

1 **Natural selection increases mutational robustness in complex diseases:**
2 **Mendelian evidence from early versus late onset common diseases**

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1 ABSTRACT

2
3 **Background.** Natural selection operates on genetically influenced phenotypic variations that
4 confer differential survival or reproductive advantages. Common diseases are frequently
5 associated with increased mortality and disability and complex heritable factors play an
6 important role in their pathogenesis. Hence, common diseases should trigger the process of
7 natural selection with subsequent population genetic response. However, empirical impact of
8 natural selection on genetics of complex diseases is poorly understood. In this paper, I
9 hypothesize that negative selection of diseased individuals leads to systemic genetic differences
10 between common diseases that primarily occur before or during the reproductive years (early
11 onset) and those that occur after the reproductive years (late onset).

12
13 **Methods.** To test this hypothesis, a comprehensive literature survey of highly penetrant (80% or
14 more) nonpleiotropic, nonsyndromic susceptibility genes (hereafter defined as Mendelian
15 phenocopies) was completed for early versus late onset common diseases, organized using the
16 World Health Organization (WHO) ICD-10 classification scheme. An average age at sporadic
17 disease onset of 30 years was selected for dividing early versus late onset common diseases.

18
19 **Results.** Mendelian phenocopies were identified for 16 primarily late onset common diseases
20 from 9 distinct WHO diagnostic categories. Late onset common diseases with Mendelian
21 phenocopies include papillary renal carcinoma, obesity, Alzheimer disease, Parkinson disease,
22 frontotemporal dementia, amyotrophic lateral sclerosis, primary open angle glaucoma, age-
23 related hearing loss, coronary artery disease, stroke, pancreatitis, thrombotic thrombocytopenic
24 purpura, systemic lupus erythematosus, inclusion body myositis, Paget's disease of bone and

1 focal segmental glomerulosclerosis (steroid resistant). In contrast, no Mendelian phenocopy was
2 found for any primarily early onset common disease ($p < 5.8 \times 10^{-4}$). Thus, highly predictive rare
3 variants are present for a subset of late onset common diseases, but not for early onset common
4 diseases.

5
6 **Discussion.** These findings suggest that genetic architecture of early onset common diseases is
7 more robust against the phenotypic expression of highly penetrant predisposing mutations than is
8 the case for late onset common diseases. The primary candidate for increased genetic robustness
9 in early onset common diseases is proposed to be natural selection.

1

2 **Introduction**

3 Random variation and natural selection are the two fundamental principles of modern
 4 evolutionary synthesis (Mayr & Provine, 1998). Conditions for the process of natural selection
 5 are met when (a) there is a phenotypic variation in a population; (b) there is a consistent
 6 relationship between the variation and survival and/or reproductive capabilities; and (c) the
 7 variation is at least in part determined by genetic factors (Endler, 1986). The phenotypic and
 8 genetic characteristics of common diseases often meet these three criteria; as such, natural
 9 selection should operate on diseased individuals. Common diseases represent genetically
 10 influenced phenotypic variations that are frequently associated with increased mortality or
 11 morbidity. Family, twin and epidemiologic studies indicate that both environmental and genetic
 12 factors contribute to common disease susceptibility. However, despite some successes of genome
 13 wide association studies in identifying common susceptibility variants, the genetic architecture of
 14 common diseases remains largely unknown (Manolio et al., 2009). Because long-term natural
 15 selection leads to population genetic changes that contribute to an individual organism's
 16 adaptation to the environment, understanding how natural selection influences common disease
 17 susceptibility loci may also increase our understanding of the genetic architecture of complex
 18 diseases.

19

20 Sequence analyses of common disease loci implicated by case-control association studies for
 21 signatures of selection reveal mostly mixed patterns of positive and negative selection
 22 (Blekhman et al., 2008). Similarly, patterns of amino-acid changing single-nucleotide variations
 23 in common disease susceptibility loci are comparable to those in neutrally evolving loci (Thomas
 24 & Kejariwal, 2004). Results from studies such as these suggest that natural selection operating

on individual common disease susceptibility loci does not leave a specific genetic signature that is readily distinguishable from neutrally evolving loci. An alternative and potentially novel approach to assess the impact of natural selection is to compare the genetic architecture of common diseases that primarily occur before or during the reproductive years with those that occur after the reproductive years. Negative selection of individuals with early onset common diseases should alter population frequencies of susceptibility variants as a result of premature death or reduced reproductive fitness associated with the disease. In contrast, diseases that primarily occur after the reproductive years should not alter population gene frequencies between successive generations.

Here, to test for genetic architectural differences in early versus late onset common diseases, highly penetrant, nonsyndromic, nonpleiotropic disease phenotypes (Mendelian phenocopies) are evaluated. The underlying assumption driving this approach is that the population genetic response to natural selection may result in differences in certain characteristics of susceptibility variants (e.g. prevalence, penetrance, variant type) between early and late onset common diseases. Highly penetrant predisposition genes were initially selected because the pathogenic role of such loci is often readily confirmed by the identification of multiple *bone fida* mutations that are virtually absent in the population, but do co-segregate with disease in rare extended families. Mendelian phenocopies were stringently confined to those with at least an 80% cumulative penetrance. To test for the long-term evolutionary impact of natural selection, 30 years was selected as the age for dividing early versus late disease onset. This age was selected, in part, because of recent studies of teeth fossils which suggest that human ancestral populations, especially those before the hunter-gatherers, lived rather short lives, rarely exceeding 30 years

(Caspari, 2011). As such, the genetic architecture of common diseases with an average age of onset of later than 30 years is unlikely to have been affected by the process of natural selection until recent times of increased longevity. The present paper offers the first known effort to examine the genetic differences between early and late onset common diseases, framed using a natural selection perspective. Current findings provide evidence of natural selection in shaping the genetic architecture of complex diseases.

Materials & Methods

Mendelian phenocopy criteria: A Mendelian phenocopy is defined as a common disease caused by a single gene mutation in a nonsyndromic and highly penetrant fashion. It is important to note that the resulting clinical phenotype of a Mendelian phenocopy is often of earlier onset, tends to be more severe, and may vary in the extent of tissue involvement, relative to the sporadic common form of the disease. However, despite these differences from the sporadic form, the phenotype of the Mendelian phenocopy must meet the diagnostic criteria for the sporadic disease and must not include additional diseases or unrelated clinical findings that are highly uncharacteristic of the sporadic form. At least three different Mendelian phenocopy mutations should be reported to co-segregate with the nonsyndromic common disease phenotype in multiple pedigrees. At least one of the mutations must have a high penetrance (at least 80%) as demonstrated either in a single extended pedigree or in several families collectively. Alternatively, the average age- or sex-dependent penetrance of the various mutations must be at least 80%.

Syndromic/pleiotropic susceptibility genes, germ line mutations of which cause not only a particular common disease but also other diseases or clinically unrelated phenotypic features, were excluded from the present analysis. Compared to the nonsyndromic loci, syndromic predisposition loci may cause a common disease through distinct pathogenic pathways that involve pleiotropic functions of the underlying gene product. As such, the pleiotropic common disease genes may not be similarly influenced by the genetic response to natural selection triggered by the more common nonsyndromic disease phenotype. Certain common diseases that are exclusively or predominantly defined by genetic causation or those that have extreme clinical heterogeneity were also excluded from the analysis. Examples of excluded common disorders include, but not limited to, Down syndrome, fragile X syndrome, Duchenne muscular dystrophy, cerebellar ataxia, spinal muscular atrophy, Von Willebrand disease, non-syndromic hearing loss, mental retardation, infertility, retinoblastoma, Beckwith-Wiedemann syndrome, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy/dysplasia, primary congenital glaucoma, cataracts, and recurrent spontaneous abortions.

Literature survey methods and data analysis: Several databases including PubMed, Scopus, ISI Web of Science and Google Scholar were searched for the following terms in various combinations: “complex disease”, “common disease”, “Mendelian phenocopy”, “Mendelian form”, “penetrance”, “highly penetrant”, “mutation”, “rare mutation”. In addition, recent review articles on the genetics of common diseases were examined selectively to identify the Mendelian predisposition loci. Salient phenotypic and clinical features of the Mendelian forms of common diseases were reviewed, and those that were associated with pleiotropic/syndromic features were excluded. The end result of this filtering process was to retain for analysis common complex

diseases that presented with a nonpleiotropic, nonsyndromic Mendelian phenocopy. In most cases, the decision to classify a disease as early versus late-onset was straightforward, based on established epidemiological and clinical information. In a few cases, some ambiguity about typical age of onset did occur. For example, a subgroup of patients with systemic lupus erythematosus, focal segmental glomerulosclerosis, and obesity are younger than 30 years of age at first diagnosis. However, because the average age of onset of these diseases in the general population is over age 30, they were classified here as late-onset diseases. This strategy, to use the average age of onset in population-based studies, was applied consistently in those rare cases where considerable variation in onset age has been reported to occur.

The diseases and their relevant genetic findings were organized for review using the first 17 categories of the WHO ICD10 classification scheme (World Health Organization, 2013) (See Supplemental File 1). The descriptive, clinical, and epidemiologic data used in this analysis were obtained from Medscape, an online peer-reviewed medical information resource for physicians and other health care providers (Medscape, 2013), unless otherwise specified. The clinical and epidemiologic data included (Supplemental File 2) were not intended to provide a clinically exhaustive review, but, rather were selected to provide the relevant information necessary for testing the present hypothesis. Fisher's exact test was used to test the hypothesis that the number of WHO diagnostic categories that contain Mendelian phenocopies was similar between early versus late onset common diseases.

Results and Discussion

A comprehensive literature survey of monogenic forms of complex diseases revealed that 16 primarily late onset common diseases have nonpleiotropic, nonsyndromic highly penetrant Mendelian susceptibility genes: four diseases of the central nervous system; four diseases of the musculoskeletal and connective tissue system; two diseases of the circulatory system; and one disease each of the neoplasia system, the endocrine, nutritional and metabolic system, the eye and adnexa system, the ear and mastoid process system, the digestive system, and the genitourinary system (Table 1). In contrast, no highly penetrant Mendelian phenocopy was identified for any primarily early onset common disease (Table 2). An expanded review of complex diseases for presence of Mendelian phenocopies is presented in Supplemental File 2. Gene mutations predispose to a few early onset common diseases in a low-penetrance fashion (less than 70%). Examples of low-penetrance mutations and the associated early onset diseases include *ALK* in neuroblastoma, *RET* in Hirschsprung disease, *GNPTAB* in stuttering, and several genes predisposing to Herpes Simplex encephalitis. Nine of the first 14 WHO ICD10 diagnostic categories that contain both early and late onset common diseases have Mendelian phenocopies for late onset common diseases but not for early onset common diseases ($p < 5.8 \times 10^{-4}$, Fisher's exact test, two-sided). In addition, no Mendelian phenocopy was identified in the three WHO disease categories (XV, XVI and XVII), which, by definition contain only early onset common diseases. All Mendelian phenocopies identified in this study represent rare coding mutations. Highly penetrant regulatory variants were not observed.

It is notable that gene penetrance for certain early onset common diseases appears to be higher when the underlying mutation is associated with syndromic features. For example, germ line mutations in the *IRF6* gene cause van der Woude syndrome, the most common

cause of syndromic orofacial clefting. The penetrance of cleft lip or palate is approximately 50% but increases to 80% when lip pits and sinuses are also included (Ghassibe et al., 2004). *PTPN11* mutations cause Noonan syndrome which is characterized by dysmorphic features as well as heart defects, including pulmonic stenosis, in over 70% of cases (Tartaglia et al., 2002). Wilms tumor, a common childhood kidney malignancy, develops in 74% of patients with Denny-Drash syndrome, which is caused by mutations in the Wilms tumor suppressor (WT1) gene (Mueller, 1994). Hirschsprung disease occurs in over 80% of Shah-Waardenburg syndrome patients who carry *SOX10* germ line gene mutations (Amiel et al., 2008). Notably, this review found that no nonsyndromic susceptibility gene has ever been linked to the corresponding early-onset common disease in a comparably highly penetrant fashion.

In summary, this study examined the hypothesis that the process of natural selection leads to systemic genetic differences between early and late onset common diseases. An analysis of rare Mendelian forms demonstrates that certain late onset common diseases, but not any early onset common diseases, have highly penetrant nonpleiotropic, nonsyndromic predisposition genes. These Mendelian phenocopies are statistically significantly over-represented for late versus early onset common diseases when the WHO-defined diagnostic categories are compared. Assuming that all genes randomly mutate and no methodological biases exist against studying and reporting familial presentations of early onset common diseases, these findings suggest that the genetic architecture of early onset common diseases is not permissive to the phenotypic expression of highly penetrant predisposing mutations. This supports the hypothesis that natural selection shapes the genetic architecture of common diseases for increased mutational robustness (i.e.,

1 maintenance of the normal phenotype in the presence of deleterious mutations). Because
 2 robustness correlates with complexity (Carlson & Doyle 2002), this study also provides evidence
 3 that the genetic architecture of early onset common diseases may be more complex than that of
 4 late onset ones. Because this observation has not been well studied, these results highlight the
 5 potential importance of examining early onset diseases from the perspective of heightened
 6 complexity.

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 8 How mutational robustness arises and what mechanisms contribute to it are areas of active
 9 investigation. Mechanistically, mutational robustness can result from genetic redundancy,
 10 including gene duplication, or may result from systems- level properties, such as feedback
 11 regulation that is controlled by multiple loci. The latter mechanism, also referred to as
 12 distributive robustness, may in fact be more prevalent than genetic redundancy (Felix & Wagner
 13 2008). In addition, certain loci such as Hsp90 can act as genetic capacitors that mask the
 14 phenotypic consequences of mutations under normal circumstances, only to reveal them in times
 15 of stress (Rutherford, Hirate & Swalla, 2007). The multi-locus genetics of common diseases
 16 suggests that increased mutational robustness in early onset complex diseases likely stems from a
 17 distributive mechanism rather than redundancy or mutational masking by a capacitor.

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 19 Understanding how natural selection promotes mutational robustness may also increase our
 20 understanding of the genetic architecture of common diseases. Many theoretical studies suggest
 21 that genetic robustness generally evolves when mutation rates are very high or when there is
 22 abundant environmental variation or stochastic noise. As far as multicellular complex organisms
 23 are concerned, environmental factors can affect large numbers of individuals whereas rare

mutations affect only a few. Thus, increased mutational robustness might be a correlated outcome of environmental robustness (i.e., congruent robustness) in complex organisms, possibly because certain environmental factors or mutations may cause perturbations in the same biological pathways (Felix & Wagner, 2008; Lehner, 2010). Thus, increased mutational robustness in early onset common diseases may be a consequence of environmentally induced selection, rather than a response to rare mutations. In fact, the presence of many early onset Mendelian diseases with high penetrance, including autosomal recessive inherited metabolic diseases and monogenic syndromic presentations of common diseases, support the view that mutations alone are not sufficient to drive genetic robustness in humans. Thus, environmental factors that have a population level health impact are likely the primary driving factors that secondarily lead to mutational robustness.

Increased genetic robustness in early onset common diseases and the considerations above support a model that natural selection, triggered by novel disease associated environmental factors, leads to the accumulation of protective gene variants in the population. These protective alleles in turn may buffer the phenotypic impact of deleterious disease-predisposing coding mutations in early onset common diseases. In contrast, the low population frequency of such protective variants may lead to high penetrance of coding mutations in late onset common diseases. This process is illustrated in Supplemental File 3.

The model predicts that coding mutations in general will tend to have higher penetrance for late onset common diseases than for early onset common diseases. It should be noted that the model has been built by evaluating highly penetrant coding variants that are virtually absent in the

population. Whether coding risk variants of higher population frequency will also confer higher relative risks for late onset common diseases than for early onset ones remains to be tested in a separate survey of whole genome association and exome sequencing studies.

More broadly, these results shed some light on the origins of genetic robustness. Whether genetic robustness is favored by natural selection has been difficult to assess because empirical examples are rather limited (Felix & Wagner, 2008; de Visser et al., 2003). Because diseases reflect maladaptation of the whole organism, current findings derived from a broad repertoire of common diseases support the hypothesis that natural (environmental) selection favors mutational robustness. It should be emphasized, however, that genetic robustness can also be inferred for many late onset common diseases. For example, the diagnostic categories for infections, diseases of the blood and blood-forming organs, mental and behavioral system, respiratory system, skin and subcutaneous tissue have no highly penetrant predisposition genes either for early or for late onset common diseases. In addition, with the exception of papillary renal carcinoma, highly penetrant nonpleiotropic tumor predisposition genes are not evident for common neoplasia of late onset, a major cause of late onset mortality. Thus, genetic robustness against highly penetrant loci appears to be intrinsic in many late onset diseases. Nevertheless, the presence of Mendelian phenocopies in a subset of late onset common diseases but not in early onset ones suggests that natural selection increases and enhances genetic robustness to eliminate the impact of highly penetrant mutations. The observation that syndromic loci may still predispose to early onset common diseases in a highly penetrant fashion suggests that pleiotropism may impose constraints against the development of genetic robustness.

1 **Conclusions**

2 The occurrence of highly penetrant rare coding variants for late onset but not for early onset
3 common diseases suggests that natural selection shapes genetic architecture of complex diseases
4 to increase mutational robustness. Understanding biological basis of mutational robustness may
5 be crucial to advance our understanding of genetics of complex diseases.

6

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Table 1
Late-onset common diseases that have highly penetrant nonsyndromic susceptibility genes
(Mendelian phenocopies)^

WHO ICD-10 disease category	Common Disease	Average age at common disease onset	Mendelian phenocopy genes (OMIM #)	Mode of transmission	Penetrance	References
II	Papillary renal carcinoma	>50	<i>MET</i> (164860)	AD	>90%	(Schmidt et al., 1998; Schmidt et al., 1999; Cheville et al., 2003)
IV	Obesity	More common after 45	<i>MC4R</i> (155541)	AD	>80%	(Sina et al., 1999; Vaisse et al., 2000; Farooqi et al., 2003)
VI	Alzheimer disease	>65	<i>APP</i> (104760), <i>PSEN1</i> (104311) and <i>PSEN2</i> (600759)	AD	>85%	(Reitz, Brayne & Mayeux 2011)
	Parkinson disease	60	<i>SNCA</i> (163890)	AD	>90%	(Pankratz & Foroud, 2007; Bekris, Mata & Zabetian, 2010;

						Klein & Westenberger, 2012)
			<i>Parkin</i> (602544), <i>DJ-1</i> (602533), <i>PINK1</i> (608309)	AR	>90%	
	Frontotemporal Dementia	>50	<i>MAPT</i> (157140), <i>GRN</i> (607485)	AD	>90%	(Kertesz, 2003; Forman et al., 2006; Boeve & Hutton, 2008; Seelaar et al., 2011)
	Amyotrophic lateral sclerosis	>55	<i>SOD1</i> (147450)	AD	80%	(Valdmanis & Rouleau, 2008)
VII	Primary open angle glaucoma	>40	<i>MYOC</i> (601652)	AD	~100%	(Adam et al., 1997; de Vasconcellos et al., 2003)
VIII	Age related hearing loss	>50	<i>DFNA5</i> (608798)	AD	>95%	(van Camp et al., 1995; Uchida et al., 2011)
IX	Coronary artery disease	>40	<i>LDLR</i> (606945) <i>PCSK9</i> (607786)	AD	85% in men, 50% in women by age 65*	(Civeira & International Panel on Management of Familial Hypercholester

						olemia, 2004; Timms, et al., 2004; Humphries et al., 2006)
	Stroke	>55	<i>NOTCH3</i> (602276)	AD	~100%	(Chabriat et al., 1995; Schmidt et al., 2011)
XI	Pancreatitis	>30	<i>PRSS1</i> (276000)	AD	80%	(Rebours et al., 2009)
XIII	Thrombotic Thrombocytopen ic Purpura	40	<i>ADAMTS13</i> (604134)	AR	95%	(Levy et al., 2001)
	Systemic lupus erythematosus	32	<i>C1QA</i> (120550), <i>C1QB</i> (120570), <i>C1QC</i> (120575)	AR	>80%	(Schejbel et al., 2011)
	Inclusion body myositis	>50	<i>GNE</i> (600737)	AR	80%	(Eisenberg et al., 2001; Eisenberg et al., 2003)
	Paget's disease of bone	>40	<i>SQSTM1</i> (601530)	AD	79-87%	(Morissette, Laurin & Brown, 2006; Goode & Layfield, 2010)
XIV	Focal segmental glomeruloscleros is (steroid	32	<i>NPHS2</i> (604766), <i>NPHS1</i>	AR	~100%	(Tryggvason, Patrakka & Wartiovaara,

	resistant)		(602716)			2006; Machuca, Benoit & Antignac, 2009)
			<i>ACTN4</i> (604638)	AD	>80%	

- 1 ^See supplemental file 2 for review of diseases and genes listed in the table.
- 2 *Penetrance of *LDLR* mutations for coronary artery disease by age 65. Penetrance of *PCSK9*
- 3 mutations appears to be higher.
- 4 AD=Autosomal dominant; AR=Autosomal recessive; OMIM=Mendelian Inheritance in Man
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Table 2

Selected early onset common diseases that have Mendelian low penetrance susceptibility loci[^]

WHO ICD-10 disease category	Common Disease	Mendelian susceptibility genes (OMIM #)	Mode of transmission	Penetrance	Syndromic associations	Reference
I	Herpes simplex encephalitis	TLR3 (603029)	AD	<30%	No	(Alcais et al., 2010)
	Invasive meningococcal disease	Properdin (312060)	X-linked	<53%	No	(Fijen et al., 1999)
		Terminal components of complement cascade (e.g C7(610102))	AR	<71%	No	
II	Neuroblastoma	ALK (105590)	AD	~50%	Germ line mutations may disrupt central nervous system development in other families.	(Devoto et al., 2011; de Pontual et al., 2011)
	Medulloblastoma	SUFU (607035)	AD	~30%	Germ line mutations predisposes to meningioma in another family.	(Brugieres et al., 2010; Aavikko, et al., 2012)

V	Schizophrenia	DISC1 (605210)	AD	~50%	Mutations may predispose to bipolar disorder and major depression in different individuals.	(Blackwood et al., 2001; Chubb et al., 2008)
	Stuttering	GNPTAB (607840) E1200K variant	AD and AR	<70% with imperfect co-segregation	Other homozygous mutations cause mucopolidosis.	(Kang et al., 2010)
VI	Juvenile myoclonic epilepsy	EFHC1 (608815)	AD	~78%	Mutations may predispose to other epilepsy subtypes in other families.	(Suzuki et al., 2004; Stogmann et al., 2006)
XVII	Hirschsprung disease	RET (164761)	AD	~70% in males; ~50% in females	Gain of function mutations predispose to MEN2.	(Amiel et al., 2008)

1 ^See supplemental file 2 for review of diseases and genes listed in the table.

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