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Genetic Architecture for Human Aggression: A Study of Gene–Phenotype Relationship in OMIM

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Genetic studies of human aggression have mainly focused on known candidate genes and pathways regulating serotonin and dopamine signaling and hormonal functions. These studies have taught us much about the genetics of human aggression, but no genetic locus has yet achieved genome-significance. We here present a review based on a paradoxical hypothesis that studies of rare, functional genetic variations can lead to a better understanding of the molecular mechanisms underlying complex multifactorial disorders such as aggression. We examined all aggression phenotypes catalogued in Online Mendelian Inheritance in Man (OMIM), an Online Catalog of Human Genes and Genetic Disorders. We identified 95 human disorders that have documented aggressive symptoms in at least one individual with a well-defined genetic variant. Altogether, we retrieved 86 causal genes. Although most of these genes had not been implicated in human aggression by previous studies, the most significantly enriched canonical pathways had been previously implicated in aggression (e.g., serotonin and dopamine signaling). Our findings provide strong evidence to support the causal role of these pathways in the pathogenesis of aggression. In addition, the novel genes and pathways we identified suggest additional mechanisms underlying the origins of human aggression. Genome-wide association studies with very large samples will be needed to determine if common variants in these genes are risk factors for aggression.

Key words: aggression; genetics; OMIM

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INTRODUCTION

Genetic variants account for about 50% of the variance in human aggression [Miles and Carey, 1997]. Genetic studies of human aggression have mainly focused on known candidate genes and pathways regulating serotonin and dopamine signaling and hormonal functions [Saudou et al., 1994]. However, a recent meta-analysis of common DNA variants in 31 candidate genes (including serotonin and catecholamine genes) selected from 185 studies constituting 277 independent associations, showed no significant associations with aggression or antisocial behavior [Vassos et al., 2014]. Thus, identifying causal genes and pathways underlying aggressive behavior in humans requires additional work.

The lack of significant associations for common variants is likely due to many reasons such as sample heterogeneity, variants of small effect sizes and gene-environment interaction effects. As has been seen for other behavioral traits [Lee et al., 2013], very large samples may be needed to pin down common variant associations. We propose a novel approach based on the paradoxical hypothesis that studies of rare, functional genetic variations can lead to a better understanding of the molecular mechanisms underlying complex multifactorial disorders such as aggression. Empirical evidence support the idea that a biological pathway implicated by a rare variant could also be degraded by common variants or even by environmental risk factors. This has been observed for many genetically influenced multifactorial disorders. For example for Type 2 diabetes, many common and rare associated polymorphisms and causal monogenic variants are clustered in or near the insulin signaling network [Sharma et al., 2005]. Studies of autism

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spectrum disorders (ASDs) have found substantial overlap in the biological pathways implicated by rare Single Nucleotide Variants (SNVs), rare copy number variants (CNVs) and common DNA variants [Ben-David and Shifman, 2012]. Furthermore, genes implicated by these variants were clustered in the same pathways as genes implicated by syndromic ASDs [Sakai et al., 2011]. Studies of the ASD transcriptome have drawn the same conclusion [Lanz et al., 2013]. Thus, although any single rare variant may be observed in only one or two patients, different rare variants carried by different patients implicate similar biological networks.

The discovery of biological pathways via rare variants has been used to leverage drug development efforts that are relevant to more than just the few patients carrying a given rare variant. For example, rare variants of *PCSK9* cause a rare autosomal dominant familial hypercholesterolemia. Drugs that inhibit *PCSK9* protein lower cholesterol and are a viable treatment for common forms of hypercholesterolemia and atherosclerosis [Hooper and Burnett, 2013; Urban et al., 2013]. Canakinumab is a human monoclonal antibody that was developed and approved to treat cryopyrin-associated periodic syndrome, a rare autoinflammatory syndrome caused by mutations in *NLRP3*, the gene encoding cryopyrin [Verma et al., 2010]. Subsequently, canakinumab was approved for use in gout [Onuora, 2012; Schlesinger, 2012], a common inflammatory syndrome having a different etiology; it is also effective in treating common rheumatoid arthritis [Alten et al., 2011].

In the present study, we used the Online Mendelian Inheritance in Man (OMIM) data base [McKusick, 1998], to identify all genes with known rare variants that cause aggressive phenotypes in human Mendelian disorders. We examined the pathways and networks underlying these genes collectively and compared them with a panel of known candidate genes (N = 97) for aggression assembled by experts from the Aggressotype Consortium (http://www.Aggressotype.eu/). These pathways may reveal common mechanisms underlying the aggressive behavior in humans.

METHODS

OMIM Record Search and Filtering

We used search key worlds: "aggression OR aggressive behavior OR aggressiveness OR antisocial OR conduct disorder" in fields including "title", "text", "allelic variants" and "clinical synopsis" (http://omim.org/search/advanced/entry). We examined both the gene and phenotype records. Our inclusion criteria were: (1) the phenotype included aggressive or antisocial behavior, or conduct disorder in one or more humans and (2) a Mendelian variant causing the phenotype had been identified. The search was up-to-date as of March 4th, 2015.

Network Connectivity Assessment

We used Disease Association Protein-Protein Link Evaluator (DAPPLE) to evaluate the protein physical connectivity among the OMIM genes products [Rossin et al., 2011]. DAPPLE evaluates two types of networks: direct networks refers to the networks build from any two MIM genes, the seed proteins, that can be connected by exactly one edge, and indirect networks refer to interactions mediated via common interactor proteins (non-OMIM aggression genes) with which the associated proteins each share an edge. DAPPL uses the high confidence physical interactions derived from InWeb database [Lage et al., 2007] to define edges and using a within-degree node-label permutation to evaluate whether the input seed protein, that is, OMIM genes, were significantly connected by protein–protein interactions. This method takes into the consideration of both the protein interaction density and publication bias.

We further extended the connectivity assessment to include all type of biological interactions, such as activation/inhibition, phosphorylation and gene expression regulation. Expert-curated biological interactions from Ingenuity® Knowledge Base via Ingenuity Pathway Analysis software (IPA®, QIAGEN, Redwood City, CA [An et al., 2012]) were used to retrieved direct interactions of all available types among the seed proteins using the least stringent confidence levels in IPA. These interactions were used to construct the direct networks to visualize the connections among the input seed proteins.

Functional Assessment

Two types of functional assessment were performed to understand the underlying biological functions represented by the OMIM genes and their comparison with the Aggressotype candidate genes. First method involves constructing empirical functional networks that these genes participate in. The second approach is to evaluate the gene list enrichments in the predefined IPA canonical pathways.

We used IPA network generation algorithm (described in detail in IPA's whitepaper, http://www.ingenuity.com/wp-content/themes/ingenuity-qiagen/pdf/ipa/IPA-netgen-algorithm-whitepaper.pdf) to construct non-redundant densely connected empirical networks with default size of 35 molecules or less. Similar to the DAPPLE indirect network, additional non-seed interactors were allowed to be added in order to connect the seed proteins. Based on observations that highly-interconnected networks are likely to represent significant biological function [Ravasz et al., 2002; Ma et al., 2004], we examined the top three most significantly enriched disease and biological functions, predefined pathways, that each networks represent in order to obtain an overview of general biology associated with each network. IPA also calculates the probability of finding f numbers of seed genes (f = the number of seed genes present in the network) in a set of n genes (n = total numbers of the molecules in the network) randomly selected from the IPA Global Molecular Network. This p value is indicative how well the seed genes are connected in these modular networks, thus the strength of the association of the seed proteins with function of the network. We report the negative logs of network p-values, the numbers of seed genes represented in each network, as well as the top disease and biological functions in Tables II and III. When comparing the OMIM and candidate gene networks, we suspect that they would recruit the same common interactors during the empirical network generation if they participate in the overlapping functions. We examined this overlap by visualizing the empirical networks as interconnected nodes if one or more genes were present in both networks. The numbers of the shared genes were labeled on the edges.

IPA Canonical Pathways are well-characterized metabolic and cell signaling pathways that have been curated and hand-drawn by Ingenuity scientists. Pathway enrichment was evaluated using Fisher's Exact Test with Benjamini–Hochberg (B–H) corrections for multiple testing in IPA. The negative log of the enrichment p-values as well as the percentage of seed genes present in the total number of molecules of certain pathways were reported in Supplementary Table I in comparison with the Aggressotype candidate genes. Because many genes participate in different pathways, we presented a network visualization of overlapping canonical pathways that were significantly enrich by OMIM genes if one or more common genes were found to be in different pathways (Supplementary Figure 2).

RESULTS

Search Results

524 OMIM records were retrieved using the search key words. These records were mapped to 618 genetic loci. After examining the gene and phenotype records, we obtained 86 genes harboring mutations linked to aggressive behavior in one or more patients (Table I). Many records were eliminated because the word "aggressive" appears not as a description of behavior but as a descriptor for cancers. Aggressive behavior was observed in 95 different, single-gene human diseases (Table I). Surprisingly, this list of OMIM human aggression genes has little overlap (Fisher's Exact test $P = 0.07$) with the list of aggression candidate genes (N = 97) that had been curated and recommended by the genetics group of the Aggressotype consortium (http://www.Aggressotype.eu/) based on reviewing the literature [Veroude et al., in press]. Only two genes (*GRIA3* and *MAOA*) were known candidates.

Connectivity Between the OMIM Aggression Genes

DAPPLE identified 14 direct physical interactions among the 23 OMIM genes (Fig. 1A). These connections were not more than expected by chance alone ($P > 0.05$). When a common interactor was added to the network to connect any pair of proteins from the 86 OMIM genes, we found that 63 OMIM genes were connected via a total of 946 protein-protein interactions (PPI)(Supplementary Fig. S1). However, these connections were also not more than one would expect from chance ($P > 0.05$). In contrast, the Aggressotype candidate genes were highly significantly connected via both the direct and indirect interactions (P-values < 0.001).

Next we used IPA to expand and include all types of interactions and used the lowest stringency available in IPA, we still observed similar results to DAPPLE analysis that the majority of the OMIM genes (N = 50) do not form any direct interactions in any tissue or species with other OMIM genes. Only 36 OMIM genes were directly connected via 50 interactions of 8 types, majority of which (36 of 50 edges) was protein-protein binding (PP, Fig. 1B). Within the connected cluster of the OMIM genes (Fig. 1B), the top four genes with the most number of interactions were *APP, HTT, FMR1* and *CTNNB1*.Similar to the DAPPLE results, we also observed higher connectivity among the Aggressotype candidate genes; 71 out of 97 genes were directly connected.

Functional Assessment

IPA's network generation algorithm retrieved six non-redundant, significantly and densely connected networks in which the OMIM genes participate (Table II). It retrieved eight non-redundant networks from the Aggressotype candidate gene list (Table III). Non-redundant networks do not overlap in their molecular composition. Comparison of Tables 2 and 3 shows that the OMIM gene set shares several networks with the candidate gene set, e.g., cell cycle and cellular development, and nervous system development and function. As we see in Figure 2, the OMIM and candidate gene networks, despite being non-redundant within themselves, overlap extensively when they are visualized as nodes interconnected by edges if two networks share one or more genes in common. Collectively there were a total of 64 genes shared between the OMIM and candidate gene networks, including two seed genes (*MAOA* and *GRIA3*) and 62 additional genes recruited by IPA to construct these networks. In contrast to the little overlap between the OMIM gene list and the candidate gene list, the overlap between the networks created by IPA was highly significant (Fisher's exact $P < 0.001$).

Finally, we performed canonical pathway analysis to identify the canonical pathways shared by the OMIM and candidate genes. We found 27 canonical pathways significantly enriched by OMIM genes ($P < 0.05$), however, none passed B-H multiple testing corrections. The Aggressotype candidate genes were significantly enriched in 46 canonical pathways ($P < 0.05$), and 32 were significant after B-H multiple testing corrections. We report the negative logs of uncorrected enrichment p values in Supplementary Table II in comparison with the Aggressotype candidate genes. A number of canonical pathways were shared between the OMIM and candidate genes, notably, the serotonin, dopamine and GABA receptor signaling, synaptic long-term depression, noradrenaline and adrenaline degradation pathways. We also point out a number of novel pathways unique to the OMIM genes such as the Methionine Degradation, Neuroprotective Role of THOP1 in Alzheimer's disease and Amyloid Processing. In contrast to the empirical networks, which were non-redundant, many canonical pathways share common genes. The overlapping canonical pathways for OMIM genes were visualized as nodes interconnected by edges if they share one or more common genes (Supplementary Fig. S2).

DISCUSSION

Prior human studies of the genetics of aggression have focused on candidate gene pathways, specifically the serotonin and dopamine systems, as well as hormonal regulators. This was sensible due to earlier studies showing that these pathways play a crucial role in regulating aggressive behaviors in song birds, rodents and fish [Veroude et al., in press]. We took a novel approach by using the OMIM database to identify 86 rare Mendelian variants that cause a disorder associated with aggressive behavior in humans. These variants were associated with 95 distinct human disorders. Only two genes overlapped with a list of candidate genes for aggression that had been curated by a panel of experts based on a literature review. One is monoamine oxidase A (*MAOA*), a mutation of which causes Brunner syndrome, characterized by impulsive

TABLE I. Genes That are Associated With Aggressive Behaviors in Human

Gene MIM#	Symbol	OMIM phenotype with symptoms of aggression, conduct or antisocial disorders	Phenotype MIM#
611501	*CAMTA1*	Cerebellar ataxia, nonprogressive, with mental retardation	614756
602533	*PARK7*	Parkinson disease 7, autosomal recessive early-onset	606324
605078	*TARDBP*	Frontotemporal lobar degeneration, TARDBP-related	612069
		Amyotrophic lateral sclerosis 10, with or without FTD	612069
610513	*ATP13A2*	Kufor-Rakeb syndrome	606693
		Ceroidlipofuscinosis, neuronal, 12	606693
602201	*ECM1*	Urbach-Wiethe disease	247100
605210	*DISC1*	Schizophrenia, susceptibility to	604906
164840	*MYCN*	Feingold syndrome	164280
604277	*SPAST*	Spastic paraplegia 4, autosomal dominant	182601
152790	*LHCGR*	Precocious puberty, male	176410
		Leydig cell adenoma, somatic, with precocious puberty	176410
182125	*SPR*	Dystonia, dopa-responsive, due to sepiapterinreductase deficiency	612716
606247	*STAMBP*	Microcephaly-capillary malformation syndrome	614261
611472	*MBD5*	Mental retardation, autosomal dominant 1	156200
608148	*SATB2*	Glass syndrome	612313
605314	*HDAC4*	Brachydactyly-mental retardation syndrome	600430
116806	*CTNNB1*	Mental retardation, autosomal dominant 19	615075
605515	*FOXP1*	Mental retardation with language impairment and autistic features	613670
609512	*CHMP2B*	Dementia, familial, nonspecific	600795
613012	*UROC1*	Urocanase deficiency	276880
602445	*SERPINI1*	Encephalopathy, familial, with neuroserpin inclusion bodies	604218
613004	*HTT*	Huntington disease	143100
606201	*WFS1*	Wolfram syndrome	222300
602710	*APBB2*	Alzheimer disease, late-onset	104300
609489	*MANBA*	Mannosidosis, beta	248510
611124	*MFSD8*	Ceroidlipofuscinosis, neuronal, 7	610951
608667	*NIPBL*	Cornelia de Lange syndrome 1	122470
610045	*ALDH5A1*	Succinic semialdehyde dehydrogenase deficiency	271980
614461	*UQCC2*	Mitochondrial complex III deficiency, nuclear type 7	615824
609390	*FIG 4*	Polymicrogyria, bilateral occipital	612691
600075	*TBP*	Spinocerebellar ataxia 17	607136
605317	*FOXP2*	Speech-language disorder-1	602081
604569	*CNTNAP2*	Cortical dysplasia-focal epilepsy syndrome	610042
614426	*TTI2*	Mental retardation, autosomal recessive 39	615541
607882	*SLC52A2*	Brown-Vialetto-Van Laere syndrome 2	614707
238300	*GLDC*	Glycine encephalopathy	605899
605978	*VPS13A*	Choreoacanthocytosis	200150
608167	*KCNT1*	Epilepsy, nocturnal frontal lobe, 5	615005
613037	*INPP5E*	Joubert syndrome 1	213300
604346	*MAN1B1*	Mental retardation, autosomal recessive 15	614202
607001	*EHMT1*	Kleefstra syndrome	610253
600465	*ANK3*	Mental retardation, autosomal recessive, 37	615493
601752	*ENTPD1*	Spastic paraplegia 64	615683
602635	*DEAF1*	Mental retardation, autosomal dominant 24	615828
191350	*DPAGT1*	Congenital disorder of glycosylation, type Ij	608093
612349	*PAH*	Phenylketonuria	261600
601515	*FGF14*	Spinocerebellar ataxia 27	609307
605837	*HERC2*	Mental retardation, autosomal recessive 38	615516
613529	*CEP152*	Microcephaly 9, primary, autosomal recessive	614852
614949	*TMEM231*	Joubert syndrome 20	614970
613814	*TTC19*	Mitochondrial complex III deficiency, nuclear type 2	615157
607642	*RAI1*	Smith-Magenis syndrome	182290
609701	*NAGLU*	Mucopolysaccharidosis type IIIB (Sanfilippo B)	252920
157140	*MAPT*	Pick disease	172700
613629	*PIEZO2*	Marden-Walker syndrome	248700
605377	*DMPK*	Myotonic dystrophy 1	160900

TABLE I. (*Continued*)

Gene MIM#	Symbol	OMIM phenotype with symptoms of aggression, conduct or antisocial disorders	Phenotype MIM#
176640	*PRNP*	Huntington disease-like 1	603218
		Prion disease with protracted course	606688
139320	*GNAS*	Pseudopseudohypoparathyroidism	612463
602959	*EEF1A2*	Epileptic encephalopathy	N/A
104760	*APP*	Alzheimer disease 1, familial	104300
602054	*TBX1*	Velocardiofacial syndrome	192430
		DiGeorge syndrome	188400
603604	*PLA2G6*	Parkinson disease 14	612953
300629	*AP1S2*	Mental retardation, X-linked syndromic 5	304340
300072	*USP9X*	Mental retardation, X-linked 99	300919
300172	*CASK*	FG syndrome 4	300422
		Mental retardation, with or without nystagmus	300422
309850	*MAOA*	Brunner syndrome	300615
313440	*SYN1*	Epilepsy, X-linked, with variable learning disabilities and behavior disorders	300491
300499	*FTSJ1*	Mental retardation, X-linked 9	309549
300526	*WDR45*	Neurodegeneration with brain iron accululation 5	300894
314690	*KDM5C*	Mental retardation, X-linked, syndromic, Claes-Jensen type	300534
300256	*HSD17B10*	Mental retardation, X-linked syndromic 10	300220
300188	*MED12*	Opitz-Kaveggia syndrome	305450
		Lujan-Fryns syndrome	309520
300460	*PCDH19*	Epileptic encephalopathy, early infantile, 9	300088
300204	*MID2*	Mental retardation, X-linked 101	300928
300142	*PAK3*	Mental retardation, X-linked 30/47	300558
312180	*UBE2A*	Mental retardation, X-linked syndromic, Nascimento-type	300860
300304	*CUL4B*	Mental retardation, X-linked, syndromic 15 (Cabezas type)	300354
305915	*GRIA3*	Mental retardation, X-linked 94	300699
309550	*FMR1*	Fragile X tremor/ataxia syndrome	300623
		Fragile X syndrome	300624
300806	*AFF2*	Mental retardation, X-linked, FRAXE type	309548
300823	*IDS*	Mucopolysaccharidosis II	309900
300275	*NSDHL*	CK syndrome	300831
300019	*HCFC1*	Mental retardation, X-linked 3 (methylmalonicacidemia and homocysteinemia, cblX type)	309541
300005	*MECP2*	Rett syndrome, preserved speech variant	312750
		Rett syndrome	312750
		Mental retardation, X-linked, syndromic 13	300055
148760	*KIF11*	Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation	152950
600853	*NDST1*	Mental retardation, autosomal recessive 46	616116
608668	*ZMYND11*	Mental retardation, autosomal dominant 30	616083
616101	*TMEM240*	Spinocerebellar ataxia 21	607454

aggressiveness and mild mental retardation [Brunner et al., 1993]. The second was an ionotropic glutamate receptor, *AMPA3* (*GRIA3*), mutations of which cause X-linked mental retardation. Three affected males in a Finnish family demonstrated aggressive outburst among an array of abnormal phenotypes including mental retardation, autistic symptoms, epilepsy, short stature and other dysmorphic features [Philips et al., 2014]. *Gria3* deficiency in mice caused increased inter-male aggression [Adamczyk et al., 2012].

In contrast to the small overlap between the OMIM genes and the candidate genes, we identified several shared canonical pathways (e.g., serotonin, dopamine and GABA signaling, long-term depression and CREB signaling in neurons). Some of these pathways have been recognized previously in studies of human and animal aggression (reviewed [Veroude et al., in press]). Our analyses provide further support for their role in the genetic etiology of aggression. Our results, however, are weakened by the fact that the OMIM gene canonical pathway enrichments were not significant after correcting for multiple comparisons. This is probably because the OMIM database represents a scattered list of genes that cause aggressive phenotype in humans. In addition, our search and record filtering strategy was completely based on key words. If an aggressive behavior was described in language without using our specified key words, we would miss that gene. In contrast to the method for defining OMIM aggression susceptibility genes, most of the Aggressotype candidate genes were selected based on their participation in candidate pathways implicated by previous studies. Therefore, their highly significant canonical pathway enrichment p-values reflect the nature of their generation by the expert panel.

For these reasons, we believe that the OMIM genes represent a partial, but relatively unbiased sampling of the genetic architecture

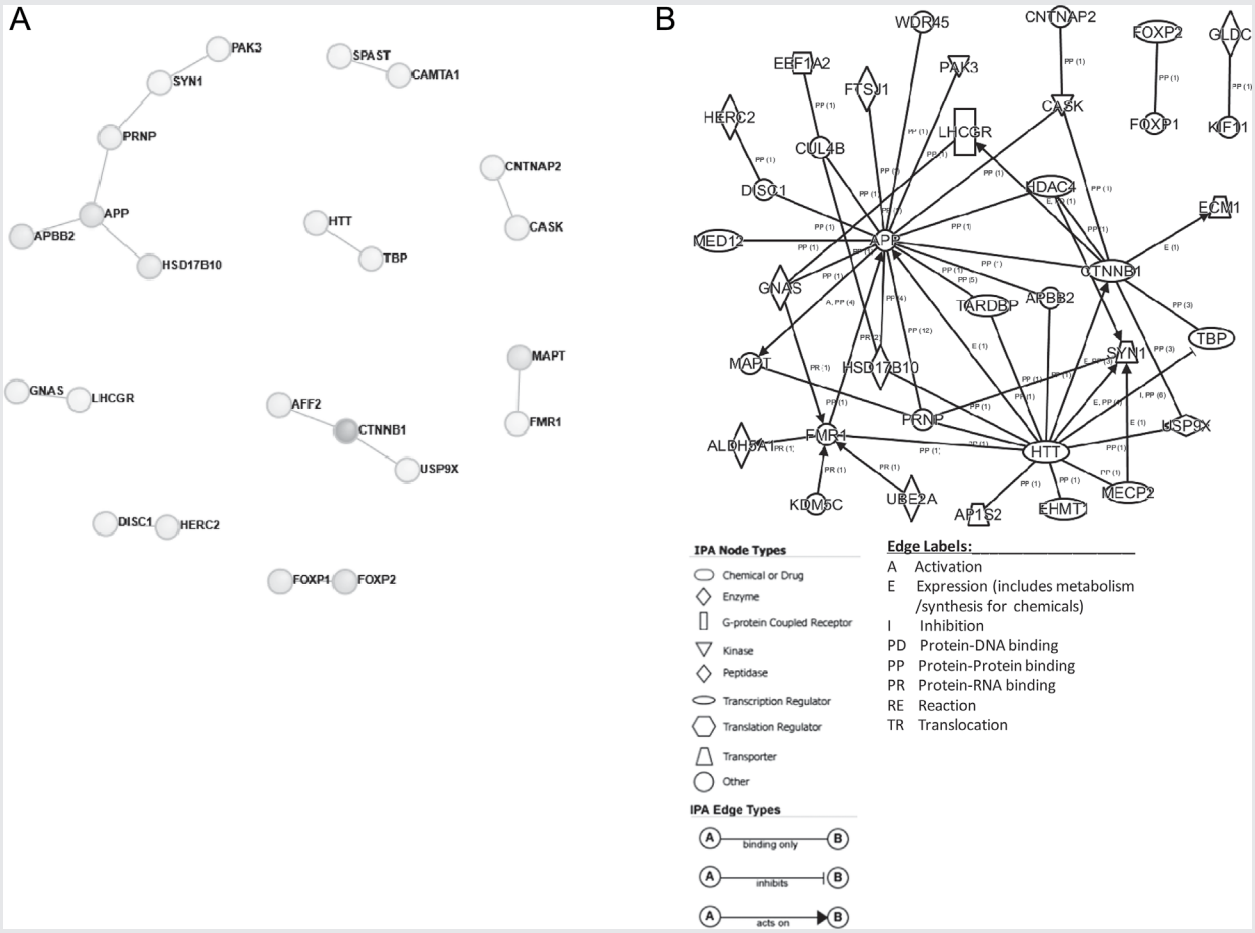

FIG. 1. Directly connected OMIM human aggression genes. A. Physical protein-protein interactions generated using DAPPLE. B. Direct interactions of all types generated using IPA. The shape of the nodes denote the type of the molecules, and type of the interactions were represented as lines (edges) and labeled letters. The numbers in the parenthesis indicates the number of findings for that type of interactions. See the IPA legends for detailed explanation.

underlying human aggression. Despite of the lack of significance after the multiple corrections, we do note that the most well-known pathways, such as serotonin and dopamine signaling, were ranked among the highest using uncorrected p-values, confirming their importance in aggression. To compensate for the incomplete genetic representation of OMIM genes, IPA's empirical network generation allows for the recruiting of additional genes known to closely interact with the OMIM genes based on prior experimental studies. The extensive overlap between the OMIM and the candidate gene networks is reflected in both their shared functional

TABLE II. IPA Networks Implicated by OMIM Genes

Network ID	-Log(p-value)	Seed genes	Top diseases and functions
1	39	19	Developmental Disorder, Neurological Disease, Hereditary Disorder
2	34	17	Developmental Disorder, Neurological Disease, Protein Degradation
3	26	14	Neurological Disease, Developmental Disorder, Hereditary Disorder
4	22	12	Neurological Disease, Cellular Compromise, Organismal Injury and Abnormalities
5	22	12	Cell Death and Survival, Gene Expression, Developmental Disorder
6	17	10	Cell Cycle, Gene Expression, Cellular Development

Network IDs correspond to those in Figure 2 in light grey. Negative log of network *P*-values and the number of seed genes present in each network were reported, as well as the Top 3 IPA disease and functional pathways.

TABLE III. IPA Networks Implicated by Aggressotype-Curated Candidate Genes

Network ID	-Log(p-value)	Seed genes	Top diseases and functions
1	43	21	Cell-To-Cell Signaling and Interaction, Nervous System Development and Function, Behavior
2	40	20	Psychological Disorders, Connective Tissue Disorders, Developmental Disorder
3	33	17	Psychological Disorders, Neurological Disease, Organismal Injury and Abnormalities
4	19	11	Cell-To-Cell Signaling and Interaction, Small Molecule Biochemistry, Drug Metabolism
5	19	11	Nervous System Development and Function, Connective Tissue Disorders, Dermatological Diseases and Conditions
6	14	8	Neurological Disease, Psychological Disorders, Endocrine System Disorders
7	5	4	Cell Cycle, Cellular Development, Cancer
8	4	3	Cell Cycle, Endocrine System Development and Function, Cell Signaling

Network IDs correspond to those in Figure 2 in dark grey. Negative log of network *P*-values and the number of seed genes present in each network were reported, as well as the Top 3 IPA disease and functional pathways.

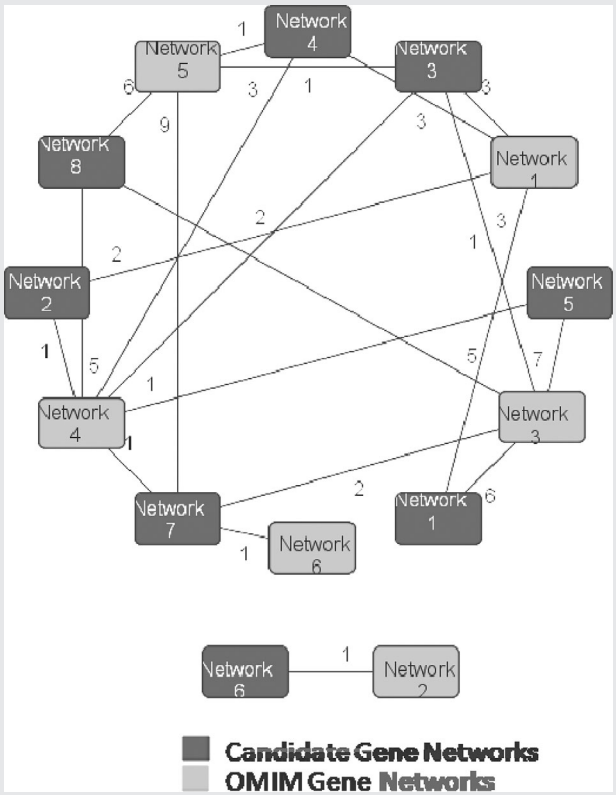

FIG. 2. Overlapping networks between the OMIM and candidate genes. The network numbers correspond to those in Tables 2 and 3. The networks were connected by edges if they share one or more genes in common. The numbers of genes shared between networks were noted on the edges.

pathways s (Tables II and III) and the additional genes recruited into the network (Fig. 2). Therefore, both canonical pathway and empirical network analyses support the idea that OMIM genes and candidate genes participate in overlapping functions, including well-known candidate pathways such as serotonin and dopamine signaling. These findings are consistent with the idea that disease causing/modifying variants for multifactorial genetically-based disorders/traits often converge on common pathways and networks [Ben-David and Shifman, 2012].

Some pathways implicated by the OMIM genes point to novel mechanisms underlying aggression, for example the ERK/MAPK signaling, methionine degradation, amyloid processing, and reelin signaling pathways. Genes in these pathways have not been examined in candidate gene studies and current GWAS are too small to be informative [Veroude et al., in press]. Caution is warranted in interpretation of these pathways given the lack of significance after correcting for multiple comparisons. However, coinciding with our findings, a recent genome-wide transcriptome analysis of inbred mouse models of aggression found that the MAPK signaling pathway was differentially expressed between the aggressive and non-aggressive lines[Malki et al., 2014]. Other evidence also supports the involvement of the above-mentioned novel pathways in aggression. For example, aggression has been observed in neurodegenerative disorders such as Alzheimer's diseases [Burns et al., 1990]. Thus, it is not surprising to see the involvement of the amyloid processing pathway. High levels of beta-amyloid precursor protein (APP) were found in children with severely autistic behavior and aggression [Sokol et al., 2006].The role of methionine degradation pathway in aggression was seen in mice with folate deficiency which results in a decline in S-adenosyl methionine and increased aggression. Supplementation with S-adenosyl methionine eliminated aggression [Lee et al., 2012]. Furthermore, dietary supplementation with S-adenosyl methionine reduces amyloid-β and tau pathology and aggressive behavior in a transgenic mouse model of aggression [Lee et al., 2012]. Reelin signaling plays an important role in neurodevelopment; perturbation of this pathways has been linked to GABA functions in schizophrenia and mood disorders [Guidotti et al., 2000; Fatemi et al., 2005]. Reelin expression was disrupted in the valproic acid-induced autism

mouse model with elevated aggression and exercise was found to ameliorate aggressive behavior through activation of the reeling signaling pathway [Seo et al., 2013].

Aggressive behaviors are common in many neurological and psychiatric disorders including neurodegenerative disorders [Burns et al., 1990; Fisher et al., 2014; Oh et al., 2015], developmental disabilities [Rojahn et al., 1993], schizophrenia [Sandyk, 1993], bipolar disorder [Ballester et al., 2012], ADHD [Cha et al., 2015],and autism [Pivovarciova et al., 2014]. Epidemiologic and molecular genetic studies show that many disorders share genetic variants in common, suggesting common underlying molecular mechanisms [de Lacy and King, 2013; Lichtenstein et al.; Smoller et al., 2013]. Consistent with the dimensional approach of the Research Domain Criteria (RDoC) initiative of the US National Institute of Mental Health, aggression is a cross-disorder dimension that may reflect some fraction of this shared etiology. Future work should determine if genes mediating aggression pathways are enriched in the polygenic background of disorders associated with aggression.

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