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Consortium on Interplay of Genes and Environment Across Multiple Studies

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Overview

The Interplay of Genes and Environment across Multiple Studies (IGEMS) group is a consortium of longitudinal twin studies of adult development and aging established a decade ago to explore the nature of social context effects and gene-environment interplay in late-life functioning. The combined data contains information from over 50,000 individual participants aged 25–102 at baseline (including nearly 20,000 complete twin pairs) with median follow-up of 9.5 years. Studies include measures of aging-relevant outcomes in three broad domains: physical health and functional ability, psychological well-being (emotional stability/depression), and cognitive health. Studies also include multiple indicators of the social environment, spanning early childhood through late adulthood, and, by virtue of different nationalities and birth years, encompass different environmental contexts with respect to healthcare, retirement systems, and other social policies.

Research has firmly established the association of social context with late-life health and functioning. Yet this research unambiguously explicates neither the basis for these associations nor how social context relates to the biological and genetic factors known to contribute to later life functioning. The advantage of twin studies is the strengthening of causal inference through co-twin control methods (McGue et al. 2010) and use of biometric models to quantify the extent to which associations between risk and outcome are driven by the same genetic or the same environmental influences (van der Sluis et al. 2012).

Several longitudinal twin samples, located in different countries and employing somewhat different measures, have individually accumulated substantial data. However, large sample sizes are needed to test gene-environment interactions, and collaborating across studies enriches environmental variation. Consequently, a collaboration among existing longitudinal twin studies was initiated, with a central focus on determining how social context is related to physical functioning (health, functional ability) and psychological functioning (well-being, cognition) in mid-life

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and older ages. Through this, a foundation has been laid for future studies of gene-environment interplay in late-life functioning.

The heuristic model that guides the investigation of gene-environment interplay in late-life functioning emphasizes the importance of two gene-environment processes, built on Schmalhausen (1946), Shanahan and Hofer (2005), Boardman et al. (2013), and Reiss et al. (2013). First, it is hypothesized that environmental exposures and social contexts do not occur at random but rather reflect an individual's genetically influenced behavior and choices (i.e., gene-environment correlation). It is known, for example, that there are heritable influences on social factors including social support, social engagement, and social isolation. It is further hypothesized that gene-environment correlations are a major contributor to late-life phenotypic stability. Data in the IGEMS consortium allow researchers to chart the contributions of changes in social context to behavioral discontinuities; the twin study design allows researchers to further explore the nature of gene-environment interplay in these transitions.

Second, it is hypothesized that experiential factors can either diminish or amplify the influences of genetic effects on late-life outcomes (genotype by environment interaction, G × E). Two alternative models of G × E are directly relevant. Evolutionary models predict that the G × E form recognized most broadly as the *diathesis-stress model* will be more pronounced in late life. Specifically, during most of life, the typical human lives in an environment that is low in stress relative to the environments in which their species evolved. In old age, biological, psychological, and social stresses are considered to be higher due to more negative change or declines. Thus, at times of relatively increased stress – such as old age – an organism's response to an unfavorable environment will depend on a unique combination of genes, so that deleterious genetic effects on physical manifestations of health will be maximized. This pattern of findings is supported by earlier work by IGEMS investigators, showing that the heritability of physical health in mid-life is maximized when current income (Johnson and Krueger 2005) is low.

Alternatively, environmental factors can suppress genetic effects. This model is particularly relevant to extreme forms of physical disability or disease, which diminish the impact of genetic factors by reducing the opportunity for self-selection of activities that maintain stable functioning.

Study Design and Features

IGEMS has grown from 5 studies to, now, 16 studies or cohorts, encompassing 5 countries: Sweden, Denmark, Finland, the United States, and Australia. The total sample size is 52,456 individuals including both members of 7064 monozygotic pairs and 12,686 dizygotic pairs, of which 3997 pairs are opposite sex. (Total Ns include members of incomplete pairs.) Brief descriptions for each participating study are provided below. Links to further information about each study can be found at https://dornsife.usc.edu/labs/igems/. Several studies have also made their data publicly available, for example, via the National Archive of Computerized Data on Aging.

Sweden

Swedish studies are independent samples each drawn from the population-based Swedish Twin Registry. The Swedish Adoption/Twin Study of Aging (**SATSA**) began in 1984. The base population comprises all pairs of twins from the registry who indicated that they had been separated before the age of 10 and reared apart, and a sample of twins reared together matched on the basis of gender, date, and county of birth. The **OCTO-Twin** Study (Origins of Variance in the Old-Old) included twin pairs who were over the age of 80 at baseline in 1991. **GENDER** is a study of unlike-sex twin pairs born between 1906 and 1925. The Twin and Offspring Study in Sweden (**TOSS**) includes 909 pairs of same-sex twins who were parents of adolescents.

Denmark

The Longitudinal Study of Aging Danish Twins (**LSADT**) began in 1995 with the assessment of members of like-sex twin pairs born in Denmark

prior to 1920. The study of Middle-Aged Danish Twins (**MADT**) includes twins ranging in age from 46 to 68 years at the original assessment. The Mid-aged Danish Twin (**MIDT**) study includes 10,487 twins representing all members of the Danish Twin Registry for the birth years 1931 through 1969 not already participating in MADT.

Finland

The older Finnish Twin Cohort (**FTC**) study started in 1975 by contacting all same-sex Finnish twin pairs born before 1958 with both co-twins alive in 1975 (N = 13,888 pairs). From this cohort, female pairs aged 63–76 in 2000–2001 participated in the Finnish Twin Study on Aging (FITSA). Follow-up examinations were in 2003–2004 and a survey in 2011. FinnTwin16 (**FT16**) is a cohort of younger twins born between 1975 and 1979. Waves 4 and 5 are included in IGEMS.

United States

Each US study consists of an independent sample. The Minnesota Twin Study of Adult Development and Aging (**MTSADA**) is a population-based sample drawn from state birth records. Two-thirds of the sample was age 60 years or older at intake. The Vietnam Era Twin Study of Aging (**VETSA**) is a community-dwelling sample of male-male twin pairs, all of whom served in some branch of US military service sometime between 1965 and 1975. Wave 1 testing took place between 2003 and 2007; wave 3 is now underway. Mid-life in the United States (**MIDUS**) is a national telephone/mail survey originally carried out in 1995–1996 that included specific recruitment methods for twins. The Carolina African-American Twin Study of Aging (**CAATSA**) used public records including census, vital statistics, social security death records, a credit reporting service, and voter registration records to identify all living African-American twins in the State of North Carolina born between 1920 and 1970. Project Talent is a longitudinal study begun in 1960, with a nationally representative sample of 377,000 US high school students born 1942–1946. Follow-up surveys were conducted at ages 19, 24, and 29. The Project Talent Twin and Sibling Study (**PTTS**) tracked 96.4% of the original PT twins and siblings of twins in the PT sample, including 21.0% identified as deceased. A survey was mailed in 2014 to this sample, now aged 69–73, and cognitive assessments are underway.

Australia

Both Australian cohorts were recruited from the Australian Twin Registry. The Australian Over 1950s study (**A50**) is based on a questionnaire mailed between 1993 and 1995 to twins age 50–95. **OATS** incorporates in-person assessments every 2 years for twins aged 65 and older, and it is currently completing its fourth wave.

The range in study years and intake ages across the 16 IGEMS studies results in unique coverage

Consortium on Interplay of Genes and Environment Across Multiple Studies, Table 1 Number of individuals by birth cohort in IGEMS studies. Columns indicate birth years, while rows indicate age at first assessment. The number of cohorts shows the number of IGEMS studies contributing data to each row

	BIRTHYEAR (% Women)							
INTAKE AGE	<1914	1915-1929	1930-1944	1945-1959	1960-1974	1975+	TOTAL	# cohorts
<35			2540 (54%)	2279 (52%)	503 (60%)	5382 (54%)	10704 (54%)	4
35-49			319 (50%)	2817 (59%)	3471 (60%)	2 (0%)	6609 (59%)	3
50-64		764 (55%)	5602 (59%)	14323 (49%)	352 (56%)	1 (100%)	21042 (52%)	4
65-79	504 (65%)	5754 (58%)	3641 (51%)	1444 (53%)			11343 (55%)	4
80-94	2484 (65%)	241 (63%)	1 (100%)				2726 (65%)	2
95+	32 (66%)						32 (66%)	1
TOTAL	3020 (65%)	6759 (58%)	12103 (55%)	20863 (51%)	4326 (59%)	5385 (54%)	52456 (55%)	

of cohorts and historical periods. As shown in Table 1, the IGEMS sample permits sequential comparisons across six cohorts. This feature is an enormous advantage in sorting out age and cohort effects.

IGEMS Measures

Measures used in IGEMS analyses include aging-relevant outcomes in three broad domains: physical health and functional ability (e.g., self-reported diseases, subjective health, BMI, grip strength, motor function, activities of daily living), psychological well-being (e.g., depressive symptoms, anxiety symptoms, subjective well-being, loneliness), and cognitive health (i.e., scores on cognitive tests; survey assessments of dementia). Predictors and covariates include health behaviors (e.g., smoking, alcohol, physical activity, cognitively engaging leisure activity), social resources, and indicators of socioeconomic status.

Given differences across studies in how similar constructs were assessed, strong emphasis is placed on harmonization of relevant phenotypes and outcomes to enable the combined analysis of the multiple sets of data. Because integrative data analysis (IDA), where data are pooled across samples to increase power and finely consider between-study heterogeneity, is the preferred method, scale scores were created that are common across studies. This requires overlapping item content across the studies as well as across time for longitudinal hypotheses. For some measures, it was possible to identify a common metric, e.g., body mass index (BMI), lung function, and blood pressure. For harmonizing education and occupation, all studies were recoded to ISCED and ISCO, as an international standard. Where a common metric was not already available, item response theory (IRT) techniques were implemented to create harmonized scores across studies. Recoding was accomplished by identifying overlapping item content and response formats and then applying psychometric analysis to establish measurement invariance via IRT and factor analytic approaches. Multiple common items should be available to test that item functioning is similar across samples. Where there were no common items across studies, a separate sample was collected to whom was administered the different measures used in different IGEMS studies to measure a given construct, with those results used to establish "crosswalks" between the different scales (Gatz et al. 2015).

Major Findings

Co-twin Control or Within Pair Methods

Co-twin control methods test whether associations between early life exposures and late life outcomes are mediated by genetic influences. Associations between exposure and outcome for individuals to twin analyses that ask whether pairs who differ on exposure also differ on outcome were compared. For example, Mosing et al. (2018) found that reduced fetal growth was associated with dementia and cognitive impairment in adulthood. As these associations were somewhat attenuated in a co-twin control analysis, there is evidence that the association is in part due to a shared etiology, which could be either genetic influences that relate to both birth characteristics and cognition or to the environment shared within families.

Other within-pair work with monozygotic pairs used MZ within-pair differences to test for the presence of gene x environment interaction without having a specific measured early environment. With this approach, established evidence of GxE for BMI, depressive symptoms, a physical illness index, and cognition (verbal, spatial, attention, working memory, perceptual speed) was established (Reynolds et al. 2016), as well as for longitudinal grip strength trajectories (Petersen et al. 2016). Results also suggested that apolipoprotein (*APOE*) may represent a "variability gene" for depressive symptoms and spatial reasoning but not for BMI or other cognitive measures, with greater intrapair differences for noncarriers of the *APOE* ε4 allele. For grip strength trajectories, a buffering effect for *APOE* ε2 carriers emerged, with lower sensitivity to environments and better-maintained performance.

Biometric Methods for Testing Gene-Environment Interplay

GxE interactions in relation to cognitive performance (Pahlen et al. 2018; Zavala et al. 2018), depression (Petkus et al. 2017), subjective health (Franz et al. 2016), BMI (Johnson et al. 2012), and grip strength (Petersen et al. 2016) were examined. For most phenotypes, unique environmental variance was greater at older ages, presumably reflecting the accumulating importance of individual differences in environmental context with age. However, there was a nonuniform pattern for genetic factors over age, in combination with SES or sex moderation. In SES moderation analyses of cognition, for verbal ability and for perceptual speed (Zavala et al. 2018), genetic variance was diminished in those with higher SES, perhaps reflective of a buffering effect on normative aging processes particularly for speed, whereas for short-term/working memory and spatial performance, genetic variance was amplified with higher SES, suggesting enriched (high SES) environments may support genetic variation. For BMI (Johnson et al. 2012), there was also SES moderation with diminished genetic influences with high education. The extent and type of moderation differed by gender, country, and age group.

Using a harmonized measure of financial strain, it was found that financial strain moderated genetic and environmental influences on subjective health, such that greater financial strain dampened the expression of genetic variance for subjective health in men, only. Lower levels of financial strain were associated with greater heritability for men (Finkel et al. 2016).

Future Plans

Two features are being added to the next phase of IGEMS work. First, analyses are capitalizing on the availability of polygenic risk scores to analyze as a complement to and in combination with twin methods. Second, measures of the macroeconomic environment are being added which we will be used to characterize the influences from growing up and growing older in different countries and at different historical times. The two main themes driving current and future work are testing models of G-E interplay to better understand the SES-health gradient and applying twin designs to study possible etiological mechanisms in Alzheimer's disease and related disorders (ADRD).

IGEMS SES Project Summary

While most research on health disparities focuses on individual-level socioeconomic status – defined as social status that accrues to occupational classification, education, and income – new research has begun to focus on the macroeconomic environment. Further, although both genetic and environmental factors are known to contribute to the SES-health gradient, the mechanisms by which the two sets of factors combine to influence health outcomes (i.e., GE interplay) are poorly understood. Models of GE interplay differ in their environmental focus (disease-triggering effects of toxic environments vs. health-promoting benefits of favorable environments) and the expected genetic contribution to disease (maximized in adverse environments, in favorable environments, or at both extremes). Understanding whether high SES preferentially promotes good health among a genetically selected subset of individuals (i.e., social enhancement), whether low SES triggers poor health among a genetically vulnerable subset of individuals (i.e., diathesis-stress), or both is essential for translating research in this area into effective prevention strategies.

Dementia Project Summary

While it is well-recognized that ADRD occurrence reflects the influences of multiple genes and multiple environmental and lifestyle risk and protective factors, designs to elucidate potentially informative gene-environment interplay have been rarer. IGEMS studies offer measures of lifestyle, health, and psychosocial risk and protective factors across different life stages. Co-twin control methods strengthen causal inferences from observational studies. Other twin designs test the extent to which the association between risk or protective factor and ADRD reflects shared genetic or shared environmental explanations. In

addition, PRS are being used as indicators of individual genetic risk for ADRD to test whether genetic risk for ADRD alters susceptibility to other risk and protective factors and PRS for specific risk and protective factors to test whether genetic risk for these factors alter their association with ADRD. A new focus reflects clarifying the nature of the relationship between education and ADRD; mid-life obesity, vascular risk, depression, and physical activity; and sex or gender differences in genetic risk, exposure to specific risk factors, susceptibility to specific risk factors, and sex differences in genetic interactions with specific risk factors. These questions importantly inform the design of interventions to prevent or slow occurrence of dementia.

Summary

The social stratification of health is well documented, pervasive, and of growing concern because it appears to be increasing over time. Reducing these social class disparities will require greater understanding of how social class impacts health than we currently have. The IGEMS consortium harnesses a combination of twin design and multiple studies representing different cohorts and contexts. The consortium demonstrates the feasibility of this type of collaboration in addressing gene-environment interplay with respect to important age-related outcomes.

Cross-Reference

► Genetics: Gene-Environment Interaction

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