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Genetic Architecture of Reciprocal CNVs

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Abstract

Copy number variants (CNVs) represent a frequent type of lesion in human genetic disorders that typically affects numerous genes simultaneously. This has raised the challenge of understanding which genes within a CNV drive clinical phenotypes. Although CNVs can arise by multiple mechanisms, a subset is driven by local genomic architecture permissive to recombination events that can lead to both deletions and duplications. Phenotypic analyses of patients with such reciprocal CNVs have revealed instances in which the phenotype is either identical or mirrored; strikingly, molecular studies have revealed that such phenotypes are often driven by reciprocal dosage defects of the same transcript. Here we explore how these observations can help the dissection of CNVs and inform the genetic architecture of CNV-induced disorders.

Introduction

CNVs have received significant attention in recent years, in part because the increased resolution of genomic analyses has uncovered such events to be both abundant in human genomes and relevant to the pathogenesis of both rare and complex traits. CNVs range in size from a kilobase (kb) to several megabases (Mb)¹. Although some CNVs are found at high frequency in human populations and are thus thought to be a potential source of genetic diversity^{2,3}, larger CNVs, especially *de novo*, are associated frequently with human disorders⁴; in addition to the documented involvement of CNVs in birth defects (e.g. craniofacial, cardiac, respiratory, renal)^{5–12}, CNVs are also understood to be enriched in the pathogenesis of neurodevelopmental and neurocognitive disorders, such as intellectual disability, schizophrenia, and autism spectrum disorders (ASD)^{6,13–20}.

The increased resolution of array-comparative genomic hybridization (aCGH) has catalyzed the hyper-acceleration of CNV discovery; recent advances in exome and genome sequencing analyses are likely to increase the pace of CNV discovery further^{21,22}. In the midst of this progress, some acute interpretative problems have arisen. First, the rarity of most CNVs precludes their statistical analysis with regard to causality. Second, because some CNVs are mediated by non-homologous recombination-prone low copy repeats^{23–25}, recurrence of such events is not deterministic of pathogenicity but reflective of local genomic architecture. Third, CNVs typically affect multiple genes, exacerbating the problem of assigning causality to particular transcripts within a CNV. Finally, the ascertainment of the clinical significance

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of CNVs is often complicated by clinical heterogeneity, non-penetrance and variable expressivity^{13,26-28}.

Given the above challenges, a central question pertains to the contribution of each gene within a CNV to the phenotype. This is a complex issue; each CNV presents unique characteristics and interpretations that are driven, in part, by its gene content and associated clinical phenotype. Nonetheless, our survey of the current data available has identified some patterns emerging in a subclass of CNVs for which the presence of low copy repeats induce the generation of both deletions and duplications of the same segment. Here, we synthesize our current understanding of the genetic causality of these CNVs and ask whether emergent genetic models can illuminate and predict the pathomechanisms caused by this class of genetic mutations.

Reciprocal CNVs and clinical phenotypes

An examination of known reciprocal CNVs and their associated clinical features has indicated that reciprocal CNV-induced phenotypes can be broadly classified into four general categories: mirrored (deletions and duplications of the chromosomal region have opposite effects), identical, overlapping, and unique. Examples of these classes are shown in Table 1.

Mirrored phenotypes

The 16p11.2¹⁸⁻²⁰, 1q21.1^{13,27}, 3q29²⁹⁻³², and 17q11.2^{33,34} CNVs are well-known lesions associated with mirrored phenotypes. Phenotypic mirroring is not ubiquitous, but appears to apply to a subset of clinical features. These include head size abnormalities for the 3q29, 16p11.2 and 1q21.1 CNVs, energy balance defects for the 16p11.2 and 17p11.2 CNVs and, to some extent, mirrored psychiatric disorders for 16p11.2 and 1q21.1 CNVs based on a model in which autism and schizophrenia are two opposite extremes of a spectrum reflecting the under- or over-development of the social brain³⁵.

Similarly, phenotypic examination of individuals with the 17p11.2 CNV revealed a mirroring co-morbidity affecting sleep regulation and energy balance control. Deletion and duplication of a 3.7Mb region in 17p11.2 result in two reciprocal syndromes, Smith-Magenis syndrome (SMS; MIM182290)³⁶ and Potocki-Lupski syndrome (LPS; MIM610883)^{37,38}. SMS is associated with moderate intellectual disability, distinctive facial features, sleep disturbances, behavioral problems, obesity and hypercholesterolemia^{39,40} whereas LPS is associated with infantile hypotonia, sleep apnea, structural cardiovascular anomalies⁴¹, kidney abnormalities⁴², learning disabilities, attention-deficit disorder, obsessive-compulsive behaviours, short stature, reduced weight, and failure to thrive⁴³.

Identical phenotypes

There are several examples in which the core phenotypes of deletions and duplications contribute to the same phenotypic spectrum. For example, 22q11.2 deletions cause DiGeorge syndrome (DGS; MIM188400)^{44,45} and velocardiofacial syndrome (VCFS; MIM192430)^{45,46}. These syndromes result in conotruncal congenital heart defects, velopharyngeal insufficiency, hypoparathyroidism, thymic aplasia or hypoplasia, craniofacial dysmorphism, learning difficulties and psychiatric disorders⁴⁷⁻⁵⁰. Duplications of the same genomic segment in DGS and VCFS patients have also been reported⁵¹⁻⁵³. The phenotype of duplication (dup) patients is variable, ranging from normal to multiple defects reminiscent of DGS/VCFS phenotypes with shared clinical features; these include heart defects, velopharyngeal insufficiency with or without cleft palate, hypernasal speech, and urogenital abnormalities.

Overlapping, unique, and variable phenotypes

Finally, some phenotypes are unique to deletions or duplications. For example, epilepsy is associated with del16p11.2 but not with the reciprocal dup16p11.2¹⁸. Others are overlapping, as exemplified by phenotypes associated with CNVs on 15p13.3 and 7q11.23; Sharp et al. reported a microdeletion syndrome characterized by cognitive impairment, seizures and a range of congenital abnormalities⁵⁴ caused by recurrent deletions of 15q13.3⁵⁵. The variable phenotype of the 15q13.3 deletion has been extended to include autism, seizures, learning disabilities^{56,57}, schizophrenia and epilepsy^{17,58-60}. Adding to the complexity, that deletion in normal family members of probands, as well as in population controls, suggests that the deletion alone is not sufficient to cause intellectual disability. The reciprocal duplication is less frequent, with a few cases described to date^{28,61}. The duplication was first identified in four patients with intellectual disability, autism, hypotonia, obesity, recurrent ear infections, and low set ears²⁸. However, none of these patients had structural brain abnormalities or the epileptic seizures seen in deletion patients.

Reciprocal CNVs and genetic architecture

Are there any common patterns that can inform our understanding of the genetic drivers of the CNV-associated phenotypes for del and dup patients? Broadly, one can consider three basic models (Fig. 1): a) the single-gene CNV model, in which the phenotypes of deletion (del) or dup patients are the product of dosage imbalance of a single gene; b) the “*simplex cis epistatic*” model, in which dysfunction of a single gene is necessary and sufficient to establish phenotype, but is subject to modulation by epistasis effect exerted by other genes within the CNV; and c) the “*complex cis-epistatic*” model in which phenotypes are the result of the simultaneous dosage imbalance of numerous genes within the CNV, some of which drive specific endophenotypes and some of which exhibit complex additive and/or multiplicative relationships.

Intuitively, the complexity intimated by the latter model is expected to be true and is consistent with our understanding of large genomic lesions, such as chromosomal abnormalities. For example, the additional copy of human chromosome 21 results in the increased expression of 29% of the genes; the remaining 71% of the expressed sequences encoded on this chromosome are either compensated for or are highly variable among individuals⁶². Thus, although most of the chromosome 21 transcripts are compensated for the gene-dosage effect, a subset of the overexpressed genes are likely major drivers and/or modulate the numerous deleterious phenotypes observed in individuals with Down syndrome⁶³. However, experimental dissection of reciprocal CNVs suggests that each of the other two models might not only be true, but in fact predominate in this class of genomic disorders. Caution is warranted, given that the number of reciprocal CNVs dissected successfully remains small and that in many instances phenotyping of patients is incomplete. Nonetheless, it is intriguing that the same paradigms are being observed in reciprocal CNVs at different regions, of different size, and with different phenotypic associations.

Reciprocal CNVs and single-gene defects

This class of CNVs is rare. Charcot-Marie-Tooth disease (CMT) is the most common hereditary motor and sensory neuropathy, and CMT type 1A (CMT1A), the most common type of CMT, is subject to a gene dosage effect⁶⁴. The primary genetic cause of CMT1A is a duplication of *PMP22* resulting from the unequal crossover between two homologous repetitive elements that flank a 1.4-Mb region of chromosome 17p12⁶⁵. Importantly, *PMP22* frame-shift⁶⁶ and loss of function point mutations⁶⁷ have been found in severely affected CMT1A patients; likewise, same loss of function point mutations in *Pmp22* were found in the Trembler-J mouse, a CMT1A model⁶⁸. The reciprocal deletion of *PMP22* is associated

with non-progressive hereditary neuropathy with liability to pressure palsies (HNPP)⁶⁹. Overexpression of *PMP22* in mice causes a defect of myelination of the neurons that fully recapitulates the CMT phenotype⁷⁰ whereas, as expected from human genetics, heterozygous *PMP22* knock-out mice revealed a pathology comparable with HNPP⁷¹. Although CMT1A and HNPP are not mirrored disorders *per se*, these data emphasize the remarkable sensitivity of myelin stability to *PMP22* gene dosage, since either over- or under-expression results in long-term myelin instability.

Reciprocal CNVs and *cis*-epistasis

This appears to be the most common variety among the handful of CNVs dissected to date. The major disease candidate gene *TBX1*⁷², a member of the T-box transcription factors family, is localized between LCR-A and LCR-B on 22q11.2. Notably, altering the dosage of *Tbx1* (both over- and under-expression) recapitulates DGS and VCFS in mice⁷³. Further, both loss of function mutations and mutations shown to enhance the activity of *TBX1* have been found in rare DGS/VCFS non-deleted cases^{74,75}. These mutations could be considered as functionally equivalent to a deletion or a duplication of *TBX1* respectively. Taken together, these data suggest that abnormal *TBX1* dosage in either direction disrupts the same developmental pathways and result in similar developmental defects commonly ascribed to DGS/VCFS's phenotypic spectrum.

It is important to note, however, that although *TBX1* is the major driver of the 22q11.2 CNV phenotypes, patients with *TBX1* point mutations are phenotypically not identical to patients with 22q11.2 deletions. For example, *TBX1* is responsible for conotruncal anomaly face feature, cardiac defects, thymic hypoplasia, velopharyngeal insufficiency with cleft palate, and parathyroid dysfunction with hypocalcemia; however, there is no evidence of intellectual disabilities in patients with *TBX1* mutations, suggesting that either other loci drive this component of the phenotype or that *TBX1* might be subject to *cis* epistasis to develop cognitive defects⁷⁶. The latter is supported by the detection of *Tbx1* message in the frontal cortex and the hippocampus in mice⁷⁷.

Similar to the 22qdel/dup CNV, a single gene has been proposed to be the major driver of mirrored phenotypes of the 16p11.2 CNV. Systematic screening of genes whose overexpression in zebrafish embryos causes microcephaly led to the identification of *KCTD13* as a major driver for the neuroanatomical phenotypes of the 16p11.2 CNV⁷⁸. Consistent with this observation, suppression of the same gene gave rise to macrocephalic embryos and the phenotypes were ascribed to changes in neurogenesis and apoptosis in the developing brain⁷⁸. Genetic evidence supported this finding further. First, an atypical deletion of five genes, including *KCTD13*, segregated in a family with isolated ASD⁷⁹; second, a patient with ASD was found to harbor a *de novo* deletion of a portion of *KCTD13*⁷⁸. Further, epistatic analysis of *KCTD13* in zebrafish embryos highlighted a contributory effect of two more genes from within the CNV, *MVP* and *MAPK3* on the expressivity of the head size phenotype⁷⁸; notably, all three genes (*KCTD13*, *MAPK3* and *MVP*) are present in the aforementioned 5-gene deletion⁷⁹. Moreover, the patient with the *de novo* *KCTD13* deletion also harboured an inherited heterozygous deletion distal to 16p11.2, suggesting a possible interaction with lesions outside this CNV⁷⁸.

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Mutations in *RAI1* have been found in Smith-Magenis syndrome⁸⁰ suggesting that haploinsufficiency of *RAI1* is probably responsible for the behavioral, neurologic, and craniofacial aspects of this syndrome. These phenotypes are also observed in dup patients with Potocki-Lupski syndrome. Further, increased anxiety and hyperactivity, growth retardation, and altered motor and sensory coordination, were observed in *Rai1*-overexpressant mice, recapitulating phenotypes observed in patients with 17p11.2 duplication⁸¹. These data suggest that over- and under-expression of *RAI1* cause similar phenotypes that are pathognomonic of the two syndromes. The 17q11.2 del/dup patients also exhibit mirrored metabolic balance and sleep control disorders. Detailed analyses of the del and dup mice models fully recapitulated the mirrored metabolic phenotype observed in patients, whereas a defect of the circadian rhythm has only been found in the del mice to date⁸². Two mouse models have been generated subsequently to mimic over- and under-expression of *RAI1* (*TgRai1* and *Rai1*^{+/-} respectively). These studies pointed to the fact that neither the duplication nor the deletion CNV-associated phenotypes can be attributed exclusively to the *RAI1* dosage. The *Rai1*^{+/-} and del mice share the same phenotype, whereas the *TgRai1* and dup mice phenotypes are discordant with an absence of changes in the serum chemistry and body composition in the *TgRai1* mice compared to the dup mice³³. As such, the mirrored metabolic and sleep control phenotypes seen in SMS/PTLS seem unlikely to be driven by *Rai1* dosage alone. We speculate that copy number change of *RAI1* and other genes in *cis*, such as the candidate *SREBF1*⁸³, with one of them exerting a synergistic or additive epistatic effect on the other, is required to fully manifest the reciprocal phenotypes of SMS and PTLS.

Genetic heterogeneity underlying non-reciprocal phenotypes

We have been unable to find an example in which two genes within a reciprocal CNV can drive a similar/mirrored phenotype that is shared among patients with the same del/dup. Nonetheless, each type of lesion bears phenotypes, in addition to the reciprocal/similar manifestations, that are unique; in such instances, the composite phenotype of the CNV appears to be the synthesis of defects driven by more than one genes under a classical paradigm of a contiguous gene syndrome. For example, two genes have been implicated in the etiology of the Williams-Beuren syndrome, each gene responsible for a different phenotypic component of del/dup patients. Haploinsufficiency of elastin (*ELN*) is responsible for the supravalvular aortic stenosis and other arteriopathies but not cognitive defects in patients with WBS^{84,85}. Further, the identification of a small deletion including *ELN* and *LIMK-1* in two families with partial WBS implicated *LIMK-1* hemizygosity in impaired visuospatial constructive cognition⁸⁶. Finally, suppression of *GTF2I* and *GTF2IRD1* in mice recapitulated some WBS phenotypes such as microcephaly, retarded growth, and skeletal and craniofacial defects^{87,88}, suggesting that these two transcription factors are either possible drivers of the aforementioned phenotypes or modifiers exerting an epistatic effect to modulate cardiac and cognitive defects driven by the major drivers *ELN* and *LIMK-1* respectively.

Such observations are also reported for other CNVs. For example, in addition to mirrored phenotypes observed in the 16p11.2 CNV, epilepsy has been found only in del patients^{89,90}. The recent finding of loss-of-function mutations in *PRRT2*, one of the 29 genes of the 16p11.2 CNV, in patients with epilepsy and seizures⁹¹ suggests that 1) *PRRT2* is sufficient to cause epilepsy and seizures and 2) *KCTD13* is unlikely the only driver of the 16p11.2 phenotypes.

Reciprocal CNVs, variable penetrance and variable expressivity

A complicating factor of these *post-hoc* analyses of CNV architecture is that most CNVs exhibit marked variability and non-penetrance. Moreover, phenotyping of siblings or parents is often missing or is partially reported; mild phenotypes are often not subjected to aCGH, leading to fewer duplication discoveries compared to deletion; and poor investigation and estimation of CNV burden in controls remains a source of concern. Despite these limitations, some potentially valuable observations are emerging that are likewise informing architecture of reciprocal CNVs. First, duplications appear to be more frequently inherited, whilst deletions are more frequently reported in patients to be *de novo*, suggesting that the latter are more likely to be penetrant^{92,93-95}. Second, duplications are generally milder and have greater variability in expressivity than deletions^{92,96}.

With regard to gene content, we are cautious in reaching conclusions about the relative prevalence of the three gene-based models (Fig 1). The handful of examples available to us predict that the “*cis*-epistasis” model is the most predominant. This would in turn predict that specifically for reciprocal phenotypes in reciprocal CNVs, there will be a single major driver influenced by proximal genetic content (as well as variation elsewhere in the genome). This is a testable hypothesis; for instance, the 16p11.2 data implicating haploinsufficiency of *KCTD13* in ASD would predict a role for the same gene in the development of schizophrenia. More broadly, there are numerous examples of reciprocal CNVs in the morbid human genome whose genic etiology is not yet understood. For example, a 9-gene deletion on 1q21.1 is associated with microcephaly^{13,27}, while the dup is associated with macrocephaly^{13,27}; once again our model would predict that dosage imbalance of a single transcript should account for both phenotypes.

Finally, a “*cis*-epistasis” model (Fig 1) also predicts that “fixing” the dosage imbalance of a single driver gene within a CNV might represent an efficient means of identifying contributory interactors, which would be challenging to recognize using standard genetic or statistical methods. Initial data from the 16p11.2 CNV offer an indication that this approach is experimentally tractable but, naturally, such studies need to be reproduced for other regions. For this purpose, sensitizing the genetic background of appropriate model organisms to either haploinsufficiency or increased expression of the candidate CNV driver could be an useful template for the systematic screening for the ability of both *cis* and *trans* factors to change the penetrance and/or expressivity of driver-induced phenotypes.

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Figure 1. Theoretical models to explain penetrance and phenotypic variability of reciprocal CNVs

Schematic representation of a genomic segment encompassing five genes (Gene A-E) flanked by low-copy repeats (LCRs). LCRs are depicted as blue arrows with the orientation indicated by the direction of the arrowheads. Recombination between LCRs results in reciprocal deletions and duplications. The “single gene” model posits that a single primary gene is the major driver of the phenotype; the single primary driver accounts for 100% of the expressivity and penetrance. Conversely, the cis-epistasis models posit that one or multiple genes are necessary and sufficient to cause phenotypes but epistasis interactions modulate the expressivity and penetrance of the phenotype(s). Two models arise: 1) A single primary driver or 2) Multiple primary drivers are sufficient to cause independent or same phenotypes. The other genes within the CNV modulate the penetrance and/or expressivity of the phenotype(s) primarily driven by the major driver(s).

Table 1

Phenotypes of the reciprocal CNVs for which at least one major driver has been identified.

CNV locus	Total genes	CNV primary driver(s)	Deletion Phenotypes	Duplication Phenotypes
Mirrored Phenotypes				
1q21.1 ^{13, 27}	7	<i>Unknown</i>		Head size Psychiatric disorders
2q13 ⁶	6	<i>Unknown</i>		Head size
3q29 ²⁹⁻³²	21	<i>Unknown</i>		Head size
16p11.2 ^{19, 20, 90, 97-99}	29	<i>KCTD13</i> <i>PRRT2</i>		Head size Psychiatric disorders Metabolic homeostasis
17q11.2 ^{33, 34}	44	<i>RAI1</i>		Sleep regulation Metabolic homeostasis
Similar or Overlapping Phenotypes				
2q11.2 ^{100, 101}	20	<i>Unknown</i>	ASD *	ASD *
7q11.23 ^{15, 92, 102, 103}	24	<i>ELN</i> <i>LIMK-1</i>	Distinctive facial appearance Cardiac abnormalities Infantile hypercalcemia Growth retardation/developmental delay	Facial dysmorphism Language and speech delay Autism behavior Epilepsy
8p23.1 ^{104, 105}	22	<i>GATA4</i>	Dysmorphic features Developmental delay Heart defects	Dysmorphic features Developmental delay Heart defects
8q24.3 ^{6, 101, 106, 107}	3	<i>Unknown</i>	ASD *	ASD * Epilepsy ¹⁰⁸
9q34.3 ^{6, 109, 110}	97	<i>Unknown</i>	Craniofacial features Microcephaly Speech delay/developmental delay Respiratory failure	Non-syndromic, IQ>70 *
15q13.3	6	<i>CHRNA7</i>	Intellectual disability Epilepsy Seizures Variable dysmorphism of the face and digits	Intellectual disability Autism Recurrent ear infections, low set ears Obesity
16p13.11 ^{26, 111, 112}	7	<i>Unknown</i>	Microcephaly Sever intellectual disabilities Epilepsy	Microcephaly/macrocephaly Moderate intellectual disabilities Autism spectrum disorders

CNV locus	Total genes	CNV primary driver(s)	Deletion Phenotypes	Duplication Phenotypes
			Short stature Cardiac defects Dysmorphism	Cardiac defects Dysmorphism
17p13.3 ¹¹³⁻¹¹⁵	41	<i>Unknown</i>	Miller-Dieker syndrome (MIM 247200): Lissencephaly Intellectual disabilities Facial dysmorphism	Microcephaly Dysgenesis of the corpus callosum Cerebellar atrophy Developmental delay/intellectual disabilities Attention deficit-hyperactivity disorder Facial dysmorphism
17q21.31 ¹¹⁶⁻¹¹⁸	5	<i>KANSL1</i>	Mild-to-moderate intellectual disability Distinctive facial features Epilepsy Heart defects Urogenital anomalies	Severe developmental delay Microcephaly Facial dysmorphism Abnormal digits and hirsutism Failure to thrive
22q11.2 ^{44, 46, 47, 49, 51, 52}	33	<i>TBX1</i>	Dysmorphic facial features Velocardio-facial syndrome (cleft/lip palate, velopharyngeal insufficiency) Congenital heart disease (conotruncal) Learning disabilities Hearing loss	Dysmorphic facial features Velopharyngeal insufficiency cleft/lip palate Congenital heart disease (conotruncal) intellectual disabilities Speech delay Hearing loss Failure to thrive

* Incomplete phenotyping of the patients harboring the lesion