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Review article

Neurogenomics in Africa: Perspectives, progress, possibilities and priorities

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ABSTRACT

The understanding of the genetic basis of neurological disorders has grown rapidly in the last two decades. Despite the genomic heterogeneity within African populations, large-scale candidate gene or linkage and exome studies are lacking. However, current knowledge on neurogenetics in African populations is limited and geographically very uneven. Isolated reports indicate the existence of autosomal dominant or recessive conditions incorporating cerebrovascular, movement, neuromuscular, seizure and motor neuron disorders in Africans. In addition, few African families with neurodegenerative disorders associated with dementia have been characterized in North, West and South Africa. The current insurgency in genomic research triggered by among others the Human Health and Heredity (H3) Africa Initiative indicates that there are unique opportunities to advance our knowledge and understanding of the influence of genomic variation on the pattern, presentations and prognosis of neurological disorders in Africa. These have enormous potential to unmask novel genes and molecular pathways germane to the neurobiology of brain disorders. It would facilitate the development of novel diagnostics, preventative and targeted treatments in the new paradigm of precision medicine. Nevertheless, it is crucial to strike a balance between effective traditional public health strategies and personalized genome based care. The translational barriers can be overcome through robust stakeholder engagement and sustainable multilevel, multigenerational and multidisciplinary capacity building and infrastructural development for genomic medicine in Africa.

Contents

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1. Introduction

Our understanding of the genetic basis of neurological disorders has grown rapidly in the last two decades. This has been accomplished largely by the 'positional cloning' research paradigm that utilizes linkage studies to localize specific genes on chromosomes and the subsequent identification of causative genes by targeted screening of Mendelian neurological disorders [1,2]. However, most neurological disorders are polygenic disorders with non–Mendelian inheritance. The clinical phenotype is often the culmination of several complex processes and interacting pathways that involve genetic, epigenetic and environmental factors [3]. As such, the exact influence of genetic factors on neurological disorders varies giving rise to differing phenotypic manifestations.

In monogenic neurological disorders e.g. Huntington's disease, spinocerebellar ataxias, patterns of inheritance which may be autosomal dominant or recessive, are easier to elucidate whereas the genetic contributions to polygenic neurological disorders such as stroke, Alzheimer's disease and the epilepsies may result from common variants with small effect sizes, rare variants with large effect sizes, or a combination of both [4]. For populations in Africa, on the one hand there are some published studies exploring the genetic underpinnings of certain neurological disorders including Parkinson's disease, age-related dementias, and spinocerebellar ataxias while on the other hand there is barely any specific genetic knowledge on stroke, rare disorders or headache syndromes (Tables 1 and 2). Moreover, virtually all the available published data among Africans were derived from linkage analysis and limited candidate gene studies with no published evidence of genome wide association studies (GWAS) or next generation sequencing approaches.

It is not clear what proportion of the burden can be attributed to genetic transmission but current estimates show Africa bears a high burden of all cause neurological disorders. By 2010, all causes of neurological, mental health and substance-use disorders including cerebrovascular diseases and pain were estimated to account for more than 29% of the global burden of disease [5,6]. In tandem with increased life expectancy, the global burden of disease has shifted from premature death to increased years lived with disability per 100,000. By 2013, the disability-adjusted life years (DALYs) attributed to neurological disorders including cerebrovascular disease and neurogenic pain for sub-Saharan Africa alone are estimated to be 4.4% compared to 11% for all developing regions of the world [7]. The spectrum of neurological disorders encompasses childhood developmental conditions to ageing-related dementias [6,8]. Given the origin of previous widely published reports, genetic studies on neurological studies have been carried out in only 17 countries in Africa out of 58 independent states with the currently estimated population of 1.2 billion. They have been concentrated in 4 North African countries including Morocco, Algeria, Tunisia and Egypt and 13 countries in sub-Saharan Africa including Burkina Faso, Central African Republic, Gambia, Ghana, Kenya, Mali, Malawi, Nigeria, Rwanda, Sudan, South Africa, Tanzania and Zambia (Tables 1 and 2). The expectedly high burden of neurological disease together with the substantial genomic heterogeneity of African populations [9,10] offers a unique opportunity to identify and understand other novel genes and molecular pathways, which contribute to the neurobiology of brain disorders. This may lead to new and better detection, prevention and treatment options in people of African ancestry and possibly by extension, other global populations particularly in the new paradigm of personalized precision medicine [11,12].

In this article, we discuss the basis of African genomic variation and provide an overview of the status of knowledge on the genetics of neurological disorders in Africa (Fig. 1). We also highlight the current genomic revolution triggered by the H3Africa Initiative [13], identify potential future gains in knowledge and suggest priorities for effective translational genomics in Africa.

2. Perspectives on what is known

2.1. African human genomic variation

African populations harbor the broadest genomic diversity, lowest levels and most divergent patterns of linkage disequilibrium, as well as smaller haplotype block sizes among the world's human population [9,14]. Studies of genomic variation in Africa suggest that the present pattern of variation within and between populations is a product of several factors. These include demographic history, population structure, diversities of geographical location, language classification and different patterns of subsistence, dietary differences, multiple migration with accompanying high levels of genetic admixture and survival related to exposure to infectious diseases [15,16].

Tishkoff and colleagues [9] identified 14 ancestral population clusters in Africa with four predominant clusters that broadly represent populations from major African geographical regions and the four dominant African language families. These are Niger-Kordofanian spoken primarily by agriculturalist populations located in large contiguous regions of sub-Saharan Africa (SSA) from West Africa to eastern and southern Africa, Nilo-Saharan spoken predominantly by pastoralist populations in central and eastern Africa, Afroasiatic spoken predominantly by agro-pastoralists and pastoralist populations in northern and eastern Africa, and Khoesan, a language family that contains click consonants, spoken by hunter–gatherer San populations in southern Africa as well as the Hadza and Sandawe hunter–gatherers in Tanzania.

The remaining 10 are mainly restricted to specific geographic regions, languages, or in some cases, individual populations. More recently, Shriner and colleagues [17] analyzed ancestry data from 12 global and regional diversity projects with genome-wide genotype data for 3528 unrelated individuals from 163 samples from around the world. They identified 19 ancestral components with 94.4% of individuals showing mixed ancestry. Furthermore, they validated the earlier findings [9] and identified an additional ancestral component in Africa. These are the Omotic speaking peoples of Ethiopia. It should, however, be noted that the people of North Africa have an ancestral origin (predominant Arabian and Berber) which is quite different from sub–Saharan African populations.

Our knowledge of African human genomic variation is burgeoning. This was previously limited by the small number of African populations involved in the International HapMap project [18] and the 1000 Genomes Project (http://www.1000genomes.org/). In these projects, participation was limited to Niger-Kordofanian-speaking Yoruba and Esan from Nigeria, Mende from Sierra Leone, Bantu-speaking Luhya from Kenya, and Nilo-Saharan-speaking Maasai from Kenya. Therefore, a large proportion of African human genomic variation remained unexplored.

Recent reports from the African Genome Variation Project (AGVP) have robustly confirmed and provided more detailed characterization of African genomic diversity [10]. The AGVP utilized dense genotypes from 1481 individuals and whole-genome sequences from 320 individuals across sub-Saharan Africa. Novel evidence of complex, regionally distinct widespread hunter-gatherer and Eurasian admixture across sub-Saharan Africa was apparent and substantial hunter–gatherer and Eurasian ancestry admixture of up to 23% and 50% respectively were found in many African populations with detailed chronology of the timing of the admixture. For instance, whereas the Eurasian admixture among the Yoruba is estimated to have occurred 7500–10,500 years ago, it is more recent among the Fula tribe of Gambia occurring only about 320–780 years. These admixtures provide evidence for back–to-Africa migration, the existence of hunter gatherer population in West Africa and a pattern of gene flow consistent with the Bantu expansion.

The AGVP also found new loci related to susceptibility, pathogenesis, severity and outcome of several diseases including malaria, Lassa fever, trypanosomiasis, trachoma and hypertension. For example, they identified highly differentiated variants within genes involved in osmoregulation (*ATP1A1* and *AQP2*); deregulation of AQP2 expression and loss-of-function mutations in *ATP1A1* haven been associated with essential and secondary hypertension, respectively [19,20]. The study also established an efficient genotype array design capturing common genetic variation in Africa. This implying use for useful for future African genomic studies [21].

Genomic variation and related phenotype data on complex traits contribute novel information. This would be useful for identifying population-specific variants that play a role in gene function, phenotypic adaptation and susceptibility to complex diseases such as stroke in populations of African descent. As discussed above, African populations probably harbor the widest human genomic diversity, thereby providing a promising avenue to better understand human adaptation and disparities in health and disease. However, this opportunity has not yet been fully explored. The *APOE* ε4 allele, a well-studied example that contributes to a small extent to individual and population risks of traits such as vascular disease and dementia, exists at variable rates in different populations. Frequency of homo– or heterozygous *APOE* ε4 allele varies across populations but confers different attributable risks of Alzheimer's disease. The risk being higher among the Japanese with a lower frequency but much lower among people of African ancestry with higher allele frequencies. This suggests a possible intervening role for epigenetic interactions from certain modifier genes or other possible environmental factors [22].

2.2. Cerebrovascular disorders

2.2.1. Stroke

The enhanced predisposition, different pattern of subtypes, greater severity and often poorer outcome of stroke and related disorders in people of African descent is well established. There are only a handful of stroke genetic studies from Africa. Saidi and colleagues investigating a Tunisian stroke cohort reported moderate to strong associations between ischaemic stroke and polymorphisms in several genes including plasminogen activator inhibitor, ApoE ε4, human plasminogen activator, human platelet antigen, angiotensin converting enzyme *Del*/*Del* variant, angiotensinogen, endothelial nitric oxide synthase and aldosterone synthase [23–29]. A single study from Egypt noted that the presence of *ACE* D allele significantly predisposed to stroke in children with sickle cell anaemia [30] (Table 1). Notwithstanding sickle-cell disease is highly prevalent in Africa and as one of the most common severe monogenic disorders involving haemoglobin polymerization is a frequent cause of strokes [31]. In a recent Zambian study (Table 2) examining the relationship of *APOE*, *ACE* and *MTHFR* polymorphisms and stroke phenotypes, only the *APOE* ε2ε4 genotype was found to be significantly associated with both haemorrhagic and ischaemic strokes respectively [32]. However, because North Africans differ from sub–Saharan African populations in ancestral origin [17], significant differences may be anticipated in the genomic profile of stroke and its subtypes. Therefore, the urgent need to specifically identify genes that confer risk for or protection against stroke independent of hypertension and other common risk factors in this population cannot be overemphasized.

2.2.2. Hereditary stroke disorders

Several hereditary cerebrovascular disorders likely exist in Africa. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is associated with mutations in the *NOTCH3* gene and presents with migraine headache, depression and ischaemic stroke in the deep gray structures and subcortical white matter, cognitive decline and dementia. There is now complete proven congruence between detection of the characteristic granular osmiophilic material (GOM) in vascular smooth muscle cells of small arteries and *NOTCH3* gene screening. [33] CADASIL cases identified by either skin biopsies or gene screening have been reported from Tunisia, Sudan, Tanzania and South Africa [34–37] (Tables 1 and 2). In the Tunisian case, the index patient harbored the less frequent C>T transition at nucleotide 994 of exon 6 (c.994C[T) in *NOTCH3* [34].

2.3. Movement disorders

2.3.1. Parkinson's disease

Although studies describing the genetics of Parkinson's disease abound in high income countries, there are few studies in Africa overall, with more studies in Northern Africa compared to sub-Saharan Africa. Several mutations have been described in genes and susceptibility loci (www.pdgene.org), but mutations have only been described in *parkin*, *PINK1*, *DJ1* and *LRRK2* genes in Africa [38,39]. (Table 1).

Among the Maghreb populations of North Africa (Arabs and Berbers), microdeletions and exon deletions in the *parkin* gene cause autosomal recessive PD [40,41] while *PINK1* mutations occur in families with PD from Morocco and Algeria [42]. Mutations in the *LRRK2* gene, particularly the G2019S variant are most widely reported from North Africa. The frequencies of 9.7% in Egypt, 32% in Algeria and up to 41–42% in Tunisia, which are much higher than that reported from Europe and North America (<4%) [39,43]. One likely reason for the high frequency is due to the wide practice of consanguineous marriages.

In sub-Saharan Africa, published genetic studies of PD are limited to a few countries including Nigeria, Ghana, Zambia and South Africa [38] (Table 2). A Nigerian study of *parkin*, *LRRK2* and *ataxin-3* genes in a small cohort of largely sporadic PD subjects did not detect any pathogenic mutations in the genes studied, although certain polymorphisms of the *parkin* gene were found [44]. The Ghanaian study of *LRRK2* detected no mutations [45] while mutations reported in the *parkin* gene were restricted to two Black South African cases [46] and one Zambian case [47]. A Zambian study found two heterozygous exonic deletions in the *parkin* gene [47]. No mutations have yet been detected in the α-synuclein gene (*SNCA*), *LRRK2*, *PINK1* and *DJ-1* genes in sub-Saharan Africa. It is particularly intriguing that common mutations in *SNCA* and *LRRK2* have not been detected in sub-Saharan Africa, and the implications of this for the history of the early migrations within, out of and back into Africa will be interesting to unravel.

Highly powered, large sample, multicenter collaborative projects of uniform methodologies are needed to unravel the novel genetic,

epigenetic and gene–environment interactions that influence the phenomics, natural history and outcome of PD in Africans [48].

2.3.2. Huntington's disease

Huntington's disease (HD) is variably described to occur in Africa. All the features of this an autosomal dominantly inherited slowly progressive degenerative movement disorder such as involuntary abrupt, irregular and aimless movements, personality changes and dementia have been described in Africans. HD occurs due to a polyglutamine–coding CAG trinucleotide repeat expansion in the *huntingtin* (*HTT*) gene on the short arm of chromosome 4 causing selective neuronal death in the striatum and cortex. Confirmed CAG repeat expansions have been described in Gambia, Burkina Faso, Senegal, Sudan and South Africa [49–52] (Table 2). Huntington's disease-like (HDL) syndromes present with a clinical picture indistinguishable from that of HD but have different genetic bases, including mutations in the prion protein gene (HDL1), the junctophilin 3 gene (HDL2), the gene encoding the TATA box-binding protein (HDL4/SCA17), and a recessively inherited HD phenocopy in a single family (HDL3) [53]. The HDL2 disease is an adult onset, progressive, neurodegenerative autosomal dominant disorder clinically characterized by abnormal movements, dementia, and psychiatric syndromes. It is due to a junctophilin-3 CTG/CAG expansion mutation on chromosome 16q24.3 and rates appear considerably higher among individuals of African ancestry [54] with robust reports from South African black population [55,56].

2.3.3. Spinocerebellar ataxias and dystonias

The spinocerebellar ataxias also exist in Africa. They are a group of inherited degenerative disorders of the central nervous system characterized by slowly progressive gait imbalance and incoordination resulting from dysfunctions of the cerebellum and its afferent and efferent connections. Many are polyglutamine or 'CAG Triplet Repeat Disorders' [57]. Usually classified by their mode of inheritance and causative gene or chromosomal locus, inheritance may be autosomal dominant [autosomal dominant cerebellar ataxias for which specific genetic information is known], autosomal recessive [Friedreich ataxia, ataxia-telangiectasia, ataxia with vitamin E deficiency, ataxia with oculomotor apraxia (AOA), spastic ataxia], or X-linked [SCAX1]. To date, 32 autosomal dominant SCAs have been mapped, and the genes causing 20 of these disorders have so far been identified [58].

Table 1
Neurological disorders and currently known genetic traits and genes affected in Africans (Northern Africa).

Major neurological category[a]	Disorder subtypes	Country/countries	Cases/familial traits	Gene defects
Cerebrovascular diseases	Stroke: ischaemic/haemorrhagic	Tunisia	Ischaemic stroke	↑*PAI-1*; ↓*Tpa*; ↑*APOE* ε4; ↓*APOE* ε3 *APOE* ε4 associated with IS, SVD and statin use *HPA–1*, *HPA–5*, *AGT* and *eNOS* genes are associated with stroke [23–29]
		Egypt	Sickle cell anaemia	*ACE* D allele associated with stroke [30]
	CADASIL	Tunisia	1 case	*NOTCH3* mutation + skin biopsy confirmed [34]
Movement disorders	Ataxias	Tunisia	AD cerebellar ataxia type 1	Linked to *SCA2* locus on chr 12q [62]
			AR spastic ataxia of Charlevoix Saguenay (ARSACS)	Linked to chr 13q11–12 [63,64]
			Early onset cerebellar ataxia with oculomotor ataxia (AOA1)	*Aprataxin* mutations [65]
		Morocco	Ataxia with oculomotor apraxia type 2 (AOA2)	Mutations in the *SETX* gene [66]
			Ataxia telangiectasia	*ATM* gene defects [67]
	Dystonias	Tunisia	Dystonia associated with AR juvenile parkinsonism	Homozygous two-base AG deletion in exon 2 of *Parkin* 2 [41]
	PD	Algeria	EOPD	EOPD linkage to chr 6q25.2–27 *Parkin* locus and deletion of exons 8 and 9 in *Parkin* linked to ARJP [145]
		Algeria, Morocco Tunisia	Familial and sporadic PD	*LRRK2* G2019S mutation found in (43% of North African probands [43] *PINK 1* mutations [42,146]
		Tunisia	ARPD	Microdeletion of *Parkin* gene [41]
Seizure Disorders	Juvenile epilepsy	Tunisia	Genetic epilepsy with febrile seizures plus (GEFS +)	Mutations in *SCN1A*, *SCN1B*, *GABRG2* [96,97] New locus 17AC chr22 in intronic region of *TBC1D22A* gene [98]
		Tunisia, Algeria and Morocco	Idiopathic generalized epilepsy (IGE)	*TAP-1* functional polymorphisms at the I333V and the D637G loci [99] linkage to chromosome 21q 22.3 [104]
			Unverricht–Lundborg disease (ULD)	Founder effect of the haplotype A variant of the *cystatin B gene* [105] Novel missense mutations c.1364T>C (p.Leu455Pro) in the *ALDH7A1* gene [107]
		Tunisia	Pyridoxine-dependent Epilepsy (PDE)	
Adult epilepsy	Cortical myoclonic tremor and epilepsy	Egypt	Adult epilepsy	Frameshift mutation in contactin 2 (*CNTN2*) gene (TAG-1) [102]
Demyelinating disorders	Multiple sclerosis	Morocco, Tunisia Egypt	Multiple sclerosis	*HLA-DRB1*15* allele [109,110] association of *MTHFR A1298C* with MS [111]; *PAFR A224D* mutation in relapsing-remitting MS [112]; *TNF-α* 376 GG [113]
Neuromuscular disorders	Dystrophies	Egypt	DMD/BMD	*Dystrophin* gene mutations [114–116]
		Tunisia	AR–LGMD	Maps to chr 19q13.3 [125]
			LGMD2E	Homozygous missense mutations in exon 3 [126]
		Morocco	AR-LGMD2C	c525delT mutation of *SGCG* gene [127]
Neurotumours	Meningiomas	NA	NA	NA
	Astrocytomas	Morocco	Primary glioblastoma	*TP53* mutations detected [133]
Dementias	AD	Morocco	AD	Mutation in *APP*, *PS1* and *PS2* genes [81,82]
		Morocco, Egypt, Tunisia	AD and general population	*APOE* variants (ε2ε3ε4) (several authors)

Abbreviations: AD, Alzheimer's disease; ARJP, autosomal recessive juvenile parkinsonism; ARPD, autosomal recessive Parkinson's disease; BMD, Becker muscular dystrophy; chr, chromosome; DMD, Duchenne muscular dystrophy; EOPD, early onset Parkinson's disease; IS, ischaemic stroke; NA, not available; SVD, small vessel disease.

[a] There appear no reports on familial cases on or the genetics of pain, cavernous malformations, aneurysms, Huntington's disease, meningiomas, dementia with Lewy Bodies, frontotemporal dementia or vascular dementia.

Autosomal recessive forms of ataxia predominantly occur in Northern Africa (Table 1) whereas the autosomal dominant forms appear to be more common in sub–Saharan Africa (Table 2), especially SCA 1,2, 3, 6, and 7 [59–71].

Dystonias, characterized by sustained involuntary contractions of agonist and antagonist muscles, bizarre repetitive and twisting movements or abnormal posturing, appear relatively common in populations with a high frequency of consanguinity. Genetic forms of dystonia have been reported in association with autosomal recessive juvenile parkinsonism in a Tunisian family [41] while an isolated autosomal recessive idiopathic torsion dystonia [72] and a novel non-sense GCH1 mutation with dopa-responsive dystonia (DRD) [73] have been reported in two South African families respectively.

2.4. Dementias

Although there is substantial literature on the epidemiology of dementias in Africa, much of this is focused on Alzheimer's disease, vascular cognitive impairment and vascular dementia [74,75]; and HIV-associated neurocognitive disorders [76]. There are single reports on frontotemporal dementia [77], dementia with Lewy bodies and cognitive impairment and dementia related to Parkinson's disease [78–80].

Mutations have been reported in the Alzheimer's disease (AD) genes and susceptibility loci: Amyloid Precursor Protein (*APP*), Presenilin 1 (*PSEN1*) and Presenilin 2 (*PSEN2*) and *APOE* ε4 among Africans [74]. Novel frameshift mutations were recently detected in exons 16 and 17 of the *APP* gene in a cohort of sporadic and familial Moroccan AD patients with strong correlation with clinical symptoms in the early–onset familial cases [81]. Novel frameshift mutations were similarly reported in the *PSEN1* and *PSEN2* genes in this cohort [82]. In a study of a large South African Xhosa family with early onset AD affecting 12 individuals across 4 generations, a novel Ile143Met (ATT to ATG at nucleotide 677) *PSEN1* mutation was found and associated with profound neurofibrillary pathology [83].

The apolipoprotein E (*APOE*) appear to have been studied more than other dementia–related genes/loci in Africa. Existing in 3 allelic forms

Table 2
Neurological disorders and currently known genetic traits and genes affected in Africans (Sub–Saharan Africa).

Major neurological category[a]	Disorder subtypes	Country/countries	Cases/familial traits	Gene defects
Cerebrovascular diseases	Stroke: Ischaemic/haemorrhagic	Zambia	Ischaemic (IS) and haemorrhagic (ICH) stroke	*APOE* ε2ε4 associated with IS and ICH
	CADASIL	South Africa	5 cases	Diagnosed by skin biopsy [35]
Movement disorders	Ataxias	Mali	SCA types 2, 3 and 7	*CAG* repeats [68]
			Ataxia telangiectasia	*ATM* gene defect [69]
		Nigeria	SCA type 3 (MJD)	*ATXN3* CAG repeats [70]
		Rwanda	SCA type 2	*CAG* repeats [59]
		South Africa	SCA type 1	*CAG* repeats in chr 6p [60]
			SCA type 7	*CAG* expansion in chr 3p [61,71,147]
			SCA types 1, 2, 3, 6, and 7	
	Dystonias	South Africa	Dopa-responsive dystonia	*GCH-1* mutations [148]
	PD	Nigeria	Sporadic and familial PD	No pathogenic *LRRK2*, Parkin, *ATX3* mutations [39]
				No pathogenic *LRRK2* mutation [45]
		Ghana	Sporadic and familial PD	Novel *LRRK2* missense variant p.Ala1464Gly) and *Parkin* microdeletion of possible pathogenic role were found [47]
		Zambia	Sporadic and familial PD	*Parkin* mutations reported in two Black South Africans [46]
				LRRK2 mutation found in 2% of PD probands [73]
		South Africa	Sporadic and familial PD	Novel *PINK1* P305A variant detected in familial PD [149]
	HD	Gambia, Burkina Faso, Sudan South Africa	Huntington's disease	*CAG* repeat expansions [49–52]
Seizure disorders	Juvenile epilepsy	Mali	Lafora disease	Missense mutation in the *NHLRC1* gene [101]
		Malawi, Kenya, Tanzania and Ghana	Malaria-associated seizures	Focal (IL–20 receptor (rs1555498); Prolonged (complement receptor (rs 17047660); *G6PD* (rs 1050828); Complex (CD–ligand (rs 3092945); EMR-1 (rs373533); *IL-17* (rs708567); Repetitive (EMRI-rs313533); coma/cerebral malaria (*IL-10* (rs3024500) [108]
Neuromuscular disorders	Dystrophies	Nigeria	Dystrophia myotonica	Family kindred with de novo mutation [121,122]
		South Africa	Dystrophia myotonica	Rarity of myotonia in black South Africans [124,150,151]
		Rwanda	DMD/BMD	*Dystrophin* gene deletion [119,120]
		Ghana	DMD/BMD	Deletion of *dystrophin* gene [118]
			DMD	Duplication of *dystrophin* gene (exons 8 and 9) [117]
Neuropathies		South Africa	HIV-associated sensory neuropathy	*IL4* polymorphism associated with HIV-associated neuropathy [152]; *KCNS1* also associated [130]
				TNF block gene variants [131,132]
Neurotumours	Meningiomas	South Africa	Meningioma	Loss of heterogeneity and NF2 mutation [134]
Dementias	AD	South Africa	Early-onset familial AD	*PSEN1* mutation [83]
		Nigeria, Kenya, CAR,	AD and general population	*APOE* variants (ε2ε3ε4) (several authors)
	FTD	South Africa	FTD	*CHMP2B* mutations [92]

Abbreviations: AD, Alzheimer's disease; BMD, Becker muscular dystrophy; chr, chromosome; CAR, Central African Republic; DMB, Duchenne muscular dystrophy; FTD, frontotemporal dementia; ICH, intracerebral haemorrhage, IS, ischaemic stroke; PD, Parkinson's disease; SCA, spinocerebellar ataxia.

[a] There appear no reports on familial cases on or the genetics of pain, cavernous malformations, aneurysms, adult epilepsy, astrocytomas, dementia with Lewy Bodies or vascular dementia.

(*APOE ε2*, *APO ε3*, *APO ε4*), *APOE ε2* is protective whereas APO ε4 is associated with age–at–onset and increases the risk of AD in a dose–dependent manner among Caucasians. Frequencies of *APOE ε4* vary widely in Africa: 2.5% (in Moroccans), 19.8% (Yoruba Nigerians), 32% (Kikuyu Kenyans) and 40% (in the Pygmies of Central African Republic) [84–86].

Evidence from recent laboratory research [87] suggests that the high frequency of *APOE ε4* in regions of sub-Saharan Africa with the greatest endemicity for malaria is due to a selective evolutionary pressure on the allele because of its protective effect against malaria. In the cited experiment, plasma from individuals with *APOE ε4* but not *APOE ε3* inhibited the growth and disrupted the morphology of the intra-erythrocytic stage of *Plasmodium falciparum* species [87]. Nevertheless, *APOE ε4* showed a lack of association with AD among Yoruba Nigerians [88] and Kikuyus of East Africa [89]. More recent longitudinal data, however, from an enriched cohort of the Yoruba subjects demonstrated significant association between APO ε4 homozygosity and AD ($p = 0.0002$) and a weak association between one allele and incident AD and cognitive decline [90]. The possibility of certain epigenetic and/or gene–environment interactions which varied over time offers plausible explanations for the observed trend. However, *APOE ε4* showed strong association with AD in a Tunisian AD cohort [86]. Novel *CHMP2B* polymorphisms have been described in another South African family with FTD [91,92], while there are no reports yet on genetic variants associated with vascular cognitive impairment and dementia.

2.5. Seizure disorders

Epilepsy is a common neurological disease [6,93], particularly, in sub-Saharan Africa. Previous research has focused largely upon its epidemiology, aetiology and management [94]. The annual incidence of epilepsy in Africa ranges between 64 and 187 per 100,000 person-years while prevalence rates are as high as 105 per 1000 persons [94]. Its most common risk factors include febrile convulsions, birth trauma, CNS infections, and traumatic brain injury. Relatively little is known about the genetics of seizure disorders, epilepsies and epileptic syndromes in Africa with the limited available data emanating largely from North Africa and fewer from sub-Saharan Africa [5]. Most studies involved small numbers of individuals from consanguineous families with familial epilepsies and findings were mainly rare genetic variants.

There is growing evidence suggesting that some epilepsies are channelopathies caused by pathogenic variants in ion channel genes [95]. In genetic epilepsy with febrile seizures plus (GEFS+), a syndromic autosomal dominant disorder with variable expressivity and numerous epilepsy phenotypes, mutations involving voltage-gated sodium–channel genes have been reported in two Tunisian families (*SCN1A*, *SCN1B*, *GABRG2*) [96,97]. A more recent genome-wide single nucleotide polymorphisms (SNPs) genotyping followed by a whole-exome sequencing in another Tunisian family revealed a new locus 17ACchr22 located in an intronic region of *TBC1D22A* gene [98]. In another consanguineous Tunisian family with Juvenile myoclonic epilepsy (JME) with four affected out of eight children, genome-wide parametric linkage analysis and subsequent visual analysis of SNP data using AutoSNPa showed suggestive linkage to chromosome 2q and two large regions of shared homozygosity on 2q23.3 (*CACNB4*) and 2q24.1 (*KCNJ3*) but further exome sequencing yielded no mutations [99]. Two functional polymorphisms (I333V and the D637G) of the transporter associated with antigen processing-1 (*TAP-1*) gene have however been associated with idiopathic generalized epilepsy (IGE) in Tunisian families [100]. In a Malian family with parental consanguinity and two of eight siblings affected with late-childhood-onset Lafora disease, genetic analysis showed a novel homozygous single-nucleotide variant in the *NHLRC1* gene, c.560A>C, producing the missense change H187P [101].

In a consanguineous Egyptian family with an autosomal recessively inherited familial cortical myoclonic tremor and epilepsy, multipoint

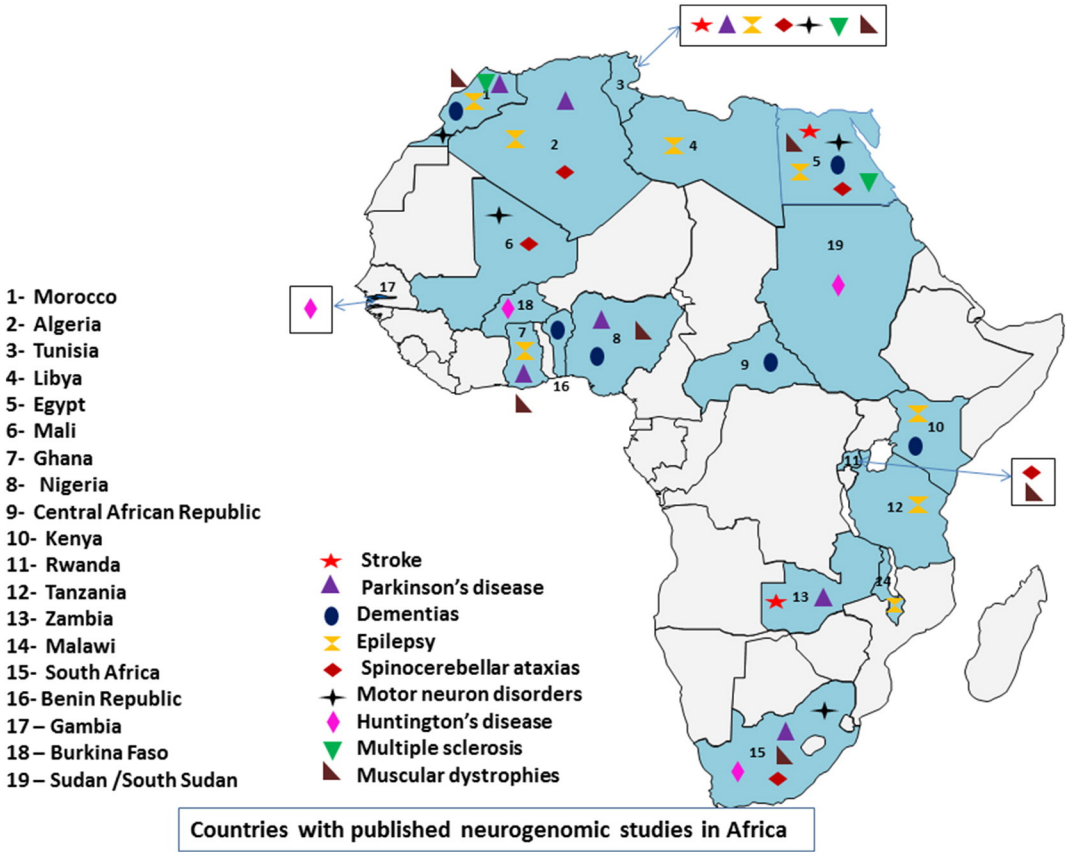

Fig. 1. Map of Africa showing countries (shaded) which have reported neurogenomic studies.

linkage analysis followed by exome sequencing unmasked a homozygous single base pair deletion (c.503_503delG) leading to a frameshift in the coding region of the sixth exon of contactin 2 (*CNTN2*) gene TAG-1 (p.Trp168fs), whose protein product helps maintain voltage-gated potassium channels at the juxtaparanodal region [102].

Unverricht–Lundborg disease (ULD), an autosomal recessively inherited disorder, is the most common form of the progressive myoclonus epilepsies. ULD is often caused by expansion of a dodecamer repeat in the cystatin B gene (*CSTB*) promoter [103]. In a study of 44 ULD patients from 19 families living in three North African countries (Tunisia, Algeria and Morocco), consanguinity was noted in 17 families (first degree in 15 families) and linkage to chromosome 21q 22.3 was confirmed in 11 families [104]. In another haplotype study of 47 ULD North African patients, Moulard et al. [105] discovered a founder effect of the haplotype A variant of the cystatin B gene in the cohort.

Pyridoxine-dependent Epilepsy (PDE) is a rare autosomal recessive condition causing vitamin B6-responsive intractable seizures in neonates and infants. PDE is caused by defects in the *ALDH7A1* gene. Novel missense mutations c.1364T>C (p.Leu455Pro).have been reported in affected Tunisian families [106,107].

In sub-Saharan Africa, a study examining the genetic risk of acute seizures in African children with falciparum malaria undertaken across four MalariaGEN African sites. These include Blantyre, Malawi; Kilifi, Kenya; Kumasi, Ghana; and Muheza, Tanzania, sites specifically sought to determine if polymorphisms of malaria candidate genes were associated with acute seizures. Using logistic regression to investigate genetic associations, the investigators found a couple of genetic associations (Table 2) that could explain the risk of seizures in >2000 cases admitted to hospitals with malaria associated seizures (MAS) across the four sites [108].

2.6. Demyelinating disorders

There are limited data on the genetics of demyelinating disorders and leukodystrophies in Africa with available data specifically emanating from the Northern sub-region. Association between *HLA-DRB1*15* allele of the HLA class II genes and multiple sclerosis (MS) was previously reported in diverse ethnic groups. This was confirmed in cohorts of Tunisian and Moroccan MS patients [109,110] while another study demonstrated an association between the methylenetetrahydrofolate reductase (*MTHFR*) gene A1298C polymorphisms and MS in a cohort of Tunisian patients [111]. Furthermore, platelet-activating factor receptor A224 mutation demonstrated a significant association with relapsing-remitting MS and consistent with a dominant model of inheritance among Tunisian MS patients [112] while a tumor necrosis factor α-376 polymorphism GG genotype showed significant association with primary progressive and relapsing–remitting MS in a small cohort of Egyptian patients [113] (Table 1).

2.7. Neuromuscular disorders

Deletions and duplications have been reported in the dystrophin gene in African subjects with Duchenne and Becker muscular dystrophy in Egypt [114–116], Ghana [117], Rwanda [118] and South Africa [119,120] while mutations in the gene coding for dystrophia myotonica have also been reported in kindreds from Nigeria [121,122] and South Africa [123,124]. Autosomal recessive limb girdle muscular dystrophy mutations in chr 19q13.3 [125], homozygous missense mutations in exon 3 [126] and c525delT mutation of *SGCG* gene [127] have been similarly reported from Tunisian and Moroccan subjects.

2.8. Motor neuron disorders

A distinct form of hereditary spastic paraplegia with amyotrophy (SPG43) has been described in a Malian family with two affected sisters. Mapping revealed a region of extended homozygosity at chromosome 19p13.11-q12 that was not shared by controls [69]. Furthermore, homozygous deletions in exons 7 and 8 of survival motor neuron protein (SMN) and neuronal apoptosis inhibiting protein (NAIP) have been described in subjects with variants of spinal muscular atrophy (SMA) from Morocco, Tunisia, Egypt and South Africa [128].

2.9. Other conditions

Associations of HIV-associated sensory neuropathy including *IL4* polymorphism [129], *KCNS1* [130] and TNF block gene variants [131,132] have been reported in South African cohorts while *TP53* mutations detected in primary glioblastoma [133] and loss of heterogeneity and NF2 mutation in meningiomas [134] have been described in Morocco and South Africa respectively.

3. Progress through the H3Africa Initiative

The Human Health and Heredity in Africa (H3Africa) Initiative [13], with funding support from the US National Institutes of Health (NIH) and the UK Wellcome Trust, is currently executing 24 different large–scale, disease–based projects involving 50–75,000 participants across the African continent [13]. This initiative promises to enhance our understanding of human genomic variation and unravel the genomic basis of several diseases on the continent, while facilitating genomic infrastructural development, capacity building and retention of genomic expertise on the continent.

The initiative includes two specific projects focusing on neurological disorders in Africans. The first project is an exploratory clinical and genetic study of inherited neurological disorders in a Malian population while the second project focuses on the genetics of stroke in people of African ancestry in two West African countries (Ghana and Nigeria) and the United States of America.

The Stroke Investigative Research and Education Network (SIREN) Project proposes to explore genomic factors in stroke in 6000 native West Africans (3000 case–control pairs) in comparison with 1000 African Americans (80% of whom migrated from West Africa) and 12,000 Americans of European ancestry in the Reasons for Geographic and Racial Disparities in Stroke (REGARDS) Study (comparison among three tracks). The wide genomic variation of African populations offers a unique opportunity to identify novel genomic variants with causal relationship to stroke across the different ethnic groups involved with the project [21,135]. The SIREN Project will utilize GWAS approaches using customized chips including unique African variants [10], Whole Genome and Whole Exome Sequencing (WGS/WES) and other emergent high–throughput next gen and next generation sequencing approaches for future analyses. In addition, 'pathway-based analysis' of genomic data [136] will chart new paths in our understanding of the molecular trajectories of stroke and unravel new options for stroke prevention, diagnostics, therapeutics and prognostics in the emerging milieu of personalized precision medicine.

4. Possibilities of future gains in knowledge

Much of what is known about neurogenomics in Africa has been achieved largely through small-scale genotyping and linkage analysis studies (Fig. 1). The advent of the H3Africa Initiative has triggered a silent genomic revolution in Africa [13]. This initiative is helping to build the necessary framework for the establishment of Afrocentric, African-driven, Africa-wide consortia on brain disorders which can, in future, utilize the infrastructure and capacity currently being developed. This will enhance the prospect of better-powered population and hospital-based studies exploring neurological disorders using high-throughput GWAS and next generation sequencing.

In contrast to first generation sequencing (Sanger sequencing) which took several years and cost millions of dollars to sequence the human genome, next generation platforms can now undertake the

same genome sequencing within a few weeks and at much lower cost [137]. Next generation sequencing technology enhances the identification of rare variants with large effect size, including unmasking missense or nonsense single-base substitutions, as well as small insertions or deletions, which often constitute 'missing heritability' and are particularly relevant to neurological disorders.

As an example, epidemiological studies in Africa have shown a weak or lack of association of *APOE* ε4 allele as a genetic susceptibility factor for AD in sub-Saharan African populations [74]. However, a direct relationship was demonstrated with cholesterol levels in Yoruba non-*APOE* ε4 allele carriers [138] as detailed above. It has been suggested that this paradox may be due to yet-to-be discovered genetic factors or gene × gene interactions [74,84] which can be unmasked by current next generation genomic technology.

With such progress, we will gain deeper insights into how the genomic heterogeneity in Africa interplays with environmental factors to influence the distribution, pattern, presentation and outcome of neurological disorders in people of African ancestry. We can also further our understanding of the neurobiology of brain disorders through the discovery of new genes, transcriptomics, proteomics and RNA studies as well as complementary mechanistic studies in cell culture and animal models. This will improve knowledge of functions and interactions of genes in disease mechanistic pathways, and thereby pave way for the development of new biomarkers for early disease recognition, and new precision targets for personalized preventative and therapeutic interventions. It is also conceivable that the large anticipated database that will be generated from African neurogenomic studies will contribute to the global human brain mapping projects [139].

5. Priorities for translational genomics in Africa

Translational genomics investigates how genomic and epigenomic individuality predisposes to health and disease and how an individual's genome expresses itself at different omic levels (transcriptomics, proteomics, metabolomics, lipidomics) in response to the environment (exposome), including e.g. drugs, nutrition and physical activity [140]. This knowledge forms the basis of personalized precision medicine with solutions that can be applied in real time to maintain health and evaluate, mitigate, improve, or delay disease progression [12,140].

Although there are ongoing debates on the T1 to T5 (globalization) translational aspects of genomics including its public health applicability and cost–effectiveness of personalized precision medicine [141–143], dogged focus must be maintained on deriving maximum clinical benefits from genomic advances in the real-world. Barriers to implementing the benefits of genomic medicine to advance health in Africa are multiple across the different phases of translation (Table 3). However, there are also facilitators that center around the necessity of continuing the cyclical and bi-directional flow of information and communication relevant to adoption of appropriate behaviors from individuals to organizations that appreciate and take up the benefits of personalized precision medicine. Therefore, robust public and stakeholder engagement and multilevel, multigenerational, transdisciplinary capacity building must accompany development of relevant infrastructure for genomic medicine in Africa.

In a continent faced with a growing burden of non-communicable diseases while HIV/AIDS, tuberculosis and malaria persist, the fundamental public health issues of access to, cost–effectiveness of and availability of healthcare services including therapeutic agents remain at the heart of growing disease burden and deserve more attention from political leaders, governments and policy makers [142].

Although it is quite hard to make the financial argument for person-focused genomic healthcare currently with all the other problems in Africa, nevertheless, investing in infrastructure for human genomic research and medicine will be a crucial and wise preparation for the future. African governments and funding organizations including the private sector must be ready to sustain the current momentum in genomics research by providing necessary support. The establishment of the Alliance for Accelerating Excellence in Science in Africa (AESA) is a great encouragement in this regard [144].

It will be crucial to strike a balance between traditional strategies of disease prevention and treatment and personalized genome–based care. For instance, while the traditional evidence–based lifestyle, behavioral and pharmacologic interventions for blood pressure control have their public health benefits and must be sustained, personalized care based on genomic information will be helpful to individuals with treatment-resistant hypertension because of a mutation–induced channelopathy amenable to a specific drug. Moreover, personalized lifestyle and

Table 3
Barriers and facilitators of translational genomics in Africa.

Phase of translation	Barriers	Facilitators
T1: Discovery Science	Under–recognition and under–diagnosis of neurological conditions Paucity of accurate epidemiologic dataset Inadequate expertise and infrastructure for accurate phenotyping of disease, neurobiorepositories, genomics studies and analysis Negative influence of cultural and religious beliefs Unavailability of African genome-specific chips	Stakeholder engagement and advocacy Capacity development of multidisciplinary expertise for neurologic care and genomics studies Infrastructural development of neurological diagnostics and genomic studies Networking and collaboration
T2: Translation to Patient	Gap between basic scientists and clinicians Sociocultural barriers eg belief system Systemic tardiness	Multidisciplinary approach to genomic projects Ongoing cyclical and bi-directional flow of communication between bed and bedside Effective and efficient clinical–scientific leadership
T3: Translation to Practice	Inadequate trained healthcare manpower supply Systemic barriers: e.g. lack of practice guidelines or practice regulation Programmatic failure due to lack of sustainability planning Poor innovation and continuous infrastructural development	Capacity building and continuous professional development Scientific leadership and clinical governance Continuous bi-directional interaction of scientists with healthcare product consumers (physicians/patients) System integrators
T4: Translation to Population	Poor research–industry-healthcare synergy Fragile public health systems Poor community science and health literacy Poverty, illiteracy and high disease burden Low technological development Political instability, lack of political will, wars, etc.	Scientific and public health leadership Continuous stakeholder engagement Enhanced research–industry–healthcare synergy Economic empowerment and technological development strategies, especially mobile technologies
T5: Translation to Global (international) implementation	Knowledge and practice generated from developing countries often regarded as inferior for implementation	Need for global health agencies to disseminate knowledge to appropriate influential governmental agencies and policy makers

T1: Discovery Science e.g. Discovery of genomic biomarker for Alzheimer disease (AD) susceptibility.
T2: Translation to Patient e.g. Development of biomarker into a screening test for use in clinical practice.
T3: Translation to Practice e.g. Evaluation of the impact of a delivery model for screening with the biomarker.
T4: Translation to Population e.g. Evaluating the uptake of the new screening test in a population of at–risk–individuals.
T4: Translation to Global implementation e.g. Dissemination of information to relevant health policy advisers.

behavioral interventions could be delivered based on specific risk prediction, prognostic information obtained from individual genomic information. Likewise, targeted therapies can be administered based on individual neuropharmacogenomics information. The costs of these technologies are likely to continue to reduce with improving availability in the nearest future. Therefore, a double–edged approach is required for investing necessary resources into both traditional approaches and genome–based personalized care for their growth and impact on human health and disease.

Health and genomic education across the lifespan will also be necessary to correct misconceptions and erroneous ideologies, and encourage uptake of both effective traditional strategies and targeted genomic-based approaches. Capacity building for neurological and genomic research and care–basic scientists, neurologists, neurogenomicists, neuropsychologists and other relevant cadres of healthcare professionals must be emphasized for the delivery of optimum person–focused genomic healthcare.

Search strategy and systematic review

A systematic literature search of PubMed and Medline was done with combinations of search terms, including “Africa” and “genetics” or “genomics”, with topic headings including “cerebrovascular diseases”, “stroke”, “CADASIL”, “cavernous malformations”, “aneurysm”, “ataxia”, “dystonia”, “Parkinson's disease”, “Huntington's disease”, “Alzheimer's disease”, “Lewy body dementia”, “Frontotemporal dementia”, “vascular dementia”, “vascular cognitive impairment”, “seizure disorders”, “epilepsies”, “epileptic syndromes”, “demyelinating disorders”, “multiple sclerosis”, “neuromuscular disorders”, “muscular dystrophies”, “myasthenia gravis”, “headaches”, “meningioma”, “astrocytoma”. PubMed was searched for relevant articles in the English Language or English translation of articles in French until June, 2015.

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