial models. Modern segregation analysis performed by Krieger et al. (1980) on 1,068 families of a tri-racial

population of North-eastern Brazil revealed no evidence for major loci involvement in systolic and diastolic blood pressures. These results were again similar to those obtained by Mortan et al. (1980) for a sample of Japanese Americans. By reexamining the single gene model for BP in single kindred selected for cardiovascular disease Marazita et al. (1987) found a mixture of two distributions for DBP. Province et al. (1990) found a mixture of two distributions for both systolic and diastolic blood pressure in a large census based study. However, Marazital et al. (1987) did not find evidence for any major gene from segregation analysis.

In the large Framingham Heart study Carter and Kannel (1990) reported a rare gene for low SBP. In that study (using POINTER methodology), they observed positive results for two of the three conditions needed to infer a major gene. From a French-Canadian population study Rice et al. (1990) reported evidence for commingling for SBP in the form of two skewed distributions (both in parents and offsprings combined data and the parents' data only). Their results are compatible with a major gene effect on SBP, although the evidence was not convincing. Recently Perusse et al. (1991) presented evidence in support of a major gene effect for high SBP which was gender and age dependent. Evidence for a major recessive gene for BP in large Tecumseh community Health Study (Province et al., 1992) was found, although after adjusting the BP for obesity (body mass index), the support for the major gene disappeared. Nirmala et al. (1992) reported evidence consistent with a relatively common major recessive gene for SBP in the non-inbred Andhra population sample prior to skewness transformation. But after transformation of the data for residual skewness the evidence for only a multifactioral component resulted. For the pooled sample (inbred + non-bred samples) also the evidence supporting a major gene effect disappears and only a multifactorial effect with generational differences is significant, after the data were transformed for skewness. For DBP, they reported both a major non-transmissible effect accounting for about 20 % of the variance and a multifactorial component accounting for about 55 % (offspring) and about 15 % (parents). For the non-inbred DBP data, transformation for residual skewness removed the major non-Mendelian effect altogether. They further suggested that inbreeding effects for SBP, with a pattern of smaller variance due to multifactorial sources (i.e., polygenic and/or cultural) in the sample which included consanguineous families. Adding consanguineous families reduced the evidence for Mendelian transmission of the major effect.

Molecular Genetic Studies

The initial stage of research on BP and hypertension concentrated on quantifying the influence of genes on BP variation (Monroe and Caulfield, 2000). The contribution of genetic factors to BP variation has been established to be in the region of approximately 30-50% (Ward, 1990; Staessen et al., 2003). The fact that genes play a role motivated plethora of studies to identify genes and mutations associated with BP and hypertension. The approaches to the understanding of genetic basis of BP and hypertension have been: (i) investigation of rare forms of Mendelian forms of hypertension, (ii) candidate gene studies, (iii) comparative mapping and genome wide screening in both animal and human models, using linkage and association studies (Naber and Siffert, 2004; Garcia et al., 2003).

The discoveries of rare Mendelian forms of hypertension have revolutionized our knowledge of BP and volume regulation in understanding the bio-chemical pathways involved in the regulation of BP (Luft, 2003). There are only few monogenic forms of Mendelian hypertension reported so far in the literature. A list of monogenic forms of hypertension reported till date is presented in table 4. Till date, all the genes identified as responsible for hypertension phenotype has come from the studies of Mendelian forms of hypertension, and all are kidney-specific, operating by affecting sodium balance (Mein et al., 2004).

The approach of candidate gene study involves analyzing genes that code for proteins with a potential influence on BP regulation in large cohort or case-control studies of unrelated individuals (Naber and Siffert, 2004). Candidate genes may be selected from chromosomal loci which have been mapped in linkage analysis. In most cases candidate genes are identified on the basis of their biochemical or physiological functions which appear likely to affect BP regulation (Naber and Siffert, 2004). A variety of candidate genes have been investigated, including the rennin-angiotensin-aldosterone system, sodium epithelial channel, catechola-minergic / adrenergic function, renal kallikrein system, alpha-adducin

Table 4: Mendelian forms of human hypertension

Disease	*Mutation*
Glucocorticoid-remediable aldosteronism	Duplication of gene encoding aldosterone synthase and 11β-hydroxylase
Apparent mineralocorticoid excess	Mutation in the gene 11β-hydroxylase
Hypertension exacerbated by pregnancy	Mutations in the ligand binding domain of the mineralocorticoid receptor
Pseudohyperaldosteronism type 2(Gordon's syndrome)	Mutation is WNK Kinase 1 and 4 encoding genes[1]Mutation in at least 1 or 3 genes mapped to 1q31-42, 12p13 and 17p11-21
Hypertension with brachydactyly	Mutations mapped on 12p11.2-12.2
Peroxisome proliferators-activated receptor γ	Missense mutation
Liddle's syndrome	Mutations in the EnaC*β- or γ-subunit
Pheochromocytoma syndromes[2]	Mutation on RET gene on chromosome 10, VHL gene on chromosome 3, NF1 gene on chromosome 17 [2]

Table adapted from Naber and Siffert (2004); 1: Garcia et al. (2003), 2: Luft (2003)

and others involving lipoprotein metabolism, hormone receptors and growth factors (Timberlake et al., 2001). A list of potential candidate genes for essential hyper-tension is given in table 5.

Genome wide scans (GWS) exploit familial relationship and rely on use of highly polymorphic anonymous markers spread across the genome to pinpoint the location of genes increasing the susceptibility to hypertension or regulating BP (Samani, 2003). Past few years saw reporting of many genome wide scans for hypertension and BP variation. Two of the earlier genome wide scan studies were by Kruskal et al. (1999) and Xu et al. (1999). Kruskal et al. (1999) used a highly discordant sib-par design and found 4 regions with significant linkage for SBP located on chromosomes 2p, 5q, 6q and 15q in a Caucasian population. Xu et al. (1999) reported that no chromosome region showed genome wide significant level linkage with SBP and DBP in a GWS in discordant, highly concordant and low concordant Chinese sib-pairs of more than 200,000 adults from China. Four regions on chromosome 11, 3 16 and 17 gave suggestive linkage to SBP and one region on chromosome 15 to DBP. The two studies of Kruskal et al. (1999) and Xu et al. (1999) did not show any overlap of regions containing BP QTL.

Samani (2003) summarized the finding of the genome scan from 20 different studies. Most of the scans report nominal or suggestive linkages. Only four studies reported significant linkages (Levy et al., 2000; Allayee et al., 2001; Angious et al., 2002; Kristjansson et al., 2002), out of which two (Angious et al., 2002; Kristjansson et al., 2002) were done on relatively isolated populations which are likely to be homogenous. A number of regions on chromosomes 1q, 2p, 3p, 6q, 7q, 11q, 12q, 15q, 16q, 18q and 19p have been found in more than one study. Thus numerous chromosomal regions with evidence of linkage were reported (Samani, 2003; Mein et al., 2004; Garcia et al., 2003).

Table 5: Examples for potential candidate genes for essential hypertension

Related mechanisms	*Selected genes*	*Selected polymorphisms*	*Chromo-some*
Renin-angiotensin system	Angiontensinogen (AGT)	C-532T; G6A; T174M; M235T	1
	Angiotensin converting enzyme (ACE)	Alu deletion/insertion intron 16	17
	Angiotensis II type 1 receptor (AT1R)	A1166C	3
	Aldosterone synthase (CYP11B2)	C-344T	8
Sympathetic nervous system	α2B-adrenergic receptor (α2AR)	Glu deletion/insertion 297-309	2
	β1-adrenergic receptor (β1AR)	Arg389Gly; Ser49Gly	10
	β2-adrenergic receptor (β2AR)	Arg16Gly; Gln27Glu	5
G protein signaling	B3-subnit (GNB3)	C825T	12
	G protein coupled receptor kinase 4 (GKR4)	R65L; A142V; A486V	4
	GPR10 (PRLHR)[1]	G-62A and C914T	10
Vasoactive peptides	Endothelial nitric oxide synthase (NOS3)	T-786C; G894T	7
	Carbamyl-phosphase synetase (CPS1)	T1405N	2
	EDHF aynthase (CYP 2C8	R139K; K269F; K399R	10

Table adapted from Naber and Siffert (2004); 1: Frank et al. (2004)

Table 6: Genome scans for blood pressure and hypertension

Study	*Acronym*	*Setting*	*Phenotype*	*Participants*	*Results*
Krushkal et al.	GENOA	USA	SBP	69 discordant sibpairs. White Americans	2p (57–59 cM); 5q (188–192 cM) 6q (134–155 cM); 15q (84–101 cM)
Xu et al.	-	China	SBP; DBP	207 discordant sibpairs, 258 high concordant sib-pairs and 99 low concordant sibpairs	3p (5.5 cM) (SBP); 11q (63 cM) (SBP) 16q (64 cM) (SBP); 17p (23.5 cM) (SBP); 15q (105 cM) (DBP)
Sharma et al.	-	UK	Hypertension	169 ASPs with early hypertension (_50 y). Whites	11q (126 cM)
Hsueh et al.	-	USA	SBP; DBP	28 large pedigrees (436 parent-offspring trios, 1326 sibpairs, 1342 avuncular pairs, 1311 first cousin pairs). Amish	2q (205–224 cM) (SBP& DBP)
Rice et al.	Quebec Family Study	Canada	SBP; DBP	206 nuclear families	1p (87–120 cM) (SBP); 2p (96–115 cM) (SBP); 5p (14–46 cM) (SBP); 7q (135–150 cM) (SBP); 19p (3–7 cM) (SBP)
Pankow et al.	HyperGEN	USA	Postural change in SBP or DBP	498 hypertensive sibpairs	18q (66–89 cM) (_SBP); 6p (34–42cM) (_SBP& _DBP)
Levy et al.	Framingham Heart Study	USA	Longitudinal SBPand DBP	332 white families (993 parent-offspring trios, 1548 sibpairs, 468 avuncular pairs, 742 first cousin pairs)	**17q(60 –76 cM) (SBP** & DBP); 17q (90–100 cM) (SBP); 18p (7 cM) (DBP)
Perola et al.	-	Finland	Hypertension	47 ASPs with onset _50 y in at least one sib	1q (170 cM); 2q 184 cM); 3q (165 cM); 22q (32 cM); Xp (43 cM)
Zhu et al.		China	Hypertension	1273 ASPs with hypertension diagnosed before age 60 y Han Chinese.	2q (140–165 cM)
Atwood et al.	San Antonio Family Heart Study	USA	SBP; DBP	495 individuals in 10 large unselected Mexican American pedigrees	18q (116 cM) (SBP); 21q (37 cM) (SBP); 2p (103 cM) (DBP); 8q (164cM) (DBP)
Allayee et al.	-	Holland	SBP; DBP	18 extended Dutch families (561 individuals) with familial combined hyperlipidemia	**4p (13–43 cM) (SBP);** 19p (0–10 cM) (SBP); 6q (80–102 cM) (DBP); 8p (44 cM) (DBP)
Harrap et al.	Victorian Family Heart Study	Australia	SBP; DBP	274 adult sibpairs. White	1p (65–95 cM) (SBP); q (95–132cM) (SBP); 16p (40–62 cM) (SBP); X (37–52 cM) (SBP)
Rice et al.	HERITAGE	USA	SBP; DBP	114 African American families (including 138 sib-pairs); 99 White American families (including 370 sibpairs)	2p (86 cM) (SBP) (African Americans); 3p (5 cM) (SBP) (whites); 3q (201 cM) (SBP) (whites); 11q (85 cM) (SBP) (whites); 19p (48.5 cM) (SBP) (African Americans); 12q (95 cM) (DBP) (African Americans)
Kristjansson et al.	deCODE	Iceland	Hypertension	120 families with 490 affected subjects (906 related pairs of varying degrees)	**18q(80 –94 cM)**

Table 6: Contd.....

Study	*Acronym*	*Setting*	*Phenotype*	*Participants*	*Results*
Hunt et al.	NHLBI Family Heart Study	USA	Hypertension; SBP; DBP	2959 individuals in 401 families. White Americans	1q (192 cM) (hypertension); 6q (89 cM) (SBP); 7p (58 cM) (hypertension); 7q (127 cM) (hypertension); 12q (83 cM) (hypetension); 15q (103 cM) (hypertension)
Angius et al.	-	Sardinia	Hypertension	Selected subjects from a large extended pedigree containing 35 hypertensives	**2p (26.5–27.1 cM)**
FBPP studies					
Thiel et al.	GenNet	USA	SBP; DBP	514 pairs (sib or half-sib) in 211 Afro-American families; 394 pair (sib or half-sib) in 160 white families.	1q (168–170 cM) (DBP) (whites); 11q (76 cM) (SBP) (whites); 3q (119 cM) (DBP) (whites)
Rao et al.	HyperGEN	USA	Hypertension	3403 individuals (1818 ASPs) in 489 white and 599 Afro-American families	2p (63 cM) (Afro-American)
Kardia et al.	GENOA	USA	Hypertension	989 ASPs in 229 Afro-American and 251 white families with hypertension diagnosed before age 60 y	None
Ranade et al.	SAPPHIRe	USA, Hawaii, Taiwan	Concordance or discordance for hypertension or low BP	1123 Chinese sibpairs and 302 Japanese sibpairs (661 concordant for hypertension, 184 concordant for low Bpand 580 discordant)	9q (163 cM) (low BP); 10p (30 cM) (concordant and discordant sibpairs) 14q (92 cM) (hypertension)
Caulfield et al. (2003)[1]	BRIGHT		Hypertension	2010 affected sibling pairs drawn from 1599 severely hypertensive families	**6q, 2q, 5q and 9q**
Von Wowern et al. (2003)[2]		-		Hypertension Scandinavian families with early onset of hypertension	Sib-pairs from 91 **14 (41 cM)** 2 (118cM)
Camp et al. (2003)[3]		USA	Pluse pressure	26 large Utah pedigrees	**8p (at 15.7cM), 12q (20.0 cM)**
Gong et al. (2003)[4]		China	Hypertension	A large Chinese hypertensive kindred (387 individual)	**12p**

ASPs: affected sibpairs; SBP: systolic blood pressure; DBP: diastolic blood pressure.
Results lists the approximate location of reported linkages and specifies the phenotype or ethnic groups where relevant. Results that met criteria for genome-wide significance are shown in bold.
Table adapted from Samani (2003); 1: Caulfield et al (2003); 2: Von Wowern et al (2003) 3: Camp et al (2003); 4: Gong et al (2003)

In the year 2003 results from two very large size genome wide study were reported: the US NIH funded Family Blood Pressure Program (FBPP) and the British genetics of Hypertension (BRIGHT) study. The FBPP comprised of four multi-centric networks; each centre recruiting participants from multiple ethnic group. None of the networks found a chromosomal region with genome wide significant evidence of linkage. No compelling candidate genes were reported from the region of chromosome 19q which showed the highest LOD score of 2096 for DBP (Kardia et al., 2003; Rao et al., 2003; Thiel et al., 2003; Mein et al., 2004).

The BRIGHT study represents the largest homogenous Caucasian resource that has been published (Mein et al., 2004). 2010 affected sibling pairs drawn from 1599 severely hypertensive families were phenotyped and a 10 centi-Morgan (cM) GWS was performed (Caulfield et al., 2003). Non-parametric linkage analysis identified a principle locus on chromosome 6q that attained genome wide significance. Three further loci (at 2q, 5q and 9q) also showed genome wide significance when assessed under a locus-counting analysis. Comparison of these two large genome scan studies (FBPP and BRIGHT) did not reveal any overlap between the linked regions (Mein et al., 2004).

Von Wowern (2003) found one region on chromosome 14 which attained genome wide significance and a locus on chromosome 2 with suggestive linkage in a smaller study of Scandinavian families. Gong et al. (2003) found a locus on chromosome 12p in a study of large Chinese hypertensive kindred. This region overlaps with the region containing the gene for autosomal dominant hypertension with type E brachydactyly. In a study for pulse pressure Camp et al. (2003) found suggestive evidence of linkage on chromosome 8p and 12q based on genome scan among 26 large Utah pedigrees. But the results were not concordant with a previous study for pulse pressure in other ethnic group.

Genome wide scan with 378 microsatellite markers typed on 792 individuals in 196 families from south west Nigeria by Cooper et al. (2002) identified linkage signals for SBP on 19p (D19S714) and for DBP on 2p (D2S1790) , 3p (D3S1304), 5q (D5s1462), 7p (D7S3046), 7q (D7S821) and 10q (D10S1221). Some other regions of interest were also found on chromosome 1, 6, 8, 9, and 11. They concluded that the current evidence appears to implicate, in particular 2p, 3p and 19p. In other study on Nigerian population Adeyemo et al. (2005) found evidence of genome wide significant linkage for SBP on chromosome 6q, 7p and 7q and for DBP on 7q based on a multi stage genome scan. A list of GWS studies for BP/hypertension is given in table 6.

The development of novel rat model systems that mimic many elements of human disease, have potential to revolutionize the hunt for genes that determine susceptibility to hypertension (Cowely Jr., 2006). Genome wide scanning has been widely used to map BP QTLs in inbred hypertensive rat stains. Reproducible rat and mouse QTSs present good candidates for comparative mapping in human hypertension (Monroe and Caulfield, 2000). Julier et al. (1997) and Baima et al. (1999) have used the comparative mapping approach and found evidence for linkage of marker on human chromosome 17.

Studies like Haluska et al. (1999) and Cargill et al. (1999) reported new SNPs using chip-based technology that might be important in BP regulation. SNPs are detected in candidate genes for BP homeostasis. Haluska et al. (1999) reported two extra SNPs per gene in people of African ancestry.

Yamamoto et al. (2006) reported that T102C functional polymorphism of the serotonin 2A receptor gene (5-HT2A T102C) and C/T (Lys 198 Asn) polymorphism of the endothelin-1 (Et-1 G/T) are interactively associated with hypertension in a study of two large Japanese populations.

There have been a few studies on molecular level in India which dealt with hypertension or related cardiovascular diseases (CVD). Studies on Indians like that of Nair et al. (2003), Sharma et al. (2006), Tripathi et al. (2006) and Kaur et al. (2006) focused on prevalence of gene polymorphism associated with hypertension/CVD in patients of CVD in contrast to normal controls. Of the above four, only Sharma et al. (2006) could get a similar result for Indians as was reported in previous studies elsewhere. In a study of ACE polymorphism in India, Mastana and Nunn (1997) reported that the ACE deletion allele was observed with a greater frequency in hypertensive than in the normotensive individuals as has been previously observed among the populations of African-American and Japanese origins. Subsequently, similar results for ACE deletion allele were obtained among populations of other ethnicities.

A review of all human genome scan studies

for BP, hypertension and pre-eclampsia genes by Mein et al. (2004) showed that all human chromosomes except 13 and 20 have shown BP, hypertension or pre-eclampsia loci. More than one study found evidence for BP loci on 1, 2, 8, 11, 12, 15, 16, 18, and 19. Reporting of so many different loci linked to BP and hypertension indicates that multiple loci with very modest influence may be responsible for hypertension and BP regulation. The reported genome scan studies suggest that there are no major genes for hypertension, and it is highly likely that there are many genes with genotype relative risks of 1.2 – 1.5 (Mein et al., 2004). There is always a risk of reporting false positives in genome wide scan studies. It is a challenge to confirm the loci showing statistical significant linkage association as a predisposing hypertension. To have high power in association studies for detecting genes with lower relative risk requires large sample size. Studies with large sample size tend to loose on homogeneity; and here lies the problem of large scale genome wide scan studies. Study design and statistical testing has to be refined for having appropriate power in the genome wide association studies to detect genes with lower relative risk.

CONCLUSIONS

From the forgoing pre-molecular studies on the effects of the genetic and environmental factors on BP, it was clear that, whatever the mode of inheritance, there is significant genetic influence which is responsible for BP variation. But the problem however remained to be resolved is whether BP is influenced by a major gene effect modified by environmental factors and/or whether multi-factorial inheritance predominates. Although, some investigators reported major gene effect for BP (Carter and Kannel, 1990; Rice et al., 1990: Perusse et al., 1991; Nirmala et al., 1992), others did not find any support for a major gene (Morton et al., 1980; Kreiger et al., 1980: Marazita et al., 1987). The inconsistent nature of these findings led to the speculation that there is considerable genetic and /or environmental heterogeneity in determination of BP.

The reporting of so many linkage/association sites on different chromosomes for hypertension and BP variation, with the advent of molecular studies especially genome wide scans, indicates that a major gene would not be ever found responsible for hypertension. Moreover, the trait being studied is not a single entity but a combination of several polygenic quantitative traits which covary interactively along with the environmental covariates in different combinations in different individuals and populations (Lele, 2004). Thus it is possible that the same gene variant may have an opposite effect on BP according to genetic and environmental back-grounds (Barlassina et al., 2002). Studying hypertension or BP regulation by breaking it down to several polygenic traits based on biochemical pathways may be the future course of research for pinpointing the genes for hypertension. Nevertheless, there is overwhelm-ing evidence suggesting that the environmental factors have a major role to play as well for the development of arterial hypertension. It might be possible that different environmental factors may have different degrees of influence on the development of hypertension in different geno-types (individual/populations). It is generally assumed that the predominance of the environ-mental factors' role over that of genes increases with age (Pickering, 1968). Moreover the effects of environmental variables on BP have been found to vary from one study to another and it is highly probable that the effects of many environ-mental variables are only transient and not sustained (Oliver, 1980). Nirmala (1991) reported evidence suggesting a different mode of environ-mental influence on BP in Indian population in contrast to western societies and proposed a new model called NIRMIX. It is thought desirable to have more studies of this type in diverse popu-lation groups from all over the world in order to assess the role of genetic effects in different cultural/environmental contexts. The molecular genetics studies need to take into account more and more relevant environmental variables in search for genes for hypertension and BP regulation. As the environment and life styles of the populations differ widely in different countries it is expected that they may provide knowledge of the relative roles of genes and environment in the formation of BP phenotype. Future studies on non-modernized traditional homogenous populations and the transitional populations hold the key to further resolving the problem of hypertension.

India is inhabited by many diverse tribal and caste populations which have genetic homogeneity because of the practice of endogamy. Because of the historical reasons, India offers immense genetic and cultural heterogeneity, yet

constituting precisely defined Mendelian populations with impermeable genetic boundaries. This situation provides the most ideal framework to untangle the complex nature of BP regulation and hypertension. Unfortunately most of the studies in India did not include population based samples. Future studies on Indian populations might be fruitful in establishing the precise nature of association between BP and gene polymorphisms and/or identifying new genes/mutations specific to Indian populations. Moreover, the transitional nature of the quite a few of the populations in India, also provides an opportunity to study the gene environment interactions. A better understanding of gene-gene and gene environment interaction is necessary for realizing the pharmacogenetic treatment of hypertension.

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KEYWORDS Hypertension. Environment. Risk Factors. Families. Sibs. Molecular Genetics. Genome Wide Scan.

ABSTRACT Worldwide hypertension affects almost 20% of the adult population. The rates of hypertension have shown an increasing trend in recent times especially among the developed and developing countries. A comprehensive review of the literature on the genetics of blood pressure and hypertension encompassing the pre-molecular and molecular phase of the research is being presented. Many studies have used the familial nature, family history, twins and family based approaches to establish the genetic nature of BP and hypertension. Most studies have found that environmental variables also play an important role in BP regulation. Studies trying to establish the mode of inheritance (major/minor genes) of BP/hypertension, in the pre-molecular phase, have been either inconclusive or gave conflicting results. Molecular genetic approaches in the investigation of the genetic basis of BP and hypertension have largely relied on rare Mendelian forms of hypertension, candidate gene approaches, comparative mapping and genome wide screening in both animal and human models, using linkage and association studies. Genome wide scan studies have shown that all human chromosomes except 13 and 20 have shown regions of significant association with BP or hypertension. However, the lack of consistency in the nature of associations found is glaringly apparent which may be due to the complex nature of the BP/hypertension phenotype, probably determined by multi-factorial inheritance. Future studies on traditional and transitional homogenous populations with proper sampling of individuals hold the key to further resolving the problem of hypertension. Studies on Indian populations because of their endogamous nature might be fruitful in establishing the precise nature of association between BP and gene polymorphisms.

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