Genetic factors associated with human physical activity: Are your genes too tight to prevent you exercising?

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Abstract

The benefits of physical activity (PA) on health and fitness are well known. Recently, it has become apparent from studies of heritability that there is a considerable genetic component to PA. However, PA is such complex phenotype that the measurement and quantification of it provide a challenge to a clearer understanding of its genetic basis. In this review we assessed available evidence from family and twin studies that have estimated the heritability of PA. Heritability is greater when evaluated by accelerometry compared to questionnaires, and for questionnaires higher in twin studies. Accelerometry studies suggest heritability of PA is around 51-56%. There have been many genome-wide linkage studies, candidate gene studies and four genome wide association studies (GWAS) to highlight specific genetic factors linked to different PA levels. These studies have generally failed to replicate identified loci with the exception of the melanocortin 4 receptor (*MC4R*) and this may be because of the variability in the measurement techniques used to characterise the behaviour. Future work should aim to standardise the procedures used to measure PA in the context of trying to identify genetic causes. The link of genetics to physical exercise is not so tight that it prevents voluntary interventions.

Introduction

Regular physical activity (PA) is associated with a reduced risk of having more than 26 chronic medical conditions including depression, cardiovascular disease, type 2 diabetes, obesity and cancer [1]. Consequently, all-cause mortality is negatively associated with increasing levels of PA [2,3]. Conversely, physical inactivity is associated with many chronic health conditions and has been reported by the World Health Organization to be the fourth leading risk factor for global mortality [4]. Despite the strong evidence indicating PA is an effective component of a healthy lifestyle, there is a worrying trend towards decreased physical activity worldwide. In America, a study that used accelerometers to measure PA found that less than 5% of adults engage in at least 30 mins of moderate PA daily [5]. Because of the health issues, physical inactivity imposes a significant financial burden on health care systems. Already more than a decade ago, the estimated costs of non-communicable disease due to physical inactivity were $507 billion per year in USA [6].

While many psychological, biological, social and environmental factors have been identified to be associated with PA, interventions to enhance PA have met with only modest success [7]. Historically it has been assumed that PA is largely under voluntary control, and hence amenable to intervention efforts. However, one reason for the lack of success in PA interventions may be that PA has a large genetic component that is resistant to change [8]. While almost all human behavioural traits are determined by both environmental and genetic factors, current understanding of the genetic architecture contributing to PA is limited [9,10], especially compared to other phenotypes like height, and genetic diseases like obesity and diabetes. Even more worrying is the suggestion that the association between PA and health outcomes is not causal, but instead reflects a genetic pleiotropy – that is the genetic factors driving individuals to be more active may be also causing the health benefits [11]. Physical activity varies tremendously in the time domain, yet genetics in a given individual is a fixed trait. Conceptually then while we may talk about genetics having an effect on physical activity levels, this may be more correctly stated that genetics influences a predisposition to engage in activity, which is then expressed or not in relation to environmental influences. Hence the

ultimate level of physical activity is an interaction between the genetic predisposition and the environment in which it is expressed.

Progress in understanding the genetic factors that influence PA is hampered in part by a problem of definition. Although PA was formally defined more than 30 years ago [12], it still remains unclear what researchers are really measuring and the best way to quantify such a complex phenotype with its distinct patterns, frequency, intensity and duration [13]. Therefore, the measurement and quantification of PA may be the greatest challenges to a clear understanding of genetic variation in PA. Potentially taking into account the types of PA may increase the success in identifying genetic variants.

Building on the promises of genetic epidemiology to unravel the complex genetic basis of PA, various studies have attempted not only to identify the presence of genetic factors but also to investigate the importance of candidate genes. The aims of this review are first to briefly introduce different types of PA, and the most commonly used techniques used for measurement of PA in genetics studies. Second, we will review the available literature on family, offspring, twin, genome wide linkage studies, candidate gene and genome wide association studies (GWAS). We will not cover any animal studies, and also will not cover any physical/endurance performance studies, as it has already been suggested that endurance performance and physical activity likely evolved independently and thus may have a different genetic basis [14].

Physical activity types and measurement techniques

PA has been defined as "any bodily movement produced by skeletal muscle that results in energy expenditure" [12]. This broad definition may be too simplistic to identify genetic variants that affect PA, because PA varies both in intensity and its temporal patterning. Two main approaches have been taken to try and capture this complexity. The first is using questionnaires. These questionnaires tend to have a relatively small number of questions, and they focus on attempting to quantify the participants engagement in several sub-types of activity. The main sub-types are leisure time physical activity (LTPA), habitual activity (HA) and exercise participation. These classifications are not mutually exclusive. LTPA includes all types of physical activities that are engaged in

for leisure, for example, recreational walking, jogging and cycling. Habitual activity on the other hand additionally includes things like commuting and house work. Exercise participation is restricted to those activities where the sole purpose is the exercise itself. Different questionnaires blur the lines between these categories making strict definitions impossible. Questionnaires generally aim to evaluate the time spent in the different activities, and may additionally convert this participation into a putative energy expenditure by ascribing a metabolic rate to each activity relative to basal metabolic rate (in a pseudo-unit called METs). Questionnaires are normally self-completed by participants. This type of self-reported activity may extend across several days in which case it is sometimes referred to as an activity diary.

The second type of monitoring is performed using an accelerometry device attached to the body. Popular devices can be wrist worn (e.g. Actiwatch, fit-bit, omron etc) or on a belt around the waist (e.g. Actigraph). Additional devices combine accelerometry with monitoring of heart rate (e.g. Actiheart) but as yet these have not been used in studies of the genetics of physical activity. Such accelerometry devices generate 'counts' that reflect the level of acceleration during a given time period – called the epoch of measurement. Hence, the behaviour can be classified according to the number of counts per minute in given epochs. Typically behaviour is classified into sedentary, light, moderate, vigorous and very vigorous. In addition the total activity can be classed as the total number of counts in a given period – typically one day. Devices are commonly worn for 4 to 7 days to generate an unbiased estimates of activity.

The main problems with accelerometry are that different devices generate counts in different ways and hence there are no acceptable cut-offs between these divisions. Moreover, even using the same device different authors have suggested different cut-off points between the classes. For example, Treuth and colleagues used 0-99 Counts per minute (CPM) for sedentary, 100-2999 CPM for light, 3000-5200 CPM for moderate and >5201 CPM for vigorous activity for children who are aged from 6 to 18 years old [15]. However, Freedson and colleagues used very different thresholds to define activity intensities for adults (19 years and older), 0-2690 CPM for light, 2691 – 6166 CPM for moderate, 6167-9642 CPM for vigorous and >9643 CPM for very vigorous [16].

Initially sedentary behaviour was regarded simply the absence of PA, in the last decade however this idea has been revised and sedentary behaviour is now widely considered as an independent phenotype [17]. Because the daily time spent on the physical activity and sedentary behaviour are only weakly correlated, sedentariness may represent a different behavioural paradigm. Therefore we cannot assume the factors that influencing physical inactivity are the same that are influencing PA. The genetic factors influencing sedentary behaviour have been recently reviewed [13,18] and will not be repeated here.

Accelerometry is generally more expensive to use than questionnaires. Although there is no perfect tool for the examination of PA, researchers should consider not only the cost of performing the measurement but also the reliability and validation of the methodology. In general, PA measured by accelerometry is less variable than self-report questionnaires [19]. Studies comparing PA assessed by accelerometry simultaneous to questionnaires show little concordance between them [20,21], suggesting that either they capture different things, or they capture the same thing but one is a poorer method than the other. Some authors have concluded that despite their extensive use for over 40 years, self-report questionnaires have limited reliability and validity when compared with the use of activity monitors [22,23]. This could be a problem because questionnaires are by far the most common method used in studies of the genetics of PA. This suggests future studies should perhaps use accelerometry rather than questionnaires to study the genetics of PA. However, because it is more costly and time consuming, the use of accelerometry necessarily decreases the number of subjects that can be studied within an overall project budget. Thus, researchers have to determine whether the reduced error from using activity monitors outweighs the lower statistical power arising from having a lower sample size [24]. For GWAS in general a suggestion was made recently that increasing sample size is a better strategy than improving the accuracy of determining a given phenotype [25].

Heritability of PA-family studies

Heritability is the relative contribution of the genetic variance to the total variance

of any phenotype in a given population at a certain time and is typically expressed as a percentage[26]. Heritability is not an absolute measure of genetic influence but reflects the balance between environmental and genetic factors at a particular time in a given population. Both family and twin studies have been widely used to decompose familial resemblance in PA into genetic and environmental influences. Family studies have shown that genetic factors contribute to variation in PA (Table1), with heritability estimates ranging from 9% to 57%. For example, using a sample of 375 Quebec nuclear families, one of the earliest studies determined that genetic factors explained 29% of the familial resemblance in habitual PA as measured with a 3 day activity diary [27].

While the majority of the family studies have used questionnaires and self-report, the Viva la Familia Study was the first large scale family study to use accelerometry to estimate heritability of PA [28,29]. Two papers have been derived from this study [28,29] using effectively the same data set and analysis methods. These papers estimated the heritability of total physical activity as 57% and 55%. In total, 7 out of 9 family studies used questionnaires to measure the heritability of PA and the weighted mean of heritability of using questionnaires was 26% (weighted SD=5.6%) [27,30-35]. The 2 'non-independent' studies that used accelerometry, were based on effectively the same dataset with the weighted mean heritability of the two separate analyses being 56% (weighted SD=1.4%) [28,29].

One of the studies that used questionnaires compared the difference of heritability between the sexes but found no sex specific heritability for total PA [35]. Another study conducted in Portugal explored the consistency of genetic factors between two different age groups (10–14 years and 15–19 years) and found that the heritability of PA remained stable across age in adolescence [30]. In summary these family studies suggest that heritability was greater when PA was assessed with accelerometers. No sex specific differences in heritability were found, and there were no differences in maternal-offspring v paternal-offspring correlations, indicating there are unlikely to be strong maternal effects. Heritability of PA remained stable across age in adolescence. However, these latter findings are based on questionnaire studies, and await confirmation by accelerometry.

Heritability of PA- twin studies

Routine family studies cannot disentangle the effects of genetics from shared environmental effects. However, such components can be decomposed using twin and adoption studies. The classic twin design to evaluate heritability is based on the comparison of monozygotic (MZ) twins who are genetically identical, with dizygotic (DZ) twins who share only 50% of their genes. Intrapair differences in MZ twins are primarily due to environmental factors and measurement errors, whereas intrapair differences in (DZ) twins are additionally affected by genetic factors [36]. By comparing the similarity between MZ and DZ pairs for a given trait, an estimate can be derived of the heritability. That is if the DZ twins have just about the same differences between them as MZ twins then the impact of genetics (i.e. heritability) is negligible. On the other hand, as the differences between MZ twins becomes progressively smaller than that of the DZ twins, then heritability increases. The intrapair correlation for MZ and DZ were calculated with Pearson's correlation coefficients (r), the heritability (h^2) was calculated as h^2= 2x (rMZ-rDZ). Twin studies are superior to family studies because the phenotype is measured at the same age, while in family studies generally children are measured at a different age from their parents.

In addition in contrast with family designs, twin designs allow the evaluation of additive genetic factors, shared environmental factors and unique environmental factors. Much like the family studies, the majority of the twin studies have used questionnaires to measure PA, only 5 out of 20 studies included in this review used accelerometry. Even across these 5 studies, researchers used different activity monitors that measured different components of PA. As shown in (Table2), out of the 20 studies, 8 of them specified sex and age differences without giving an overall average heritability estimate and thus were not included in the overall summary calculations. Seven studies used questionnaires to measure the PA, and the weighted mean of heritability was 40% (weighted SD = 24%) [37-43]. There were 5 studies that used accelerometry to measure PA, and the weighted mean of heritability was 51% (weighted SD = 30%) [36,44-47]. The weighted mean estimates of heritability from questionnaire and accelerometry studies were therefore closer in the twin studies than in the family studies.

There has been ambiguity in the literature about whether there is a difference in heritability of PA between the sexes. Differential heritability of PA between the sexes was originally suggested by a study of leisure time physical (LTPA) with the Baecke questionnaire in a group of 411 Portuguese twin pairs [48]. The best fitting models showed sex-specific effects for the heritability of LTPA with 63% for males and 37% for females [48]. In contrast, a Swedish twin study assessed LTPA using a questionnaire in 5334 MZ and 8028 DZ twins and found that heritability of PA levels between sexes was similar with 57% for males and 50% for females [49]. The largest twin study to date examined exercise participation using questionnaires applied to 13676 MZ and 23375 DZ pairs from 7 different countries. This study found no sex difference in heritability in 5 of the 7 countries, but a significant difference was observed in Norway ($p<0.001$) (in the 7th country data were only available for females) [50]. The inconsistent conclusions between the above studies could be due to methodology differences

Given the difficulty of tracking people for long periods of time, most of the heritability estimates so far have been based on cross sectional designs. However, two longitudinal twin studies have considered the changes in the heritability of PA with age. One study involved a 6 year follow up study of LTPA with a sample of 4280 MZ and 9276 DZ twins, participants aged between 18 and 54 at baseline. In this study the genetic modelling results showed that genetic influences on LTPA declined from baseline (44%) to follow up (34%) [51]. Using data from the same Finnish cohort, another study considered data across four time points at mean ages 16.2, 17.1, 18.6 and 24.5 years. The result suggested that, in both sexes the heritability of LTPA declined from 43%-52% in adolescents to 30% in young adulthood, which was broadly consistent with the previous study [52]. It is unclear why the impact of genetics might decrease with age apart from the possibility that environmental impacts are cumulative over time.

242 Table 2 Heritability of Physical Activity - twin studies

Author/year	Country	Sample	Techniques	Phenotype	Heritability (h^2)
Kaprio et al., 1980 [37]	Finland	1537 MZ & 3507 DZ	Questionnaire	PA	0.62
Maia et al., 2002 [48]	Portugal	203 MZ & 153 DZ	Questionnaire	LTPA	Male=0.63 Female=0.37
Simonen et al., 2004 [38]	Finland	147 MZ & 153 DZ	Questionnaire	AE	0.2
Carlsson et al., 2006 [49]	Sweden	5334 MZ & 8028 DZ	Questionnaire	PA	Male=0.57 Female=0.5
Eriksson et al., 2006 [39]	Sweden	1022 twin pairs	Questionnaire	TPA	0.49
Stubbe et al., 2006 [50]	7 countries	13676 MZ &23375 DZ	Questionnaire	EP	Male= 0.229-0.681 Female=0.311-0.705
De Moor et al., 2007 [53]	Netherland	1181 MZ & 636 DZ	Questionnaire	EP	Male=0.685 Female=0.463
De Moor et al., 2007 [40]	Netherland	1225 MZ & 716 DZ	Questionnaire	EP	0.544
Duncan et al., 2008 [41]	U.S.A	1003 MZ & 386 DZ	Questionnaire	PA	0.45
McCaffery et al., 2009 [42]	U.S.A	2710 MZ & 2327 DZ	Questionnaire	VE	0.1
Aaltonen et al., 2010 [51]	Finland	4280 MZ & 4383 DZ	Questionnaire	LTPA	Male=0.47-0.38 Female=0.42-0.31
Vink et al., 2011 [54]	7 countries	13676 MZ & 23375 DZ	Questionnaire	EP	Male= 0.13-0.64 Female=0.27-0.57
Mustelin et al., 2012 [43]	Finland	489 MZ & 785 DZ	Questionnaire	LTAI	0.41
Aaltonen et	Finland	1873 MZ &	Questionnaire	LTPA	Male=0.523-0.338

al., 2013 [52]		3460 DZ			Female=0.524-0.305
Joosen et al., 2005 [36]	Netherland	12 MZ & 8 DZ	Accelerometer	PA	0.78
Wood et al., 2008 [44]	UK	150 MZ & 224 DZ	Actigraph	AM	0.92
Fisher et al., 2010 [45]	UK	57 MZ & 60 DZ	Actigraph 7164	TPA	0.14
den Hoed et al., 2013 [46]	UK	420 MZ &352 DZ	Accelerometer	Acceleration	0.36
Gielen et al., 2014 [47]	Netherland	28 MZ & 24 DZ	Triaxial Accelerometer	HPA	0.54
Franks et al., 2005 [55]	U.S.A	62 MZ & 38 DZ	DLW	PAEE	0

Heritability (h^2) calculated from additive gene effects, *AE* adolescent exercise, *DLW* Doubly labelled water, *TPA* total physical activity, *PAEE* physical activity energy expenditure, *EP* exercise participation, *VE* vigorous exercise, *LTPA* leisure time physical activity, *LTAI* leisure time activity index, *HPA* habitual physical activity, *AM* Actigraph measurement

Genome wide linkage studies

Early linkage studies extended the family based study design by demonstrating co-segregation of a trait with microsatellite markers spread out evenly across the genome. Linkage studies map variability of a trait to a genomic location and depending on the density of markers and size of the sample this 'location' may be a relatively small or large region containing respectively tens to hundreds of genes [56]. Only four linkage studies for PA have been performed to date (Table 3) with only one of them using an accelerometer (Actiwatch).

Table 3 Genome wide linkage studies of physical activity

Author /year	Country	Sample	Techniques	Pheno type	Locus	Genetic marker	P
Simonen et al., 2003 [57]	U.S.A	207 nuclear families	Questionnaire	TPA	13q22-q31	D13S317	0.029
De Moor et al., 2007 [53]	Netherlands	622 families	Questionnaire	EP	19p13.3	D19S247	<0.01
De Moor et al., 2007 [58]	Great Britain	700DZ	Questionnaire	SP	3q24 4q32.3	D3S1569	<0.01
Cai et al., 2006 [29]	U.S.A	1030 children and 631 parents	Actiwatch	TPA	18q	D18S64	<0.001

TPA total physical activity, *EP* exercise participation, *SP* sports participatio

The first genome wide linkage scan was based on 432 markers in 767 subjects from 207 families in the Quebec Family study, using a 3 day physical activity diary, with the aim of identifying loci affecting PA levels. A suggestive linkage at region 13q22-q31 was found with total PA. A gene encoding the endothelin B receptor has been mapped to chromosome 13q22, and in rats the endothelin B receptor has been shown to mediate the increase in spontaneous locomotor activity induced by treatment with a low dose of endothelin 1 [57]. Another study reported significant linkage on chromosome 18 for physical activity in 1030 siblings from 319 Hispanic families participating in the Viva La Familia study [29]. Total PA mapped to markers D18S64 on chromosome 18, where the melanocortin 4 receptor gene is located. MC4R is a well known strong candidate gene associated with BMI, hence the effects of this locus on PA may be secondary to differences in BMI. This may highlight a more general issue that genetic effects on PA diagnosed by these techniques may always be secondary to other factors like BMI that then exert an influence PA levels. This study is the only one of the four studies that used accelerometry to measure PA [29].

A linkage study on 1432 genotyped sibling pairs from 622 families from the Netherlands Twin registry using 361 markers and an average marker separation of 10.6 cM suggested significant linkage of variation in exercise participation which was measured by questionnaires on chromosome 19p13.3. This region has a number of genes related to muscle performance and muscle blood flow which may indirectly affect exercise participation [53]. In a second study , involving a linkage scan on 700 British female DZ twin pairs, suggestive linkages with sports participation were found on chromosome 3q22-q24 [sodium/hydrogen exchanger 9 (*SLC9A9*)] and 4q31-q34 [including the uncoupling protein 1 (*UCP1*) gene and fatty-acid binding protein 2 (*FABP2*)] respectively. While these linkage studies have shed some light on the location of genetic variants for PA, they are hampered by the fact they can only locate relatively large regions containing many potentially important genes, so the nature of the causal variant remains speculative guesswork linked to other credible information. Moreover, they have limited power to detect modest effects. A study examining the power of linkage studies to locate disease genes showed that greater sample sizes are needed to

detect loci that have more modest relative risks [58]. Overall there were no replicated discoveries of loci across all the four studies.

Candidate genes for physical activity

More recently studies have employed association based candidate gene methods to provide additional insights into the genetic architecture underlying human PA (Table 4). Most of the examined candidate genes were derived from functional studies and evidence from animal experiments. One system that has attracted attention in this area is the reward system in the brain. This may be activated in individuals who feel rewarded by performing exercise[7].

Table 4 Candidate gene studies of physical activity

Gene	Author	Sample (n)	Technique	Phenotype	Locus	Genetic marker	P
ACE	Fuentes et al., 2002 [59]	455	Questionnaire	MILTPA	17q23.3	INS/DEL	0.279
	Wilkinson et al., 2013 [60]	355	Questionnaire	PA	17q23.3	INS/DEL	<0.0001
	Wilkinson et al., 2013 [61]	1130	Questionnaire	PA	17q23.3	Rs8066276 Rs363035	0.012 0.005
	Bruneau et al., 2017 [62]	461	Questionnaire	HPA	17q23.3	Rs4340	0.01
ANKRD6	Van Deveire et al., 2012 [63]	922	Questionnaire	HPA	6	Rs1739327	0.03
CASR	Lorentzon et al., 2001 [64]	97	Questionnaire	HTPA	3q13.33	Rs1801725	0.01
DRD2	Simonen et al., 2003 [65]	721	Questionnaire	TPA	11q23.2	454-bp DNA fragment	0.836

	Huppertz et al., 2014 [66]	8768	Questionnaire	LTPA	11q23.2	8 SNPs	>0.02
	DJ et al., 2018 [67]	12929	Questionnaire	TEV	11q23.2	9 SNPs	0.90
FTO	Berentzen et al., 2008 [68]	557	Questionnaire	LTPA	16q12.2	Rs9939609	0.859
	Hakanen et al., 2009 [69]	640	Questionnaire	PAI	16q12.2	Rs9939609	>0.99
	Liu et al., 2010 [70]	1978	Questionnaire	VPA	16q12.2	Rs9939609	0.63
IL-15R	Bruneau et al., 2018 [71]	532	Questionnaire	TLPA	10	Rs2228059	0.009
LEPR	Stefan et al., 2002 [72]	452	Respiratory chamber	PAL	1p31.3	Gln223Arg	0.007
	Richert et al., 2007 [73]	222	Questionnaire	PAEE	1p31.3	Gln223Arg	0.016
MC4R	Loos et al., 2005 [74]	669	Questionnaire	TPAS	18	MC4R-C-2745T	0.006
	Cole et al., 2010 [75]	1629	Actiwatch	TPA	18	1704	0.004
PPARD	Gielen et al., 2014 [47]	104	Tracmor IV	HPA	6	Rs2076168 Rs2267668	<0.01 <0.05

MILTPA moderate intensity leisure time physical activity, HPA habitual physical activity, VPA vigorous physical activity, TLPA time spent in light physical activity, PAEE physical activity energy expenditure, TPAS Total physical activity score, TEV total exercise volume

The association between dopamine neurotransmission and PA has been widely studied. A strong correlation was suggested between individuals carrying the dopamine D4 receptor (*DRD4*) 7R allele with increased levels of PA ($p=3.5x10^{-9}$) in the Leisure World Cohort Study [76]. However, contrasting these results, using data from the Quebec family study, no association was shown between the dopamine D2 receptor gene (*DRD2*) genotype and physical activity obtained from a three day diary [65]. Moreover, associations between eight single nucleotide polymorphisms of dopaminergic candidate genes with regular leisure time exercise behaviour revealed that none of these genetic variants were associated with exercise behaviour ($P>0.02$) [66]. Similar negative results were found in a study of 12929 participants from the Netherlands twin registry, where no association between total exercise volume or externally paced exercise volume was found for individual alleles in the dopamine system [67]. Hence overall there is little evidence to support the suggestion of associations between genetic variants in the reward system and PA.

Genetic polymorphisms linked to obesity (BMI) may exert their effects via impacts on physical activity. Hence GWAS studies of obesity [77,78] have provided a rich source of candidate genes for studies of the genetics of physical activity levels. A common variant in the *FTO* gene, rs9939609, was the first genome wide common allele linked to body mass index in adults and children [79]. Several studies subsequently addressed whether the association of *FTO* phenotype with BMI is through energy intake or expenditure [80,81]. These data suggest *FTO* affects food intake and there is no association of the *FTO* genotype with physical activity levels [68-70]. Leptin regulates body weight via binding to the leptin receptor (encoded by the *LEPR* gene). Lower leptin binding to the soluble form of the leptin receptor was shown in carriers of the Arg233-encoding allele of the Gln223Arg polymorphism of the *LEPR*. In Pima Indians the Arg223-encoding allele of the *LEPR* gene was associated with lower energy expenditure and lower physical activity levels compared to individuals with the Gln223-encoding allele [72]. Another study showed that *LEPR* was related to physical activity energy expenditure measured by doubly-labelled water in young boys [73]. The melanocortin4 receptor

(*MC4R)* is a downstream target of Agouti related protein (AgRP) and the alpha melanocortin stimulating hormone (alpha-MSH) and is an important regulator of food intake and adiposity. Studies with knockout mice have suggested that *MC4R* might be involved in the regulation of activity [82]. Interestingly, *MC4R* is found on chromosome 18 which was also identified by a linkage study for PA mentioned above [29]. In the Quebec Family Study, the *MC4R*-C2745T variant had a significant association with total physical activity (p=0.006) [74]. A link between *MC4R* variant SNP 1704 and physical activity has also been strongly suggested in Hispanic children (p=0.004) [75].

Several additional genes have also been suggested to be associated with PA. The angiotensin-converting enzyme (*ACE*) insertion/deletion (I/D) polymorphism has been widely studied for its influence on sports performance [83], however, research on its influence on physical activity is limited and inconsistent. In a population based sample of Finnish participants [59], the distribution of the *ACE* I/D genotypes did not differ significantly among those who frequently or infrequently took part in moderate intensity leisure time physical activity (p=0.279). However, in 355 stage I hypertensives [60], in whom physical activity had been assessed using a standard questionnaire, the *ACE* genotype contributed to more than 50% of the variance in PA (F=16.03, P<0.0001). In a group of 1130 Mexican youths, those who had at least one copy of the minor allele for SNPs in *ACE* (rs8066276, p=0.012) were more likely to meet PA recommendations [61]. A study in European American adults also showed that the *ACE* I/D polymorphism rs4340 associates with weekly walking distance [62]. Other candidate genes have been studied such as the ankytin repeat domain 6 gene (*ANKRD6*) [63], calcium sensing receptor (*CASR*) [64], interleukin-15 (*IL-15*) [71] and peroxisome proliferator activated receptor delta (*PPARD)* [47] all of which have variants showing significant associations to activity levels via unknown mechanisms. To summarise, there is presently no established association between genetic mutations in the reward system and PA, also no association between BMI related genes and PA. Most of the studies have generally failed to replicate identified loci with the exception of the melanocortin 4 receptor (*MC4R*) which is located on chromosome 18 which was identified by a previous linkage

363 study [29].

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365 **Genome wide association studies (GWAS)**

366 The most recent and successful gene-discovery framework is the genome wide
367 association study (GWAS) (Table 5).

368 Table 5 Genome wide association studies (GWAS) of physical activity

Author/year	Sample	Technique	Phenotype	SNP number	gene	rs number	p
De Moor et al., 2009 [84]	1772 Dutch & 978 American	Questionnaire	Exercise no exercise	470719	*PAPSS2*	rs10887741	3.81E-06
Kim et al., 2014 [85]	8842 Korean	Questionnaire	PA	344893	NA	NA	NA
Hara et al., 2018 [86]	13980 Japanese	Questionnaire	LTPA	873254	*NPSR1-DPY19L1*	rs10252228	2.2E-09
Klimentidis et al., 2018 [87]	91084 Britain	Wrist-worn accelerometer	HPA	11800000	*CRHR1*	rs55657917	5.0E-12

369 *PA* physical activity *LTPA* leisure time physical activity *HPA* habitual physical activity

GWAS overcomes the challenge of candidate gene studies by embracing an unbiased approach to discovery through association across the entire genome. Moreover, it is superior to genome wide linkage studies because it enables much more precise location of the potentially causal SNPs involved in the phenotype. The main downsides of GWAS are the costs of the analysis, and the need for large numbers of individuals to generate significant hits [25].

To date (Sept 2018) there have been four GWAS studies of PA[84-87], but only one of these was based on accelerometry. The first GWAS for PA was published in 2009 [84] and included individuals studied by questionnaire from the USA and the Netherlands. The strongest evidence of an association was observed for the SNP rs10887741 on chromosome 10 located in the intron region of the 3'-phosphoadenosine 5' – phosphosulfate synthase 2 (*PAPSS2*) gene (pooled $p=3.81x10^{-6}$). The *PAPSS2* gene encodes an enzyme involved in sulfonation of various molecules, including glycosaminoglycans. Mutations in *PAPSS2* have been reported to cause spondylo-epimetaphyseal dysplasia, which is characterized by short stature and short limbs both in humans and in mice [88].

Another GWAS of the Korean population with the sample size of 8842 reported the most significant association between a SNP (rs7023003) and exercise participation measured by a validated questionnaire did not reach genome wide significance [85]. A Japanese study conducted this year used a self-administered questionnaire that measured leisure time exercise using 13980 samples found one novel SNP (rs10252228) located in the intergenic region between *NPSR1* and *DPY19L1* was significantly ($p=2.2x10^{-9}$) associated with LTPA. However, there was no evidence indicating that rs10252228 affected the expression of any genes, also in the later replication study of candidate genes no significant association was detected [86]. The largest most comprehensive GWAS for PA used analysis of data from the UK Biobank combined with wrist worn accelerometers to measure habitual physical activity of approximately 100000 participants [87]. The SNP rs55657917 variant in the corticotropin releasing hormone receptor 1 *(CRHR1)* gene was the most strongly associated with average

acceleration ($p=5.0x10^{-12}$) which was also related to neuroticism, pulmonary function and sense of pain. All four GWAS studies conducted to date have identified significant loci, but none of them were replicated between studies. Only one GWAS study to date has used accelerometry. Considerably more work needs to be done in this area.

Discussion:

Although it is widely stated that physical activity represents a modifiable determinant of behaviour, with considerable health impacts, our ability to intervene may be compromised if there is a large genetic component. Work over the last 2 decades on the heritability of PA, combined with genetic studies that attempt to pinpoint exactly which genes are of importance, clearly suggest that there is a potentially large genetic influence on PA levels. However, there is considerable variation between studies. For example, estimates of heritability vary widely, from 9 to 92%, and very few genetic 'hits' are replicated across multiple investigations.

There are several reasons for this variability and confusion. First, physical activity encompasses a wide range of actual behaviours. Although PA was defined more than 30 years ago [12] it remains unclear what researchers are measuring, and the best way to quantify such a complex phenotype. This leads to problems because different types of PA may have a different genetic basis and heritability. The second issue is that even if individuals were to perform the exact same behaviour, different studies use different methodologies to quantify it. The two main types of approach: questionnaires and accelerometry, generate completely different data that potentially capture different aspects of the phenomenon, and have different levels of mapping onto the actual movement patterns of the individual. There are limited validation studies that quantify comparability of different approaches and their repeatability, but these tend to show poor comparability between questionnaire and accelerometry based approaches [19]. Studies have shown that people often over estimate their PA by using questionnaires and the percent of overestimation varies with race, degree of overweight, and weight loss. These problems with questionnaires are not restricted to physical activity assessments[83] and they create both systematic and random errors. Therefore we should

not expect that these different approaches will generate similar outcomes with respect to genetics. Clearly, if the phenotype measurement is not accurate and repeatable, then heritability estimates and any downstream association analysis may be compromised [89].

The third issue is that measuring PA by accelerometry is time consuming, and hence the sample sizes for such studies tend to be much smaller than for questionnaire based approaches. Smaller sample sizes have lower power to detect significant effects. Finally, different studies have used populations of different sex and age, in different locations at different times of year, and that's why physical activity may differ in relation to individual [8] and environmental attributes [90,91]. These factors may affect estimates of heritability and the ability to detect significant genetic variants. Genome wide linkage studies have identified genomic regions containing genetic variants related to PA. However, in the current four linkage studies, no marker suggested to be important was repeated across studies. Candidate gene approaches start form the level of the gene and evaluate if there is a difference in activity levels between different genotypes. Several genes have been studied, including those linked to BMI. However, the results from different studies of the same genetic variant have generally not been consistent. Four GWAS studies of PA have been conducted to date, and all these failed to replicate the previous linkage association and candidate gene studies apart from the *MC4R* gene [84]. Moreover, there was no overlap in the significant loci between these different GWAS studies.

At present probably the most we can say is that quantification of PA using accelerometry seems to indicate greater heritability and identifies more potential genetic variants than the use of questionnaires. It is likely that the impacts of genetics on physical activity are substantial (>= 50% of the variance). This may have implications for public health interventions that start form a standpoint that this is a largely environmentally determined behaviour under voluntary control. In reality our ability to intervene and increase levels of PA may be more limited than we imagine. Nevertheless, this still leaves 50% of the variation potentially malleable. A recent study confirms that even if there is a strong genetic influence this does not mean our levels

of PA are immune to manipulation. This study compared monozygotic twins that were discordant for physical activity levels over a period spanning 30 years. The active twins were considerably leaner and had much healthier blood profiles (lower LDL cholesterol and lower HbA1c) than their inactive identical twins [92]. It seems that even if there is a large genetic component to activity, the link of genetics to activity is not so tight to overcome voluntary behavioural interventions. Your genes are not too tight to prevent you exercising.

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Table 1 Heritability of Physical Activity- family studies

Author/year	Country	Sample (n subjects)	Technique	Phenotype	Heritability (h^2)
Perusse et al., 1989 [27]	Canada	1610	Questionnaire	PA	0.29
Simonen et al., 2002 [31]	Canada	696	Questionnaire	TPA	0.19
Mitchell et al., 2003 [32]	U.S.A	1364	Questionnaire	PA	0.09
Seabra et al., 2008 [33]	Portugal	9500	Questionnaire	PAI	0.23
Choh et al., 2009 [34]	U.S.A	521	Questionnaire	TPA	0.29
Diego et al., 2015 [35]	Portugal	1034	Questionnaire	TPA	0.28
Pereira et al., 2018 [30]	Portugal	12385	Questionnaire	LTPA	0.297-0.322
Butte et al., 2006 [28]	U.S.A	1030	Actiwatch	TPA (count)	0.57
Cai et al., 2006 [29]	U.S.A	1030	Actiwatch	TPA (count)	0.55

PA physical activity, *TPA* total physical activity, *LTPA* leisure time physical activity, *PAI* physical activity index